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.

Bosutinib

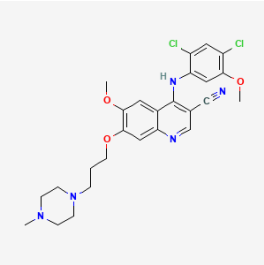
Evidence Summary

Bosutinib enhances autophagy, among other cellular activities. Open label clinical studies suggest that bosutinib may have efficacy in ALS. Preclinical work indicates potential utility in dementia.

Neuroprotective Benefit: Open label studies indicate that bosutinib may mitigate decline in ALS and stabilize or improve daily functioning in DLB. Preclinical models suggest several potential mechanisms of action. Robust RCT trials are needed.

Aging and related health concerns: Bosutinib is an effective first-line treatment for chronic myeloid leukemia. It has not been explored for use in other diseases.

Safety: Gastrointestinal side effects are commonly reported during use of bosutinib. Regular hepatic monitoring is recommended, as is monitoring blood counts and renal function. Preliminary work suggests an overall similar safety profile in non-CML groups.

Availability: By prescription	**Dose**: Up to 500 mg per day by mouth for patients with CML; doses of 100 to 400 mg per day by mouth for patients with neurodegenerative disease have been tested.	**Chemical formula:** $C_{26}H_{29}Cl_2N_5O_3$  **MW**: 530.4 g/mol Source: PubChem
Half-life: Approximately 22.5 hours.	**BBB**: Penetrant.	
Clinical trials: The largest meta-analysis identified included 518 patients who received bosutinib.	**Observational studies**: The largest observational study identified included 87 patients.	

What is it?

Chronic myeloid leukemia (CML) is a type of cancer characterized by uncontrolled proliferation of myeloid cells. Approximately 90% of patients with CML have a genetic abnormality wherein a part of the *ABL1* gene on chromosome 9 is translocated to the *BCR* gene on chromosome 22, known as the Philadelphia chromosome (Jabbour & Kantarjian, 2024; NCI). This *BCR:ABL1* fusion gene results in BCR:ABL1, an oncoprotein tyrosine kinase that is constitutively active, driving downstream signaling pathways that lead to growth and survival of the aberrant cells. The tyrosine kinase inhibitors imatinib, bosutinib, dasatinib, and nilotinib are frontline treatments for CML (Jabbour & Kantarjian, 2024).

Bosutinib is a dual SRC/ABL kinase inhibitor (Jabbour & Kantarjian, 2024). It is approved for use in adults and children 1 year of age and older who have chronic-phase Philadelphia chromosome-positive CML who are newly diagnosed or resistant or intolerant to prior therapy, as well as in adults with accelerated or blast phase Philadelphia chromosome-positive CML with resistance or intolerance to prior therapy (FDA).

Kinases, including tyrosine kinases, have been a target of interest in various neurodegenerative diseases. Aberrantly phosphorylated protein(s) are pathological hallmarks of several neurodegenerative diseases, including phosphorylated tau in Alzheimer's disease and phosphorylated α-synuclein in Parkinson's disease (PD). The downstream signaling pathways of kinases can also include cellular activities relevant

to neurodegenerative disease such as growth, survival, autophagy, and neurotransmission (Wu et al., 2025).

As a note on nomenclature, Abl, c-Abl, and Abelson are all accepted names of the protein (Uniprot); this report will use Abl for consistency.

Neuroprotective Benefit: Open label studies indicate that bosutinib may mitigate decline in ALS and stabilize or improve daily functioning in DLB. Preclinical models suggest several potential mechanisms of action. Robust RCT trials are needed.

Types of evidence:

- 1 meta-analysis and systematic review
- 1 randomized controlled trial
- 3 open label studies
- 1 case report
- 3 reviews
- Numerous laboratory studies

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

No study was identified that reported on bosutinib and cognitive function in non-dementia populations. No studies appear to have explored whether bosutinib has any effects on dementia prevention or on preventing decline.

Human research to suggest benefits to patients with dementia:

There is very preliminary evidence of the potential for effect of bosutinib or other tyrosine kinase inhibitors in dementia.

A meta-analysis and systematic review by Gorsch Berton et al., 2024 investigated the effects of Abl tyrosine kinase inhibitors in patients with PD and dementia with Lewy bodies (DLB). The meta-analysis

included 5 studies: 4 testing nilotinib, another second-generation tyrosine kinase inhibitor used for CML, and 1 testing bosutinib. The study of bosutinib is described below:

Pagen et al., 2022 reports on the results of a double-blind randomized placebo-controlled trial of bosutinib in patients with dementia with Lewy bodies (DLB). The study enrolled 26 patients and randomized them to receive 100 mg of daily bosutinib for 12 weeks and had an additional study visit after a 4-week washout period. The primary outcomes of the study were safety and pharmacokinetics. The secondary outcomes were assessments of biomarker levels. Cognitive function was an exploratory endpoint. The researchers confirmed that bosutinib crossed the blood-brain barrier of DLB patients. They also found that bosutinib treatment resulted in a significantly greater decrease of phosphorylated, activated Abl in both plasma and CSF compared to placebo as well as a significant decrease in plasma phosphorylated Src, suggesting target engagement. There was also a significant decrease in CSF α-synuclein in the bosutinib group compared to the placebo group. The clinical meaningfulness of the change in α-synuclein level is not yet known. The researchers hypothesized that this dosage of bosutinib was at or near the lowest effective therapeutic dose.

Patients who received bosutinib had a significant improvement in daily functioning, an exploratory outcome, at 12 weeks compared to placebo. After a 4-week washout, there was no longer a significant difference. While there was no significant difference on ADAS-Cog between the groups, the mean difference between the groups decreased during the washout period; this indicates there may have been a non-significant increase in cognitive dysfunction during the washout period. There was also a trend towards improvement on the Trail Making Test-Part B for the bosutinib group at 12 weeks; their performance then declined at the visit after the washout period. It should be noted that the study was not statistically powered for clinical outcomes.

Mahdavi et al., 2021 describes an open-label study of bosutinib in patients with probable AD or Parkinson disease spectrum disorders with dementia (PDD). Patients received up to 300 mg of bosutinib daily; dosing was titrated up, and the protocol allowed for dose reductions if there was an intolerance. Dosing lasted for 12 months and participants were then followed for an additional 12 months. The primary cognitive outcome of the study was the change in clinical dementia rating scale as estimated by the Quick Dementia Rating System, which is a self-report questionnaire by the caregiver; the scores provide an estimate of CDR score. These estimates were then compared to population-based estimates of cognitive decline. The expected rate of decline was calculated to be a 22% conversion rate from MCI to dementia, and 29% progression rate to a more advanced stage of dementia. Secondary outcome

measures included other assessments of cognitive function such as the Montreal Cognitive Assessment (MoCA) and Repeatable Battery Assessment of Neuropsychological Status (RBANS). At the end of 12 months of dosing in 31 patients, the researchers measured the cognitive function of the participants. They report that compared to the population-based estimates of cognitive decline, bosutinib-treated patients in this study had less decline as measured by the QRDS/CDR (HR=-3.5; 95% CI -3.64 to -3.3, p<0.001). The researchers also compared the 12-month results to the baseline findings, and reported the following results:

Assessment	Improved	Stable	Decline
QRDS/CDR	45.16%	45.16%	9.68%
MoCA	22.6%	25.8%	51.6%
RBANS	22.6%	58.1%	19.4%

They also reported results from 16 patients who had completed the 24-month follow-up from baseline (that is, 12 months after completion of 12-month bosutinib dosing); these data are the change from 12-month follow-up:

Assessment	Improved	Stable	Decline
QRDS/CDR	18.8%	50%	31.2%
MoCA	50%	43.8%	6.2%
RBANS	31.2%	37.5%	31.2%

There are several significant limitations to this study, including the small size, open-label design, and cognitive assessment based on self-report or caregiver-report rather than a trained clinician. Participants also were allowed to receive concurrent supplements or therapies that could influence cognitive function and could also participate in other studies at the same time, including one of transcranial ultrasound. It is not possible to disentangle potential effects of bosutinib from the confounders in this trial.

A follow-up abstract from Zielinski et al., 2021 briefly reports on results from an additional 21 patients to the sample of 31 above, for a total of 52 patients who completed 12 months of dosing with bosutinib. Of these 52 patients, 40% had improved estimated CDR scores, 38% had stable scores, and 22% had worse scores. The abstract reports that they planned to give another update in 2022, but no further follow-up

information was found. In addition to the limitations of the study itself, abstracts are not peer reviewed and do not include a lot of detail, limiting potential evaluation of the data.

A case report of two patients with Parkinson's disease (PD) and concurrent cancer treated with imatinib, a first-generation tyrosine kinase inhibitor that targets Abl and other kinases, reported that during treatment with imatinib the patients experienced subjective mitigation of PD symptoms and stability or improvement of motor symptoms as measured by the MDS-UPDRS (Watson-Fargie et al., 2018).

Bosutinib is also under investigation for potential utility in amyotrophic lateral sclerosis (ALS). A study used iPSC-derived motor neurons from ALS patient tissue to screen compounds for potential repurposing utility and bosutinib was the most promising compound identified (Imamura et al., 2017); this study will be discussed in greater detail in the 'Mechanism of action for neuroprotection' section below.

As described in Imamura et al., 2022, the group then ran an open-label phase 1 dose escalation study of bosutinib in 13 patients with ALS. The study was designed with a 12-week observation period, a 1-week transition period where patients stopped riluzole, a concurrent ALS medication, and then a 12-week treatment period where patients only received bosutinib. The change in ALS disease severity as measured by ALSFRS-R was assessed during both the observation and treatment period. The treatment period consisted of a dose-escalation of 100, 200, 300, and 400 mg daily. The primary outcome of the study was safety, which is discussed in the 'Safety' section. The study also included exploratory endpoints of ALS disease progression and change in plasma biomarkers.

Of the 13 patients who received bosutinib, 9 patients completed 12 weeks of dosing with 100 to 300 mg daily of bosutinib. The study was not powered for efficacy and the outcomes were exploratory, but 5 of the 9 patients appeared to respond to bosutinib, with more stable ALS-FRS-R scores during the 12 weeks of treatment with bosutinib than during the observation period. The researchers also reported that there were changes in biomarkers over the course of the treatment period, such as a decrease in plasma neurofilament light (NFL) and urine p75, both thought to be markers of neuronal damage. Interestingly, post-hoc analysis suggested that response to bosutinib was predicted by NFL levels at baseline, hinting at a potential for biomarker identification of bosutinib-responsive ALS patients. Plasma levels of phosphorylated Abl and Src were also decreased after treatment in 7 out of 9 and 6 out of 9 patients, respectively, suggesting that there was target engagement.

The group then proceeded to an open-label phase 2 study of bosutinib in ALS patients, publishing the protocol in Imamura et al., 2024. The 24-week study aimed to enroll 25 patients with ALS, with 12 patients receiving 200 mg bosutinib daily and 13 patients receiving 300 mg bosutinib daily. The primary outcome is safety, with exploratory efficacy outcomes comparing study participants to data from an ALS registry as well as from an ALS trial of edaravone.

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

As a dual Src/Abl kinase inhibitor, bosutinib modulates a variety of critical cellular processes, many of which are relevant in neurodegenerative diseases (Wu et al., 2025). Increased levels of Abl have been reported in both AD and PD patient samples, raising the possibility that Abl inhibition may be beneficial (Pagen et al., 2022).

Preclinical studies have reported benefits of bosutinib in different models of various neurodegenerative diseases. Bosutinib is thought to increase autophagy and thus reduce levels of misfolded proteins. In a TgAPP mouse model of AD, three weeks of bosutinib treatment in 8- to 12-month-old animals increased autophagic flux and reduced levels of Aβ and tau (Lonskaya et al., 2013). Bosutinib also reduced levels of α-synuclein and phosphorylated tau in an A53T α-synuclein model of PD. Treatment was started at 2 to 3 months of age, when there is already significant α-synuclein and tau pathology, and continued for 6 weeks (Hebron et al., 2014). Similar results were observed with clearance of SOD1 in animal models of ALS (Imamura et al., 2017), and nuclear TDP-43 in transgenic TDP-43 mouse models (Wenqiang et al., 2014). Studies have also reported improvements in cognitive function in animal models with transgenic APP or TDP-43 expression with bosutinib treatment (Lonskaya et al., 2013, Wenqiang et al., 2014). Preclinical work also suggests that bosutinib may modulate neuroinflammation. In an A53T mouse model of PD, treatment with bosutinib restored plasma levels of cytokines such as IL-1α and IL-1β to wildtype levels (Hebron et al., 2014), and in a TgAPP animal model, bosutinib partially or fully restored IL-10 and CX3CL1 to that of the wildtype control (Lonskaya et al., 2015).

Many of these studies are from affiliated groups. However, similar results have been reported from other labs, such as the work in ALS models described below. Bosutinib has also been identified as a drug with repurposing potential for AD by AI-based computational frameworks of protein-protein interaction networks (Tsuji et al., 2021).

Imamura et al., 2017 discusses a phenotypic screen of iPSC-derived motor neurons; the iPSC lines were generated from tissue samples from ALS patients. Using high-throughput screening, they tested 1,416 compounds and identified 27 compounds that improved motor neuron survival more than 3 standard deviations above negative controls. Of these 27 hits, seven showed dose-dependent neuroprotective effects, and interestingly, 14 of the 27 hit compounds targeted the Src/Abl signaling pathway. Knockdown of Src or Abl with siRNA also improved motor neuron survival. The researchers selected bosutinib as a lead compound as it directly targeted Src/Abl, showed efficacy at lower doses compared to other hits, and showed dose dependence without a bell-shaped response like the one observed for dasatinib, another Src/Abl inhibitor. In these iPSC-derived motor neurons, bosutinib enhanced autophagy, reduced levels of misfolded SOD1, and mitigated changes in mitochondrial gene expression that were observed in ALS motor neurons. Bosutinib increased survival of motor neurons derived from both sporadic ALS patients and familial ALS patients. Treating transgenic SOD1 mutant mice with bosutinib starting at 8 weeks and continuing to 13 weeks modestly delayed disease onset by 10.8 days and increased survival by 7.8 days.

APOE4 interactions:

It is not known whether bosutinib has any differential effects based on APOE4 status.

Aging and related health concerns: Bosutinib is a first-line treatment for CML. It has not been explored for use in other diseases.

Types of evidence:

- 1 meta-analysis and systematic review
- 1 observational study
- 4 reviews
- 1 laboratory study

Chronic myeloid leukemia: BENEFIT

Bosutinib is an approved frontline treatment for patients with newly diagnosed Philadelphia chromosome positive CML or patients who are resistant to or intolerant of prior therapy (Jabbour & Kantarjian, 2024). A phase 3 trial known as the BFORE trial tested bosutinib in 268 patients with newly

diagnosed chronic phase CML. They report that the major molecular response rate, as defined by a low level of *BCR:ABL1* transcripts, was 73.9% by 5 years with an overall survival rate of 94.5% after 5 years (Kantarjian et al., 2024).

Safety: Gastrointestinal side effects are commonly reported during use of bosutinib. Regular hepatic monitoring is recommended, as is monitoring blood counts and renal function. Preliminary work suggests an overall similar safety profile in non-CML groups.

Types of evidence:

- 1 meta-analysis and systematic review
- 2 reviews
- 2 professional resources

The most common adverse event of bosutinib is diarrhea. More than 70% of participants report this event across studies, though most events are mild and transient, with few treatment discontinuations due to this adverse event. Hepatic, hematological, and dermatological adverse events are also common. These include increased liver enzyme levels, thrombocytopenia, anemia, and rash. Regular monitoring of liver enzymes and blood counts, especially at treatment initiation, is recommended (Lipton et al., 2024). Other gastrointestinal events such as vomiting and abdominal pain are also common (Kantarjian et al., 2024). Unlike some tyrosine kinase inhibitors like imatinib, bosutinib does not significantly inhibit c-kit or PDGF-R; inhibition of these kinases is associated with adverse events like pleural effusion or increased myelosuppression (Steinbach et al., 2013).

Rare but serious adverse events have been reported for bosutinib. While bosutinib has a lower incidence of cardiovascular events compared to other tyrosine kinase inhibitors and is often a preferred option for patients with cardiovascular multi-morbidities, cardiac adverse events have been reported at rates of approximately 10% of participants in some long-term follow-up studies of clinical trials. These events led to discontinuation of treatment in approximately 1% of these patients. Similarly, renal events have been reported at rates of 9% to 13% in some clinical trials; these events rarely led to treatment discontinuation, but regular monitoring is recommended. Pulmonary toxicities such as pleural effusion are less common in bosutinib than with dasatinib but have been reported, particularly in those with other risk factors for pulmonary adverse events. Cardiac, vascular, effusion, and renal adverse events may be more common later in treatment than earlier in treatment (Lipton et al., 2024). Some, like

cardiovascular ischemic events, tend to occur in patients with pre-existing risk factors or cardiovascular disease (Kantarjian et al., 2024). Appropriate monitoring, dose reductions or temporary interruptions, and/or considering existing risk factors when selecting a medication and/or dose may be useful for risk mitigation strategies (Lipton et al., 2024).

While the safety profile of bosutinib in patients with CML is fairly well understood, the safety profile in older adults – especially those with cognitive decline or dementia – is still under investigation.

An RCT tested 100 mg of bosutinib daily in 26 adults with DLB. The primary outcome of the study was safety. Over the 12-week trial, there were no serious adverse events and no dropouts. There was no significant difference in the number of adverse events, with 11 events in the bosutinib group and 9 events in the placebo group. The most common event was falls, which were equal in frequency in the two groups. Dizziness was reported by one patient in each group. Pain was reported by 3 patients in the bosutinib group and 1 patient in the placebo group. There was one event of transient borderline liver enzyme elevations, including ALT and AST, which self-resolved (Pagan et al., 2022).

Mahdavi et al., 2021 details an open-label study of bosutinib in 31 patients with dementia for 12 months. Patients were titrated up to a maximum of 300 mg of bosutinib daily. The only reported side effects were fatigue and gastrointestinal events like upset stomach or diarrhea; these events were reported by less than 10% of the study participants. Of the 31 patients, 22 received the full 300 mg dose; 9 were not able to tolerate the 300 mg dose due to adverse events or abnormal lab results and received dose reductions to either 100 mg or 200 mg per day. Four patients withdrew from this study for personal reasons.

Bosutinib has also been tested in ALS patients. Imamura et al., 2022 details an open label phase 1 dose-escalation study. The trial sequentially tested 100 mg, 200 mg, 300 mg, and 400 mg daily oral doses of bosutinib; each dose was tested in 3 patients for 12 weeks before proceeding to the next group and dose. No dose-limiting toxicities were seen in the 100 mg, 200 mg, or 300 mg groups; all 3 patients in the 400 mg dose group experienced dose-limiting toxicities. The dose-limiting toxicities were a Grade 3 rash papular in 1 patient and Grade 3 liver injury in 2 patients. One patient in the 100 mg group had an adverse event of Grade 3 increased liver enzymes. All participants experienced at least one drug-related adverse event. Most of the adverse events were Grade 1 or 2, and the most common adverse events were diarrhea (69.2% of patients), constipation (23.1%), and liver disorder (23.1%). There were no clinically meaningful changes in vital signs, ECG, or chest x-ray. The types and frequencies of these

events are consistent with the known safety profile of bosutinib in cancer patients. Hematological adverse events are commonly reported in CML patients; no such events were reported in this study. One patient in the 300 mg group died by suicide. The study investigators and the Safety Assessment Committee determined that this was not related to the study drug.

Studies in patients with CML have indicated that titrating the dose up can minimize GI events (Jabbour & Kantarjian, 2024); Mahdavi et al., 2021 employed a dose-titration design, whereas Imamura et al., 2022 did not.

It is worth noting that in patients with CML, it has been reported that other tyrosine kinase inhibitors such an imatinib have rare neurological toxicities, such as dementia-like findings, peripheral neuropathy, worsening of PD, or central neurotoxicity misdiagnosed as dementia (Jabbour & Kantarjian, 2024). One case report was identified wherein a 53-year-old patient with CML. After 1.5 years on dasatinib, he developed bilateral pleural effusions. He then transitioned to bosutinib treatment and the pleural effusions self-resolved after a few days. After 6 months of bosutinib treatment, he again developed bilateral pleural effusions with evidence of pulmonary arterial hypertension. He experienced seizures and an MRI revealed a microbleed with ischemic foci. The patient was switched to a different tyrosine kinase inhibitor and the symptoms resolved (Sharma et al., 2025). No other cases of seizure with bosutinib were identified as of April 2026. Like the rare but serious adverse events discussed above, these side effects call for careful monitoring and observation, and consideration of the full medical history of the patient. The frequency of these rare events in non-CML populations, whether at full dose or reduced doses, is not well understood at this time.

These rare events may not occur in non-CML populations, or at doses below typical CML doses.

Drug interactions:

Bosutinib has at least 585 known drug interactions. Of these interactions, 175 are major, 407 are moderate and 3 are minor (drugs.com). Bosutinib also has 6 disease interactions, including liver disease, renal impairment, fluid retention, and bone marrow suppression (drugs.com). Different doses are recommended for patients with hepatic or renal impairment (Kantarjian et al., 2024).

It is not recommended to use bosutinib concurrently with a strong CYP3A inducer or moderate or strong inhibitor. Proton pump inhibitors may decrease bosutinib levels; patients may opt to switch to short-acting antacids instead of proton pump inhibitors while taking bosutinib (FDA).

Research underway:

There are 11 ongoing clinical trials either testing bosutinib or comparing another drug to bosutinib that are registered on clinicaltrials.gov. All of the trials are in cancer patient populations.

NCT02921477 is an open label phase 1 trial of bosutinib in patients with different dementias. The study intended to enroll approximately 150 patients for a 1-year study of up to 300 mg bosutinib. Interim results have been published by Mahdavi et al., 2021 and Zielinski et al., 2021; the current status of this trial is unknown.

Search terms:

Pubmed, Google: bosutinib

- Off-label, cognitive function, dementia, senescence, ALS, senescence

Websites visited for bosutinib:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

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