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.

Nilotinib

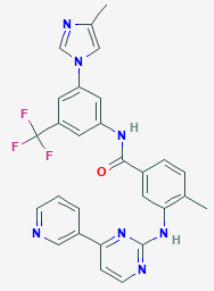
Evidence Summary

Potential neuroprotection via autophagic clearance of disease-associated proteins is limited by low CNS levels at low doses and risks for cardiovascular disease, diabetes, and atherosclerosis at high doses.

Neuroprotective Benefit: It promotes the clearance of neurotoxic proteins via autophagy in preclinical models. Benefits were not apparent in small clinical trials where CNS levels were below the level needed to impact these neuroprotective pathways in models.

Aging and related health concerns: It may increase risks for cardiovascular disease, atherosclerosis, and diabetes in people with pre-existing risk factors. Changes to blood glucose and lipids are reversible and of unclear long-term clinical significance.

Safety: It confers a significant risk for QT prolongation. Primarily associated with myelosuppression, gastrointestinal events, rash, and fatigue. It is unclear whether lower doses also pose significant risks for adverse cardiovascular events in the long-term.

Availability: Rx for chronic myeloid leukemia	**Dose**: 300 or 400 mg 2X daily orally for chronic myeloid leukemia 150 and 300 mg 1X daily orally has been tested for neurodegenerative diseases.	**Chemical formula:** $C_{28}H_{22}F_3N_7O$ **MW**: 529.527 g/mol  Source: PubChem
Half-life: 15-17 hours	**BBB**: Moderately penetrant	
Clinical trials: Over a hundred RCTs conducted in cancer, primarily for chronic myeloid leukemia. A small open-label trial was conducted in Parkinson's (n=12). Phase 2 RCTs were conducted in Parkinson's (n=76; n=75), and Alzheimer's (n=37).	**Observational studies**: Retrospective real-world studies in chronic myeloid leukemia patients show increased risks for vascular occlusive disease, diabetes, and atherosclerosis.	

What is it?

Nilotinib (Tasigna®, AMN-107) is a second-generation **tyrosine kinase inhibitor** approved for Philadelphia chromosome positive chronic myeloid leukemia. It targets multiple kinases, but has high affinity for Abl and discoidan domain receptors. Abl is involved in the regulation of cell growth, motility, survival, and autophagy [1]. Nilotinib has modest blood brain barrier (BBB) penetrance and has been demonstrated to promote the autophagic clearance of a variety of proteins associated with neurodegenerative diseases including alpha-synuclein, tau, amyloid, and TDP-43 [2]. As a result, a group at Georgetown University has spearheaded an effort to repurpose nilotinib for use in neurodegenerative diseases, including Parkinson's disease, Lewy Body Dementia, and Alzheimer's disease.

Neuroprotective Benefit: It promotes the clearance of neurotoxic proteins via autophagy in preclinical models. Benefits were not apparent in small clinical trials where CNS levels were below the level needed to impact these neuroprotective pathways in models.

Types of evidence:

- 1 open-label, non-controlled clinical trial in Parkinson's disease (n=12)
- 2 Phase 2 RCTs in Parkinson's disease (n=76; n=75) + 1 open-label extension (n=63)
- 1 Phase 2 RCT in Alzheimer's disease (n=37)
- Numerous laboratory studies

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

There have not been any observational studies indicating whether cancer patients chronically treated with nilotinib have a higher or lower incidence of dementia relative to patients treated with other therapies.

Case reports indicate that nilotinib has been associated with neurological side effects in rare cases. In one case, a 38-year-old woman taking 300 mg nilotinib 2X/day for chronic myeloid leukemia presented with cognitive deficits, speech difficulties, and dystonia [3]. The cognitive impairment was associated with impaired frontal lobe and executive function. Her symptoms resolved upon discontinuation of nilotinib and returned within a few weeks of restarting nilotinib at a lower dose (150 mg 2X/day). The symptoms resolved after a further dose reduction to 150 mg once per day. The symptoms may have been related to changes in dopamine levels or cerebrovascular dynamics.

Human research to suggest benefits to patients with dementia:

The non-receptor tyrosine kinase Abelson (Abl) is activated under conditions of oxidative stress, and its activation can lead to subsequent mitochondrial dysfunction and cell death [2]. Both total (by 220%) and active phosphorylated forms (by 267%) of Abl have been found to be increased in the striatum of Parkinson's disease patients relative to age-matched controls based on postmortem tissue analysis [4]. Abl can phosphorylate alpha-synuclein and promote its aggregation [5]. The expression of discoidin domain receptors (DDR) have been found to be increased in disease-associated brain regions in patients with Parkinson's disease and Alzheimer's disease [6]. In the hippocampus of postmortem brain tissue from patients with Alzheimer's disease, DDR1, one of the targets of nilotinib, was increased by 41%, and

DDR2 was increased by 67%. In the striatum of postmortem brain tissue from patients with Parkinson's disease, DDR1 expression was increased 23%, and DDR2 was increased by 71%.

Alzheimer's disease: NO CLEAR BENEFIT

Nilotinib was tested in a single-center placebo-controlled Phase 2 RCT (NCT02947893) in patients with mild to moderate Alzheimer's disease (AD) (n=37) for one year [7]. Nilotinib was administered at a dose of 150 mg for 26 weeks, followed by a dose of 300 mg for 26 weeks. The maximum concentrations of nilotinib detected in the cerebrospinal fluid (CSF) at these doses, 3.46 nM at 150 mg and 4.7 nM at 300 mg, are below the IC_{50} for Abl inhibitions, but within the range for DDR1 inhibition. The concentrations reported in this study are slightly higher than those in trials for Parkinson's disease, which may indicate that differences in BBB leakiness may influence the level of nilotinib that gets into the brain, and thus its therapeutic profile in different patient populations. The level of amyloid was significantly reduced at 12 months in the frontal lobes, relative to placebo (median change −0.19, 95% CI, −0.32 to −0.08; p = 0.01). There was also a trend toward a reduction in amyloid in the temporal lobes, and a reduction in the Aβ42/40 ratio, relative to placebo at 12 months. The reduction in p-tau181 was consistent with the effect on amyloid. However, hippocampal volume was significantly lost over the study in both groups. Additionally, both groups showed significant reductions in cognitive performance based on the MMSE, ADAS-Cog, CDR-SoB, and ADCS-ADL. Assessment on the neuropsychiatric Inventory (NPI) and measures of caregiver distress were similar in both groups, with some behavioral disturbances, such as agitation and irritability, showing worsening with nilotinib. The negative impacts on mood and behavior were attributed to a potential impact on the dopamine system. A change in levels of a dopamine metabolite (HVA) and potential beneficial impact on performance on a subscale measure of executive function (maze) on the ADAS-Cog with nilotinib at six months were proposed to be indicators of an impact on the dopamine system, as executive function is influenced by dopamine. This study was not powered for these exploratory clinical outcomes, but overall results from this study suggest that nilotinib may exert small effects on AD biomarkers, but these changes are not accompanied by clinically meaningful benefits. Furthermore, the side effect profile may counteract any potential benefit to cognition by worsening behavioral symptoms. This study suggests that nilotinib is not the optimal autophagy-targeting therapeutic for AD.

Parkinson's disease: NO CLEAR BENEFIT

In a small open-label, non-controlled proof-of-concept study for low dose nilotinib (150 or 300 mg) (n=12) in patients with advanced Parkinson's disease (PD) or Lewy body dementia, [8] nilotinib was found to be brain penetrant, and the levels of phosphorylated Abl were reduced by 30% in the CSF

following treatment [8]. Although levels of free nilotinib were not detectable in the CSF after 4 hours, inhibition of Abl in the CSF was maintained for up to 6 hours. This trial was not powered for clinical outcomes, but found that treatment with 150 or 300 mg nilotinib for 24 weeks led to average improvements on the MMSE of 3.85 and 3.5 points relative to baseline, and an average increase of 1.85 and 2 points on the SCOPA-Cog test.

However, these results were not replicated in two larger placebo-controlled Phase 2 RCTs. Both of these studies were also underpowered for clinical outcomes, but no consistent benefits were seen on exploratory analyses of motor and cognitive outcomes. In a multi-center placebo-controlled Phase 2 RCT (NCT03205488), patients with moderate PD (Hoehn and Yahr stage 2.5-3.0) (n=76) were treated with nilotinib at 150 mg or 300 mg for six months [9]. The CSF/serum level of nilotinib was only 0.2% to 0.3%, and concentrations were below the IC_{50} for Abl inhibition. There were no significant impacts on CSF levels of dopamine or dopamine metabolites, and no significant effects on MDS-UPDRS scores. There were trends toward worsening on MDS-UPDRS-3 scores with nilotinib in patients taking levodopa.

In a single-center Phase 2 RCT (NCT02954978) (n=75), patients with moderate PD, based on Hoehn and Yahr stage 2.5-3.0, were treated with nilotinib at 150 mg or 300mg or placebo for 12 months [10]. Nilotinib was found to be weakly BBB penetrant, and the concentrations detected in the CSF, 0.94 nM with 150 mg and 1.6 nM with 300 mg, are below the IC_{50} for Abl inhibition (20 nM), and there was no evidence of Abl inhibition in these patients following nilotinib treatment. There were no significant differences in total levels of α-synuclein in the CSF with nilotinib relative to placebo, and decreases in oligomeric α-synuclein were not consistent across treatment groups. There was a decrease in phosphorylated tau (p-tau181) in the nilotinib-treated groups. There were no significant differences on MDS-UPDRS measures, indicative of no benefit to motor performance. There was no benefit to cognitive performance based on the MoCA, and possible evidence of worsening in the 300 mg nilotinib group. Dopamine metabolites were found to be altered in the CSF following nilotinib treatment, however, the pattern was not consistent across doses or metabolites.

Next-generation sequencing was performed on the CSF samples to assess changes in miRNA expression. There were no changes with a single dose of nilotinib, but there were changes with year-long nilotinib treatment which were the opposite of those seen in placebo patients, suggesting a potential impact on disease progression-related changes [11]. The affected miRNAs primarily related to genes associated with autophagy and angiogenesis. At the 300 mg dose, DDR1 was impacted (hsa-miR-5195-3p), which is consistent with the concentration of nilotinib in the CSF at this dose (1.6 nM) being within the range of the IC_{50} (1-8 nM) for inhibition of DDR1.

Following the completion of this study, the participants (n=63) went through a three-month washout period and then were re-randomized 1:1 to a 12-month open-label study at doses of 150 mg or 300 mg

nilotinib [12]. There were no significant improvements on motor or cognitive assessments over the 27-month assessment period, however, patients taking 300 mg nilotinib were relatively stable in these measures over time, while those in the 150 mg experienced declines, particularly on motor measures. Although these studies were not powered for clinical outcomes, together these findings suggest that inhibition of DDR1 may help slow mechanisms of disease progression in PD, but due to its impact on multiple kinases, the therapeutic profile of nilotinib at doses that inhibit DDR1 is not optimized for clinical benefit in this population. It is also unclear how the impacts on the other kinases are contributing toward the benefit: harm ratio, which is necessary to determine the optimal combination of kinases to target. It is possible that nilotinib may offer more benefits at earlier stages of disease.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Tyrosine kinase inhibitors, such as nilotinib, have been hypothesized to be beneficial for neurodegenerative diseases by promoting the clearance of aggregation-prone proteins through autophagy. Nilotinib has also been associated with other neuroprotective effects in preclinical models, including the enhancement of synaptic function and reduction of neuroinflammation. Since nilotinib targets multiple tyrosine kinases, its effects may vary depending on the tyrosine kinases expressed under different conditions within a given tissue.

Autophagy

Abl Inhibition: As a tyrosine kinase inhibitor with high potency for Abl, nilotinib has been shown to be protective against the accumulation of alpha-synuclein and other aggregated proteins associated with neurodegeneration in preclinical models [2]**.** Parkin is an E3 ubiquitin ligase which tags proteins with ubiquitin to direct their degradation via autophagy or the proteasome [13]. Auto-ubiquitination of parkin is important for its stability and activity [14], and the ubiquitin specific protease USP13, which removes ubiquitin from parkin, thus deactivating it, was found to be upregulated (>3.5 fold) in the midbrain of PD patients [15]. Parkin promotes the clearance of damaged mitochondria and various neurotoxic proteins, including alpha-synuclein, and mutations in the parkin gene play a causative role in some familial forms of PD [13]. Parkin is also implicated in sporadic forms of PD, as postmortem brain tissue indicates that PD patients have a shift toward decreased levels of active soluble forms and increased levels of inactive insoluble forms of parkin [16].

Parkinson's disease: The tyrosine kinase Abl is known to inhibit parkin E3 ligase activity, and several Abl targeted tyrosine kinase inhibitors have been shown to promote parkin activation and stability.

Preclinical studies indicate that nilotinib can increase the levels of active ubiquitinated parkin and promote its interaction with beclin-1, which facilitates autophagic processes [16; 17; 18]. Nilotinib promotes autophagic flux at the step of transferring cargo for degradation from autophagic vesicles to lysosomes [4; 16; 17; 19]. In rodent models of alpha-synuclein overexpression, nilotinib treatment (10 mg/kg i.p. 3 to 6 weeks) reduced levels of alpha-synuclein and phosphorylated tau by promoting autophagic clearance [4; 17; 20]. Nilotinib was also protective against dopaminergic loss and behavioral deficits in the MPTP model of PD [21; 22], suggesting that the oxidative stress mediated induction of Abl may drive some of the downstream neurological damage in this model. The pro-autophagic effects appear to be largely mediated through parkin, since they are attenuated in parkin knockout animals [17; 18]. Parkin is a target gene of p53, and increased p53 activation has been detected in the brains of PD patients and rodent models [23]. In models, Abl-mediated impairment of autophagy was found to be p53 dependent. In the TgA53T PD model, nilotinib (10 mg/kg) starting at an early stage, reduced p53 activation, increased autophagic flux, and extended the lifespan by delaying disease onset. Nilotinib has also been shown to modulate immune responses in disease models but not in wildtype mice, with different effects on peripheral and central immune compartments [20].

Multiple systems atrophy: In a mouse model of multiple systems atrophy (PLP-SYN), nilotinib (10 mg/kg i.p. for 12 weeks) reduced phosphorylation of α-synuclein at tyrosine 39, a feature also found in postmortem brain tissue of patients with MSA, which was consistent with inhibition of Abl at this dose [24]. However, nilotinib had no impact on α-synuclein aggregation or neurodegeneration, suggesting that this modification does not impact disease progression.

Alzheimer's disease: Nilotinib has been found to be beneficial in preclinical AD models by promoting autophagic protein clearance. In rodent AD models (Tg-APP or hippocampal Aß injection), nilotinib treatment (10 mg/kg i.p. daily for 3 weeks) decreased Abl activation and led to a shift toward more soluble ubiquitinated parkin and less insoluble parkin [16; 18]. This was accompanied by a decrease in levels of soluble and insoluble Aß42 and a reduction in amyloid plaques, and suggests that promoting parkin activation can enhance amyloid clearance. The efficacy of nilotinib may be reduced in the context of low levels of functional tau, as one study found that tau is also important for autophagic flux and acts at a step in the pathway downstream of where nilotinib acts [19]. Nilotinib improved bioenergetics in astrocytes derived from 3xTg AD model mice by influencing mitochondrial dynamics, in an NF-kB-dependent manner [25].

The dysfunction and/or degeneration of dopaminergic neurons may contribute to executive function deficits in AD. In the Tg2576 AD mouse model, treatment with nilotinib (1 mg/kg i.p.) starting at 1.5 months of age prevented changes in dopaminergic neuron excitability typically seen in this model [26]. This may be related to the preservation of autophagy in these neurons. The results from clinical trials suggest that the modulation of dopamine may also occur to a limited degree in patients at the doses tested [7].

Nilotinib has been shown to promote the clearance of tau and TDP-43, and to ameliorate deficits in cellular metabolism and synaptic function by restoring astrocyte function in animals overexpressing these aggregation prone proteins [27; 28]. The effect on TDP-43 is mediated through parkin, since parkin ubiquitinates TDP-43 and promotes its translocation from the nucleus to the cytoplasm [29].

Despite the beneficial effects associated with nilotinib-mediated Abl inhibition in preclinical models, the levels of nilotinib in the CNS in clinically tested doses are below the concentration needed for appreciable Abl inhibition [7; 9; 10], thus these Abl-associated mechanisms are unlikely to be relevant as part of the therapeutic mechanism in patients. Higher doses which may lead to levels of nilotinib that reach the threshold for Abl inhibition would not be a viable therapy due to hematological and cardiovascular effects at those doses. Therefore, any potential benefits of nilotinib in these patient populations would stem from the inhibition of other kinases by this multi-kinase inhibitor. These additional targets may be critical for mediating the *in vivo* neuroprotective effects of nilotinib. In a comparative study including second and third generation Abl targeted tyrosine kinase inhibitors, nilotinib was found to be more effective at clearing Aß and tau than later generation drugs with higher specificity for Abl despite having lower BBB penetrance [6]. This suggests that the inhibition of multiple tyrosine kinases may be necessary for therapeutic benefits. The best candidate is DDR1, which can be inhibited at concentrations of nilotinib tested in clinical trials, and has been associated with autophagy in preclinical models [6].

DDR1 Inhibition: Preferential DDR1 inhibitors, LCB-03-0110 and BK40143 were found to reduce levels of alpha-synuclein in PD transgenic mice (A53T), as well as reduce markers of glial activation, GFAP and Ibal-1, as well as inflammatory cytokines, IL-9, IL-13, and IFNγ [30]. These effects were dependent on DDR1, as they were absent in DDR1 knockout and heterozygous mice, suggesting that partial (50%) inhibition is sufficient for impacts on autophagy. miRNA analysis of CSF from patients treated with nilotinib in clinical trials show changes in the expression of a variety of miRNAs involved in autophagy, which may be related to its effects on DDR1.

Nilotinib may also promote synaptic function via additional mechanisms. Nilotinib was identified in a screen as an inhibitor of the tyrosine kinase EphA4 [31], which is involved in the formation of neural circuits and is dysregulated in AD. In human embryonic stem cell derived neurons expressing the mutation in presenilin associated with AD, nilotinib treatment was able to recover expression of synaptic proteins (Rab3A and SV2B) and restore synaptic function, via an unknown mechanism [32].

APOE4 interactions:
How ApoE status affects the safety and efficacy of nilotinib is not known, but since ApoE4 carriers often have higher baseline levels of cholesterol, they may be at higher risk for nilotinib-induced hyperlipidemia.

Aging and related health concerns: It may increase risks for cardiovascular disease, atherosclerosis, and diabetes in people with pre-existing risk factors. Changes to blood glucose and lipids are reversible and of unclear long-term clinical significance.

Types of evidence:

- 7 meta-analyses of studies for tyrosine kinase inhibitors in chronic myeloid leukemia (n=12 RCTs including 4270 patients; n=29 RCTs and cohort studies including 15,760 patients; n=13 RCTs including 3155 patients; n=10 RCTs including 3043 patients; n=17 RCTs including 7127 patients; n=13 RCTs including 5079 patients; n=7 RCTs including 3425 patients)
- 3 meta-analyses of tyrosine kinase inhibitors on risk for adverse events (n=29 studies, 5533 patients; n=43 studies, 10,769 patients; n=9 studies, 3475 patients)
- 1 meta-analysis of studies testing c-kit inhibitors in melanoma (n=19 studies, 601 patients)
- 1 meta-analysis of studies testing nilotinib in gastrointestinal tumors (n=3 studies, 218 patients)
- 3 clinical studies for blood profile changes with nilotinib treatment (n=27, n=36, n=168)
- 7 Real world observational studies on risk for adverse events (diabetes n=51, n=2004; hyperlipidemia n=1280; cardiovascular disease n= 25, n=63, n=82, n=73)
- Numerous laboratory studies

Cancer

Chronic myeloid leukemia: BENEFIT

Tyrosine kinase inhibitors are the standard of care for patients with Philadelphia chromosome positive chronic myeloid leukemia, and nilotinib is FDA approved for this indication. The Philadelphia chromosome is a translocation between chromosomes 9 and 22 resulting in the formation of the fusion gene BCR-ABL, which forms an oncogenic constitutively active tyrosine kinase (ACS).

Imatinib (Gleevec®) is the first-generation tyrosine kinase inhibitor, while nilotinib, dasatinib, and bosutinib are second generation, and ponatinib and radotinib are the third-generation inhibitors [33]. The newer generation inhibitors have higher potency and/or specificity for Abl than the earlier inhibitors. For example, nilotinib has 20 to 50-fold higher potency and selectivity for Abl relative to imatinib. However, they are all multi-kinase inhibitors, thus the safety and efficacy profile of each drug is related to the particular kinases that they target with highest affinity.

Meta-analyses of clinical studies have found that next generation tyrosine kinase inhibitors, including nilotinib, were more effective for chronic myeloid leukemia in terms of the number of patients who achieved cytogenic and molecular responses, while improvements to overall survival were similar to imatinib [33; 34]. Separate meta-analyses found that nilotinib was associated with the lowest incidence of hematological adverse events, such as anemia, leukopenia, and neutropenia [35], and lower levels of gastrointestinal adverse events, relative to other tyrosine kinase inhibitors [36]. However, other meta-analyses indicate that it is amongst the tyrosine kinase inhibitors with the highest rates of cardiovascular-related adverse events and hepatotoxicity [34; 37; 38]. Nilotinib is typically used as a second-line treatment in patients refractory to imatinib. Despite the superior efficacy of next generation tyrosine kinase inhibitors, imatinib appears to be the safer treatment for patients with comorbidities [34].

Melanoma: POTENTIAL BENEFIT

A meta-analysis of 19 single-arm studies, including 601 patients with unresectable or metastatic mucosal, acral or chronically sun-damaged melanoma, examined the impact of c-Kit inhibitors on objective response rates (ORR) [39]. Nilotinib was associated with the highest objective response rate (ORR 20%; 95% CI 14 to 26%) of the tested inhibitors, which included imatinib, nilotinib, dasatinib, and sunitinib. Though, imatinib had slightly better response rates in the subpopulations of mucosal melanoma (24% vs 18%), and for acral lentiginous melanoma (27% vs 22%).

Gastrointestinal stromal tumors: POTENTIAL BENFIT FOR TUMORS WITH KIT MUTATIONS
A meta-analysis of three studies involving 218 patients found that different genotypes of gastrointestinal stromal tumors were differentially responsive to nilotinib [40]. Tumors with KIT mutations were more responsive relative to those without mutations (Odds Ratio [OR] 3.26, 95% CI 1.14 to 9.28), with KIT exon 11 mutation-containing tumors being the most responsive (OR 5.30, 95% CI 1.79 to 15.68).

Diabetes: INCREASED RISK
In preclinical models, tyrosine kinase inhibitors have been shown to improve glucose levels and reduce insulin resistance [41]. As a result, several tyrosine kinase inhibitors are thought to be suitable for repurposing as anti-diabetic agents. However, nilotinib often exerts the opposite effect, and induces hyperglycemia in a subset of patients [42].

A real-world retrospective study (n=2004) comparing patients treated with nilotinib and dasatinib found that there was a higher incidence of patients developing Type 2 diabetes following treatment with nilotinib (Hazard ratio [HR] 2.77, 95% CI 1.58 to 4.86) [43]. A separate real-world study comparing patients taking nilotinib, imatinib, and dasatinib (n=168) found that nilotinib treated patients has significantly higher levels of fasting glucose, insulin, c-peptide, and insulin resistance, although the rates for developing diabetes or metabolic syndrome were around 30-40% for all treatment groups, and not significantly higher for people taking nilotinib [44]. Nilotinib also reduces endogenous insulin production [45]. Nilotinib associated hyperglycemia is reversible with drug cessation, and it is still unclear whether it is clinically meaningful [43]. The glucometabolic changes are most likely to occur in those already predisposed to developing diabetes. One study developed a predictive genetic risk score (including the genes: IRS1, GRB14, ARL15, PPARG, PEPD, ANKRD55/MAP3K1, PDGFC, LYPLAL1, RSPO3, and FAM13A1) and found that higher genetic risk scores were associated with a higher risk for nilotinib associated diabetes/prediabetes (HR 1.42, 95% CI 1.04 to 1.94) [42].

Cardiovascular disease: INCREASED RISK
Nilotinib is associated with several adverse cardiovascular events in clinical trials and real-world use. These effects are most common in patients that already have preexisting risk factors for cardiovascular disease, suggesting that nilotinib augments these risk factors to push subclinical disease over the threshold to being clinically relevant.

QT prolongation: Nilotinib has a **black box warning for QT prolongation**, which can induce tachycardia, and led to sudden cardiac death in 0.3% of patients in early clinical trials (Tasigna® product insert). Patients with a history of QT prolongation or myocardial infarction were excluded in subsequent trials, but a subset of patients have continued to experience this adverse event.

Hypertension: In a meta-analysis of 29 studies including 5,533 patients with chronic myeloid leukemia, use of nilotinib was associated with an incidence rate for arterial hypertension of 18% [37]. The risk for hypertension with nilotinib was significantly higher than for imatinib (Relative Risk [RR] 2; 95% CI 1.39 to 2.88), though rates and risk for hypertension with nilotinib was less than for the third-generation tyrosine kinase inhibitor, ponatinib. Similarly, in an observational study of 73 patients with chronic myeloid leukemia treated with imatinib, nilotinib, or dasatinib, those treated with nilotinib showed worse blood pressure control [46].

Vascular occlusive events: In a meta-analysis of ten RCTs for chronic myeloid leukemia patients taking tyrosine kinase inhibitors, nilotinib (OR 3.42; 95% CI 2.07 to 5.63), dasatinib, and ponatinib were all found to have higher risk for vascular occlusive events relative to imatinib [47]. A separate meta-analysis of 12 RCTs in the same population found that the effect is driven by an increased risk for arterial occlusive events (nilotinib OR 3.69; 95%CI 2.29 to 5.95), with no significantly increased risk for venous occlusive events [48]. Notably, the **increased risk for arterial events with nilotinib** was consistent across trials, whereas there was more variability for the other drugs, with risk being driven primarily by a small number of trials. In another meta-analysis of both RCTs and cohort studies (n=29), nilotinib was associated with a significantly increased risk for major arterial events (RR 5.3; 95% CI 3.0 to 9.3, $p < 0.001$) and a higher risk for peripheral arterial occlusive disease (RR 5.5; 95% CI 2.6 to 11.8) [49]. The incidence for peripheral arterial occlusive disease in patients with chronic myeloid leukemia is 0.3 per 100 patient-years (95% CI 0.2 to 0.4; $I^2 = 73.2\%$), which is increased to a rate of 1.3 per 100 patient-years (95% CI 0.8 to 1.8; $I^2 = 73.2\%$) for nilotinib treated patients.

The risk for vascular events appears to be highest in the subset of patients already at high risk for cardiovascular disease. A real-world analysis of the French Pharmacovigilance Database found that the majority of cases of peripheral arterial occlusive disease occurred in people over the age of 60 (84%) and in people with two or more preexisting cardiovascular risk factors (88%) [50]. While the presence of pre-existing risk factors increases the risk for a nilotinib-related adverse cardiovascular event, there are reports of cardiovascular events in individuals without these risk factors. In a case report, a 55-year-old

man treated with nilotinib for chronic myeloid leukemia, developed accelerated atheromatous cerebrovascular disease with severe left middle cerebral artery stenosis [51].

Atherosclerosis: Nilotinib has been found to alter the plasma lipid profile in chronic myeloid leukemia patients in a manner that promotes atherosclerosis. There are ongoing lawsuits filed against Novartis regarding the link between use of nilotinib (Tasigna®) and the development of atherosclerotic related adverse events (drugwatch.com). The product label was updated to include a warning for atherosclerosis in Canada, but not in the US.
A real-world retrospective study (n=1280) found that relative to dasatinib, nilotinib is associated with a higher incidence of hyperlipidemia (HR 1.75; 95% CI 1.07 to 2.87) [43], and patients taking nilotinib were also found to have higher levels of total cholesterol and LDL-c in a separate comparative study [44]. In a small prospective study (n=27), nilotinib treatment significantly increased total cholesterol (from 1.80 g/L ± 0.38 to 2.24 g/L ± 0.47, P<0.0001), LDL-c (from 1.13 g/L ± 0.30 to 1.46 g/L ± 0.38, P<0.0001), and HDL-c (from 0.44 g/L ± 0.1 to 0.58 g/L ± 0.18, P<0.0001) within the first 3 months [52]. The proportion of patients with low levels of HDL-c (<0.4 g/L) decreased from 40.7% to 7.4% within 12 months. Although higher levels of HDL-c are generally associated with lower risk for cardiovascular disease, any potential benefits appear to be outweighed by the concomitant increase in LDL-c. The proportion of patients with non-optimal LDL-c increased from 48.1% to 88.9%, and 22.2% of patients had to initiate a cholesterol-lowering drug intervention during this period.

Patients with preexisting risk factors for cardiovascular disease are the ones most likely to develop atherosclerosis in response to nilotinib treatment. A retrospective real-world study found that the Systematic coronary risk evaluation (SCORE) chart, which was developed by the European school of cardiology, can be used to stratify patients according to atherosclerotic risk [53]. In their small study (n=82), none of the low risk stratified patients had atherosclerotic events, while 29% of the high-risk patients did.

Patients treated with nilotinib show a higher proinflammatory state, relative to those treated with the other tyrosine kinase inhibitors. This proinflammatory, pro-oxidative state may be related to the increase in LDL-c [46]. In a preclinical study, nilotinib was found to upregulate pro-atherosclerotic adhesion proteins (ICAM-1, E-selection, VCAM-1) on human endothelial cells, and suppress their proliferation and migration [54]. These effects stemmed from the inhibition of a set of kinases that are relevant to angiogenesis and atherosclerosis (TEK, ABL-2, JAK1, MAPK). Furthermore, nilotinib promoted

liquid plaque accumulation in the aortic wall of high fat diet fed mice. This work provides mechanistic support for the ability of nilotinib to promote atherosclerosis in patients.

Bone loss: POTENTIAL HARM (Preclinical)
In vitro studies have found that nilotinib impairs bone metabolism in cell culture. In the human osteoblastic cell line SaOS-2, nilotinib inhibited bone mineralization and osteoblast differentiation, while promoting an environment conducive to bone-reabsorbing osteoclasts [55]. Nilotinib was also found to have anti-myogenic effects in a skeletal myoblast cell line, C2C12 [56]. It is unclear whether these negative impacts on the skeletal system also occur *in vivo*.

Safety: It confers a significant risk for QT prolongation. Primarily associated with myelosuppression, gastrointestinal events, rash, and fatigue. It is unclear whether lower doses also pose significant risks for adverse cardiovascular events in the long-term.

Types of evidence:

- 7 meta-analyses of studies for tyrosine kinase inhibitors in chronic myeloid leukemia (n=12 RCTs including 4270 patients; n=29 RCTs and cohort studies including 15,760 patients; n=13 RCTs including 3155 patients; n=10 RCTs including 3043 patients; n=17 RCTs including 7127 patients; n=13 RCTs including 5079 patients; n=7 RCTs including 3425 patients)
- 3 meta-analyses of tyrosine kinase inhibitors on risk for adverse events (n=29 studies, 5533 patients; n=43 studies, 10,769 patients; n=9 studies, 3475 patients)
- 1 clinical trial for dose reduction of tyrosine kinase inhibitors in chronic myeloid leukemia patients (n=174)
- 2 Systematic reviews for tyrosine kinase inhibitors (Cardiovascular toxicities, Safety and efficacy in elderly patients)
- 7 clinical studies for non-cancer indications (Parkinson's disease n=12, n=75, n=76; Alzheimer's disease n=37; chronic cerebellar ataxia n=12; systemic sclerosis n=10; spondylarthritis n=28)
- Retrospective of RCTs with tyrosine kinase inhibitors for acute kidney disease (n=468 patients)
- 7 Real world observational studies on risk for adverse events (diabetes n=51, n=2004; hyperlipidemia n=1280; cardiovascular disease n= 25, n=63, n=82, n=73)
- Numerous laboratory studies

The majority of safety information related to nilotinib treatment comes from patients with chronic myeloid leukemia. Nilotinib contains a black box warning for QT prolongation and patients are supposed to undergo ECG monitoring prior to starting treatment, 7 days after initiation, and then periodically throughout the treatment period [57]. It is **contraindicated in anyone with hypokalemia, hypomagnesemia, or long QT syndrome** (Tasigna product insert). It also has a warning for myelosuppression including neutropenia, thrombocytopenia, and anemia. The most common non-hematological side effects are skin rash, pruritus, headache, nausea, and fatigue.

Nilotinib is also associated with **increased risks for arterial occlusive disease, atherosclerosis, and diabetes**, especially in patients who are already at high risk for developing these conditions [43; 48; 54]. Various screening tools have been developed to stratify patients according to baseline risk factors [42; 50; 53]. However, one study found that the risk for developing cardiovascular adverse events may increase with treatment duration [54], and/or that clinical trials may have underestimated the drug-associated incidence of cardiovascular toxicities since these kinds of events can be delayed for years after starting treatment [58]. In chronic myeloid leukemia patients, the safety and efficacy of nilotinib does not appear to significantly differ in elderly patients (>65 years old) relative to younger patients [59].

Nilotinib is generally well-tolerated in chronic myeloid leukemia patients, and has a relatively favorable safety profile in comparison to other tyrosine kinase inhibitors used in this population [33]. Each tyrosine kinase inhibitor has a distinct toxicity profile based on its specificity for different classes of tyrosine kinases. Imatinib is considered the safest, but is also least efficacious and is not BBB penetrant [33], and is associated with a higher incidence of acute kidney injury [60]. Ponatinib has a black box warning for heart failure and is associated with a high risk for hypertension [57]. Dasatinib has the highest risk for pulmonary toxicities, and increases risk for bleeding, heart failure, and acute kidney injury [57; 60].
Bosutinib also has a favorable safety profile with the primary adverse events being gastrointestinal and myelosuppression [61]. Notably, bosutinib was found to be similar or superior to nilotinib in promoting autophagic clearance in several animal models of neurodegenerative disease [6; 17; 18; 20; 27; 28; 29; 62].

There have been a few clinical trials performed in non-cancer patient populations, including systemic sclerosis, spondylarthritis, and an analysis of off-label use for chronic cerebellar ataxia at standard doses (600 to 800 mg) [63; 64; 65]. The adverse events were largely similar to those seen in clinical trials for

chronic myeloid leukemia, including the risk for QT prolongation. In most cases adverse events were mild or transient, and could be mitigated through dose reduction.

The long-term safety profile for nilotinib when used at lower doses (150 to 300 mg) has not been well-established. In the DESTINY trial, chronic myeloid leukemia patients transitioned from standard to half-dose (200 mg 2X daily) for 12 months [66]. In these patients, adverse events including gastrointestinal events, rash, and fatigue improved within the first 3 months, however 21% of patients also developed new grade 1 or 2 musculoskeletal symptoms during the study. In the non-controlled trial in patients with Parkinson's disease (n=12), one patient withdrew from the trial due to myocardial infarct and 2 patients experienced transient QT prolongation [8]. Other adverse events included gastrointestinal events, mild infections, headache, skin irritation, and transient liver enzyme elevations. This suggests that lower doses of nilotinib are associated with the same types of adverse events as standard doses, but that the severity may be reduced. It is not yet clear whether the lower doses also lead to metabolic changes that increase the risk for diabetes and hyperlipidemia.

Doses of 150 to 300 mg of nilotinib were generally well-tolerated in RCTs ranging from six to 12 months. In a one-year Phase 2 RCT in patients with moderate PD, there were more serious adverse events in patients treated with nilotinib relative to placebo (150 mg: 6 [24%]; 300 mg: 12 [48%]) vs placebo 4 [16%]) [10]. Transient elevations of pancreatic enzymes were also seen with nilotinib at these doses. Common adverse events were musculoskeletal, respiratory, skin disorders, and gastrointestinal-related. In patients continuing treatment during an open-label phase and followed for a total of 27 months, common adverse events were skin lesions (24%–30%) attributed to local infections or healing wounds and upper respiratory tract infections with nilotinib [12]. Severe adverse events leading to discontinuation were renal failure and non–ST-segment elevation myocardial infarction (NSTEMI). In a six-month Phase 2 RCT in patients with moderate PD, there were more adverse event-related withdrawals with nilotinib, primarily involving elevations of amylase or lipase [9].
In a one-year Phase 2 RCT in patients with mild to moderate AD, nilotinib was associated with more adverse events than placebo, with the majority of nilotinib-treated patients experiencing mood swings (70.6%), including agitation and irritability, particularly at the 300 mg dose [7]. Common adverse events included headache, gastrointestinal, skin, and respiratory disorders.
The lack of QT prolongation and major adverse cardiovascular events in these studies was taken to be evidence of lower degrees of cardiovascular impairments at these lower doses, relative to those used for cancer. However, commentaries on these studies have noted that in chronic myeloid leukemia, there is a dose and duration-dependent relationship between nilotinib treatment and adverse cardiovascular

effects [67]. Adverse cardiovascular events were rare within the time frame of a 12-month trial, but incidences (7.5% at 600 mg/day and 13.4% at 800 mg/day) increase. This suggests that due to the chronic nature of the dosing that would be needed for neurodegenerative diseases, these lower doses may still pose a significant risk for adverse cardiovascular outcomes. Additionally, due to stringent trial inclusion criteria, individuals with cardiovascular risk factors were excluded from these studies, and the overall PD and AD patients' populations, which are enriched for elderly individuals are likely to have higher levels of these risk factors, and thus would be at higher risk for nilotinib-related adverse cardiovascular effects.

According to Drugs.com, there are 257 major drug interactions with nilotinib, and one major food interaction with grapefruit. Nilotinib is an inhibitor of the cytochrome P450 enzyme CYP3A4, and has interactions with other drugs that are inhibitors or inducers of this enzyme. Nilotinib also has disease interactions with QT prolongation, pancreatitis, cardiovascular disease, fluid retention, bone marrow suppression, electrolyte abnormalities, hepatic impairment, and lactose intolerance.

Sources and dosing:

Nilotinib is marketed under the trade name Tasigna® by Novartis Pharmaceutical. It is available in 150 mg or 200 mg oral capsules. The standard dosage for patients with chronic myeloid leukemia is 300 mg or 400 mg 2X daily with doses taken 12 hours apart, but adjustments down to half the standard dose (200 mg 2X daily) can be used to mitigate adverse events. It is necessary to fast two hours before and one hour after taking each dose of nilotinib, and high fat foods have a significant effect (increase) on drug bioavailability [33]. However, a small clinical study suggests that the pharmacokinetics are similar between 300 mg BID fasted and 200 mg BID with a meal, and that taking it with a meal may increase compliance and lower symptom burden [68].

The optimal dose for efficacy in neurodegenerative diseases has not been established. Doses of 150 mg and 300 mg once per day were insufficient to inhibit Abl or offer clinically meaningful benefits in tested populations [7; 9; 10]. The higher dose (300 mg) may impact DDR1, but is also associated with more side effects.

Research underway:

According to Clinicaltrials.gov there are currently 63 active clinical trials for nilotinib. The vast majority are for patients with chronic myeloid leukemia or other types of cancer. There are a couple of trials for neurodegenerative diseases.

A Phase 3 trial is testing nilotinib (bioequivalent) at doses of 84 mg and 112 mg for 18 months. The estimated enrollment is 1275 patients with early Alzheimer's disease, and the estimated study completion date is in 2026 (NCT05143528).

A Phase 2 trial is testing nilotinib at a dose of 200 mg for six months in Dementia with Lewy bodies patients. This is the same group that did the studies in AD and PD, and similarly will focus on safety along with a variety of exploratory outcomes (NCT04002674).

Search terms:

Pubmed, Google: Nilotinib +

- Alzheimer's disease, Parkinson's disease, neurodegeneration, autophagy, cancer, aging, cardiovascular, diabetes, safety, clinical trials, meta-analysis

Websites visited for Nilotinib:

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

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