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.

Lonafarnib

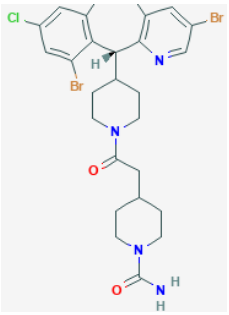
Evidence Summary

Can promote autophagy through mTOR inhibition via Ras family inhibition. Has pleiotropic effects by modulating numerous proteins, which compromises its efficacy as a therapeutic for specific diseases.

Neuroprotective Benefit: May stimulate autophagy to prevent accumulation of tau and other protein aggregates and reduce cognitive decline, but preclinical evidence suggests it is only effective prior to onset of pathology.

Aging and related health concerns: Can act as a mTOR inhibitor to promote autophagy. Minimal benefits in cancer, even in combination. May help protect liver in context of chronic hepatitis D infection.

Safety: Associated with gastrointestinal side effects including diarrhea, nausea, and vomiting in clinical trials, which can be grade 3/4 at doses above 200 mg BID. Intermittent dosing may be beneficial. Off-target effects may be unavoidable.

Availability: Clinical trials and research use	**Dose**: Orally administered In clinical trials: 200 mg DIB Max tolerated dose 150 mg/m^2 BID for Progeria 50-100 mg BID for Hepatitis D	**Chemical formula:** $C_{27}H_{31}Br_2ClN_4O_2$ **MW**: 638.8 g/mol  Source: PubChem
Half-life: Range 4-11 hours in plasma, dose dependent. Drug accumulates with repeated dosing.	**BBB**: Penetrant	
Clinical trials: Open-label Phase 1 and 2 trials for cancer (n range=12 to 105), Open-label Phase 2 for Progeria (n=27, 36), Phase 2 RCT or Open-label for Hepatitis D (n range=14 to 58)	**Observational studies**: None	

What is it?

Lonafarnib (SCH66336, Sarasar®) is a non-peptidomimetic **farnesyltransferase inhibitor** developed by Merck. Farnesylation, a type of prenylation, is a post-translational modification in which the isoprenoid farnesyl pyrophosphate is covalently modified to cysteine residues on proteins that contain the CAAX motif [1]. This post-translational modification is involved in the regulation of many proteins, but has been best studied in the context of the Ras/Rho/Rac superfamily of small G-proteins. Since protein prenylation is important for the activation of Ras family proteins, protein prenylation can serve as inhibitors to these signaling proteins, which play important roles in cellular growth and function.

Due to the prevalence of oncogenic Ras mutations in cancer, farnesyltransferase inhibitors were originally developed for this indication, but were found to be largely ineffective due to compensation by alternative prenylation pathways. Lonafarnib has also been successfully tested in Phase 2 trials for progeria and hepatitis D infection, as farnesylated proteins play key roles in the pathogenesis of these diseases. Lonafarnib has been licensed to Eiger BioPharmaceuticals for development in these indications. The farnesyltransferase inhibitor LNK-754 from the former Link Medicine, was tested in Alzheimer's disease, but development was subsequently discontinued.

Neuroprotective Benefit: May stimulate autophagy to prevent accumulation of tau and other protein aggregates and reduce cognitive decline, but preclinical evidence suggests it is only effective prior to onset of pathology.

Types of evidence:

- 2 studies for levels of isoprenoids in AD brain
- 1 laboratory study for lonafarnib, additional studies for other prenylation inhibitors

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia: None

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

Alzheimer's disease: Potential benefit at very early stages (preclinical)

Protein prenylation is hypothesized to contribute to the pathophysiology of AD [2]. The isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate become covalently attached to the cysteine residue of target proteins through the activities of farnesyl transferase and geranylgeranyl transferase, respectively.

The levels of these **isoprenoids have been shown to be elevated in the brains of male AD patients** (n=13), which may lead to increased levels of protein prenylation [3]. A separate study found that the expression of the enzymes involved in the synthesis of farnesyl pyrophosphate and geranylgeranyl pyrophosphate was elevated in the frontal cortex of AD patients (n=96) relative to controls (n=55), and that the expression of these synthetases was correlated with levels of p-tau and neurofibrillary tangle density [4]. Higher expression of the isoprenoid synthetases was also associated with an earlier age of disease onset. The strength of these correlations was slightly higher for farnesyl pyrophosphate synthetase.

Since these isoprenoids are cholesterol biosynthetic intermediates, their levels are reduced by statins. The statin-mediated reduction of isoprenoids has been shown to reduce Aβ production by promoting non-amyloidogenic APP processing [5]. However, statins are not ideal for mitigating prenylation-associated AD pathology. While suggestive, a change in isoprenoid levels does not necessarily indicate a corresponding change in the level of protein prenylation, especially for farnesylation. Statins may have a

greater effect on levels of geranylgeranylation than on farnesylation, but preclinical evidence suggests that farnesylation plays a greater role in cognitive decline [2].

In the APP/PS1 mouse model, genetic reduction (haploinsufficiency) of farnesyltransferase, but not geranylgeranyl transferase, was able to rescue spatial memory deficits in the Morris water maze [2]. This is consistent with the finding that inhibition of farnesyltransferase was able to enhance synaptic plasticity in hippocampal slices [6].

The farnesyltransferase inhibitor LNK-754 was tested in Phase 1 RCTs in healthy elderly and patients with mild AD (NCT00903253, NCT01013610). Following the AD trial, the Link Medicine program was licensed to AstraZeneca (Press Release), and development was discontinued. Based on a preclinical tauopathy model [7], targeting mild cognitive impairment (MCI), or at a stage prior to the onset of prominent tau pathology, may be necessary for farnesyltransferase inhibitors to exert clinical benefit.

Frontotemporal Dementia: Potential benefit prior to tau pathology onset (preclinical)

Lonafarnib was found to prevent pathological tau accumulation by promoting tau degradation in preclinical FTD models, however, the treatment was only effective when administered prior to the emergence of tau pathology.

Chronic intermittent treatment of the rTg4510 model with lonafarnib (80 mg/kg 5 days on/5 days off via gavage) starting before the onset of pathology reduced the development of neurofibrillary tangles, reactive gliosis, and brain atrophy [7]. Treatment also restored nest building behavior, but did not rescue the deficit in marble burying behavior in this model. In cell culture, lonafarnib was found to stimulate autophagy and facilitate degradation in the endosomal-lysosomal compartment. Although lonafarnib mediated inhibition of farnesyltransferase affects the farnesylation of a variety of proteins, the authors attribute the beneficial **effects on tau reduction to the inhibition of the small Ras family G-protein, Rhes**. Rhes is able to oppositely regulate autophagy via mTOR dependent and mTOR independent mechanisms, thus the effect of Rhes modulation depends on the cellular environment.

If farnesyltransferase inhibitors are **only therapeutically beneficial when administered prior to the onset of pathology**, it is unclear whether they would be useful as disease modifying agents for FTD patients with established disease. If clinical benefit is mitigated at later stages due to changes in the prenylation of other proteins, then a more Rhes selective therapy may be a more promising option.

Amyotrophic lateral sclerosis: Unlikely to benefit unless used in combination with a geranylgeranyl transferase inhibitor (preclinical)

Protein prenylation inhibitors emerged as potent axon outgrowth stimulators in a small molecule screen [8]. The combination of a farnesyltransferase inhibitor and a geranylgeranyl transferase inhibitor improved axon outgrowth in a mouse optic nerve crush model, and in iPS-derived motor neurons from ALS patients. Expression of geranylgeranyl transferase (PGGT1B) was found to be 6-fold higher in postmortem tissue from early onset ALS patients relative to late onset ALS (n=12), suggesting that this mechanism regulates axon regeneration and modulates disease progression in patients. Notably, enhanced axon outgrowth was only seen when both farnesyltransferase and geranylgeranyl transferase were inhibited, suggesting that the proteins mediating this effect are subject to both forms of prenylation, and the use of a farnesyltransferase inhibitor alone is unlikely to benefit patients.

APOE4 interactions: Unknown

Aging and related health concerns: Can act as a mTOR inhibitor to promote autophagy. Minimal benefits in cancer, even in combination. May help protect liver in context of chronic hepatitis D infection.

Types of evidence:

- 27 clinical trials (2 Phase 2 for Progeria, 5 Phase 2 for HDV, 12 Phase 1 and 8 Phase 2 in Cancer)
- Several laboratory studies

Cancer: No benefit as monotherapy, potential minor benefit in combination

Farnesyltransferase inhibitors were originally developed for cancer for their ability to modulate G-proteins in the Ras/Rho/Rac superfamily. Of the thirty-nine clinical trials registered for lonafarnib on Clinicaltrials.gov, twenty-six have been for cancer indications. Mutant Ras proteins are found in approximately 25% of all human cancers, and represents a major therapeutic target [9]. Farnesylation plays a role in the activation of Ras proteins, and facilitates oncogenic cell signaling. However, **farnesyltransferase inhibition has primarily been ineffective as a therapeutic strategy for cancer** [10]. Part of the resistance stems for the alternative prenylation, via geranylgeranyl transferase, of both N-Ras and K-Ras [1]. Therefore, it can only inhibit Ras-related tumor growth driven by mutant H-Ras. Additionally, clinical response does not necessarily track with Ras mutation status or the level of

farnesyltransferase inhibition [10]. Predictive markers of responders are needed for lonafarnib to become a viable therapy for cancer.

Lonafarnib has failed as a monotherapy, however, it **may help overcome chemoresistance in some cancers** [10]. Lonafarnib showed signs of improving 6-month progression free survival when combined with temozolomide in refractory glioblastoma patients [11]. Lonafarnib was also able to show partial responses and/or disease stabilization when combined with paclitaxel in taxane-refractory metastatic nonsmall cell lung carcinoma [12; 13]; with gemcitabine in advanced urothelial tract cancers [14]; with trastuzumab and paclitaxel in Her2/neu+ breast cancer [15]; and with imatinib in resistant chronic myeloid leukemia [16]. However, these trials were all small, and not appropriately powered for patient outcomes, so larger trials would be needed to determine if any of these combinations offer significant clinical benefit. Meanwhile, the addition of lonafarnib to paclitaxel and carboplatin [17], or cisplatin and gemcitabine [18] led to significant dose limiting toxicities and worse outcomes.

Atherosclerosis: Potential benefit (preclinical)

Farnesyltransferase inhibitors have been shown to protect against atherosclerosis in a mouse model [19]. A cell culture study indicates that the protective effect may stem from the inhibition of plaque neovascularization [20]. Lonafarnib was shown to inhibit the mobilization of vascular endothelial cells by disrupting the maintenance of cell polarity. While protective in the context of pathogenic neovascularization, these mechanisms are also important for wound healing, thus benefits may be context dependent.

Progeria: Benefit

Hutchinson-Gilford progeria syndrome is a disease involving a mutation in the laminin A gene, which disrupts nuclear architecture, and leads to accelerated aging. The mutant truncated form of laminin A known as progerin is farnesylated, which prevents its cleavage from the nuclear membrane.

Treatment with lonafarnib (150 mg/m^2 BID) has been shown to **extend mean survival in children with progeria** in clinical trials by 1.6 years [21]. Mortality was lowered from 27% (17/63) in untreated, relative to 6.3% (4/63) in lonafarnib treated patients in clinical trials [22]. Lonafarnib was associated with decreased frequency of neurological symptoms, including seizures, headaches, and strokes [23]. Treatment also reduced arterial stiffness, as measured by pulse wave velocity and echodensity, and improved mineral bone density, but had no effect on insulin resistance [24].

The slowing of these aging related phenotypes likely involves a combination of **restoring laminin homeostasis and the activation of autophagy** [25]. Farnesyltransferase inhibitors, such as lonafarnib, can promote autophagy by inhibiting mTOR signaling. The small G-protein Rheb is farnesylated, and this activated form of Rheb positively regulates mTOR [26]. Since Rheb is not subject to alternative prenylation via geranylgeranylation, farnesyltransferase inhibitors can completely block this activation process.

Since the prenylation of a large number of proteins is affected by farnesyltransferase inhibitors, some of the effects may counteract each other, thus these drugs may not necessarily ameliorate age-related phenotypes in all contexts.

Hepatitis D: Potential Benefit

Prenylation is an essential step in the lifecycle of the hepatitis D virus (HDV), thus inhibiting viral prenylation can reduce viral propagation [27]. HDV only propagates in people co-infected with hepatitis B [28].

Lonafarnib has been tested in five Phase 2a clinical trials for hepatitis D (Clinicaltrials.gov), and has **shown potential for reducing viral activity**. The serum levels of lonafarnib were found to be correlated with the decline in serum HDV RNA (r^2=0.78), with levels returning to baseline following the cessation of treatment [29]. Pharmacokinetic modeling indicated that as a monotherapy, lonafarnib would need to be administered at a dose of 610 mg BID to reduce viral levels by 99%, which is beyond the maximum tolerated dose [30]. However, **co-administration with the protease inhibitor ritonavir boosts systemic exposure of lonafarnib** by 4 to 5-fold, such that 99% viral inhibition can be achieved at clinically tolerable doses (50-100 mg) [31]. Ritonavir inhibits cytochrome P450 (3A4 isoform), thereby boosting lonafarnib serum levels by inhibiting its metabolism. The combination of lower dose lonafarnib with pegylated interferon has also been shown to be more effective at viral load reduction than lonafarnib alone [31; 32]. Due to viral interference, declines in HDV led to the re-emergence of HBV in some patients, thus it may be necessary to compliment treatment with nucleoside analog therapy. Phase 2b (NCT02968641) and Phase 3 (NCT03719313) trials testing lonafarnib and ritonavir with or without pegylated interferon are currently recruiting.

Safety: Associated with gastrointestinal side effects including diarrhea, nausea, and vomiting in clinical trials, which can be grade 3/4 at doses above 200 mg BID. Intermittent dosing may be beneficial. Off-target effects may be unavoidable.

Types of evidence:

- 27 clinical trials (2 Phase 2 for Progeria, 5 Phase 2 for HDV, 12 Phase 1 and 8 Phase 2 in Cancer)
- Several laboratory studies

Lonafarnib has been tested in over 30 Phase 1 and Phase 2 clinical trials for cancer, hepatitis D infection, and progeria. The side effect profile has been consistent across indications, and successfully used in combination. The **major side effects are primarily gastrointestinal, and include nausea, diarrhea, abdominal pain, vomiting, anorexia, weight loss, fatigue, and headaches** [10].

As a monotherapy in cancer, there were grade 3 and 4 gastrointestinal and hematological toxicities and fatigue at doses of 300 or 400 mg BID, as well as evidence of neurocortical toxicities in some patients [33; 34]. The maximum tolerated dose in most studies was established at 200 mg BID as a monotherapy, and between 100 and 150 mg BID in dual combination therapies [10]. Lonafarnib was better tolerated when administered with intermittent dosing (2 weeks on, 2 weeks off) [35]. At these doses, toxicities were typically grade 1 to 3, and lonafarnib was generally well-tolerated when combined with therapies to manage gastrointestinal symptoms [10]. The combination of lonafarnib with cisplatin and gemcitabine led to severe toxicities in 91% of patients, with dose-limiting toxicities present even at the lowest doses tested [18]. The triple combination of lonafarnib with carboplatin and paclitaxel also increased grade 3 and 4 non-hematological toxicities leading to dose reductions that rendered the chemotherapies ineffective [17]. This suggests that while lonafarnib can be safely combined with a single chemotherapeutic to overcome resistance, its combination with multiple chemotherapeutics can exacerbate adverse events to levels that require significant dose reductions, thereby negating any potential benefit of its inclusion.

In children with progeria, 150 mg/m^2 BID was well tolerated. The most common adverse events were mild gastrointestinal events, but there were no discontinuations due to side effects [24].

In patients with chronic hepatitis D infections, doses of 200 or 300 BID were associated with grade 2 gastrointestinal events, but the combination of 50 to 100 mg BID with 100 mg BID ritonavir was well tolerated with only mild grade 1 gastrointestinal events [29; 31].

Since farnesyltransferase inhibitors will invariably also target proteins and pathways other than the one desired for therapeutic benefit, side effects are unavoidable with this approach. The benefit to side effect ratio would be expected to vary for different conditions depending on the balance of proteins subject to farnesylation and the cellular signaling environment. Drugs that specifically target the farnesylated proteins of interest are likely to have a cleaner therapeutic profile.

Sources and dosing:

Lonafarnib was developed by Merck, but has been licensed to Eiger BioPharmaceuticals for development in hepatitis D infection and progeria. It is available to the research community through Merck and Eiger through a license agreement. LNK-754, and the other farnesyltransferase inhibitors in the Link Medicine portfolio were acquired by AstraZeneca in 2012, and their clinical development was subsequently discontinued. In clinical trials, 200 mg BID was most often considered the maximum tolerated dose for orally administered lonafarnib, and tolerability was improved by intermittent dosing (2 weeks on/2 weeks off). In progeria, children were dosed at 150 mg/m^2 BID. In chronic hepatitis D infection, 50 mg BID lonafarnib plus 100 mg BID ritonavir was considered the dose with the best therapeutic profile in Phase 2 trials, and is currently being tested in the Phase 3 D-LIVR trial at this dose.

Research underway:

Lonafarnib is has received Orphan Breakthrough Therapy designation from the FDA for progeria and is currently being tested in a Phase 1/2 trial in combination with the mTOR inhibitor everolimus (NCT02579044).

Lonafarnib is also being tested in a Phase 2a open-label trial with ritonavir and pegylated interferon therapy (NCT03600714), a Phase 2b trial with ritonavir (NCT02968641), and a Phase 3 trial with ritonavir and/or pegylated interferon (NCT03719313) .

Clinical development of lonafarnib for neurodegenerative diseases or other diseases is unlikely to be a priority until it has been approved for one or both of these indications.

Search terms:

Pubmed, Google: Lonafarnib, LNK-754, farnesyltransferase inhibitor

- Alzheimer's diesase, neurodegeneration, aging, cancer, cardiovascular, mTOR, autophagy, clinical trials, safety

Websites visited for Lonafarnib:

- Clinicaltrials.gov: Lonafarnib, LNK-754
- Drugs.com (Progeria related)
- PubChem: Lonafarnib, LNK-754
- DrugBank.ca: Lonafarnib, LNK-754
- Cafepharma (Progeria related)

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