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.

Pepinemab (VX15/2503)

Evidence Summary

Preliminary results indicate blocking Sema4D may have some efficacy in certain stages of neurodegenerative disease and have a role in other health conditions including cancer treatment.

Neuroprotective Benefit: Preclinical work indicates blocking Sema4D may reduce neuroinflammation, BBB deficits, and brain atrophy. Initial clinical trials showed some cognitive benefit in certain patient populations.

Aging and related health concerns: Very early trials hint at potential benefit of pepinemab in cancer treatment, and preclinical work demonstrates rationale for testing pepinemab for other indications.

Safety: Preliminary results from trials indicate that headache, nausea, vomiting, and potentially pain and/or fatigue are possible side effects of pepinemab. Further work is needed to assess immunogenicity and the potential consequences of anti-drug reactions.

Availability: in clinical development.	**Dose**: Doses of up to 20 mg/kg have been used in prior trials; doses of 40 mg/kg are currently being tested in patients with mild AD.	**MW:** Pepinemab is a 145.5 kD humanized monoclonal anti-SEMA4D antibody.
Half-life: Varies by dose. 1 mg/kg dose exhibited a half-life of 3.7 days; 20 mg/kg dose exhibited a half-life of 20 days.	**BBB**: Penetrant.	
Clinical trials: Pepinemab has been tested in several clinical trials, the largest of which enrolled 301 patients.	**Observational studies**: There are no observational studies of pepinemab.	

What is it?

Semaphorin-4D (Sema4D), also known as CD100, is a member of the semaphorin family. This transmembrane protein, also called cellular Sema4D, can also be cleaved into a soluble Sema4D. Both forms of Sema4D have three known receptors: Plexin-B1, Plexin-B2, and CD72. Sema4D and its receptors are expressed on a variety of cell types, including neurons, glia, endothelial cells, and various immune cells, though plexins are often associated with non-immune tissue whereas CD72 is often associated with immune cells, particularly those in the adaptive immune system (reviewed in Kuklina 2019; Rajabinejad et al., 2020). While Sema4D is often studied for its role as a ligand, it can also act as a receptor, including as a co-receptor (Fisher et al., 2016; Kuklina 2019).

Sema4D is involved in a variety of cell signaling pathways and ultimately plays a role in an array of cellular processes, including axonal guidance, synapse formation, angiogenesis, cell migration, bone formation, and immune system development and modulation. The diversity of cell types expressing Sema4D and cellular processes involving Sema4D result in a wide range of health conditions that may involve Sema4D, ranging from cancer progression, atherosclerotic plaque formation, autoimmune conditions, osteoporosis, and neurodegenerative diseases (Vogler et al., 2022).

Pepinemab, also known as VX15/2503, is an antibody that blocks the interaction of Sema4D with its receptors. It is being developed by Vaccinex and has been tested in trials for certain cancers, multiple sclerosis (MS), and Huntington's disease, and is currently in trials for Alzheimer's disease as well as other cancer subtypes (Vaccinex Pipeline).

Neuroprotective Benefit: Preclinical work indicates blocking Sema4D may reduce neuroinflammation, BBB deficits, and brain atrophy. Initial clinical trials showed some cognitive benefit in certain patient populations.

Types of evidence:

- 2 randomized controlled clinical trials
- 1 commentary article on an RCT
- 2 reviews
- Numerous laboratory studies

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

Pepinemab treatment has not been thoroughly explored as a prevention strategy of dementia, decline, or for any cognitive enhancing activity in healthy. However, pepinemab has been tested in patients with Huntington's disease, including those with prodromal disease, which is a stage at which treatment can be preventative. This study is discussed in depth in the next section, but pepinemab did not show any benefits in this prodromal population (Feigin et al., 2022).

Whether these results are applicable to other, non-genetic dementias, or in healthy adults, is not yet known.

Human research to suggest benefits to patients with dementia:

Huntington's disease (HD) is a genetic neurodegenerative disease that typically becomes symptomatic in midlife. Individuals with a family history of HD can receive genetic testing that can reveal whether they will develop the disease. HD shares pathological and clinical characteristics with other neurodegenerative diseases, including protein aggregation of a characteristic protein (in this case,

huntingtin), metabolic and mitochondrial dysfunction, and selective neuronal loss and concomitant brain atrophy, and cognitive, behavioral, motor, and functional decline.

Pepinemab has been tested in HD patients in a trial called SIGNAL-HD. The Phase 2 phase of SIGNAL-HD enrolled a total of 265 patients with HD; 86 of the participants were prodromal and not yet showing overt symptoms of HD, and 179 of the participants were in the early symptomatic stage of HD. Participants were randomized to monthly infusions of either placebo or 20 mg/kg of pepinemab for 18 months. The coprimary efficacy outcome measures were the clinical global impression of change (CGIC) and two components of an HD cognitive assessment battery (HD-CAB). The latter two components are measures of executive function, spatial planning, working memory, timing, and psychomotor coordination. The trial included several other secondary and exploratory endpoints, including change in overall HD-CAB composite score, changes in brain volume based on MRI, changes in glucose metabolism as measured by FDG-PET, and other assessments of HD progression such as the Unified Huntington's Disease Rating Scale (UHDRS).

SIGNAL-HD failed to meet either of its coprimary endpoints. The authors reported benefits or trends towards benefit with pepinemab treatment in several of their secondary, exploratory, or post-hoc analyses in different subgroups. There was a reduction in atrophy in HD-relevant brain regions in the early manifest group ($p=0.017$) and a trend towards a decrease in ventricular enlargement ($p=0.06$) in pepinemab treated patients compared to placebo. They found increases in FDG-PET signal in almost every brain region analyzed, though they did not observe an increase in three HD-relevant areas.

In exploratory assessments of cognitive measures, the authors found trends towards benefit for pepinemab. When they examined the individual components of HD-CAB, they found that all trended towards improvement in patients receiving pepinemab, and that the composite score showed nominally significant benefit of pepinemab vs. placebo. This effect was stronger in participants who were cognitively impaired at baseline, and not observed in cognitively intact patients. When they stratified results of the CGIC by baseline cognition, they observed that there were fewer patients who were determined to have progressed on pepinemab than on placebo in the subset of patients that were cognitively impaired at baseline. The researchers also qualitatively observed that there may have been a preservation of 'learning effect' in the pepinemab treated patients as compared to placebo in early manifest patients (Feigin et al., 2022).

The Phase 1/2 stage of SIGNAL-HD enrolled 36 patients who were in the late prodromal or early manifest stage of HD. These 36 participants were randomized to either placebo or 20 mg/kg of pepinemab for six months. The study results were presented at Alzheimer's Disease & Parkinson's Disease Conference 2020. The presenter shared that the study met its primary endpoint of safety and tolerability. They also shared that a preliminary interim analysis had found consistent increase in FDG PET signal in participants receiving pepinemab compared to placebo. After the end of the six-month trial, placebo participants were allowed to 'crossover' to the pepinemab arm. After another six months, the FDG-PET signal in these crossover participants had increased to that of the treatment group (AlzForum Conference Summary).

Pepinemab has also been tested in 50 patients with multiple sclerosis (MS). This study was a Phase 1 trial with no efficacy data, and therefore is discussed in the "Safety" section of this report. Pepinemab is currently being tested in 50 patients with Alzheimer's disease in a trial known as SIGNAL-AD; more details can be found in the "Research Underway" section.

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

Sema4D, particularly in its interactions with its receptor Plexin-B1, may contribute to neurodegeneration in multiple ways. One of the main hypotheses is that Sema4D increases neuroinflammation. Sema4D is generally thought to activate immune cells such as microglia and can cause increases in microglial production of inflammatory molecules such as IFN-β and nitric oxide (Smith et al., 2015; Kuklina 2019; Tsuchihashi et al., 2020). Blocking Sema4D mitigates microglia activation (Smith et al., 2015). Sema4D may also activate astrocytes, altering morphology and metabolic function, and blockade of Sema4D appeared to ameliorate these changes (Evans et al., 2022).

Sema4D can also disrupt the blood brain barrier (BBB) through disruption of tight junctions and therefore the neurovascular unit (Smith et al., 2015; Kuklina 2019; Tsuchihashi et al., 2020). Blockade of Sema4D has been shown to reduce BBB dysfunction and mitigate microglial activation in animal models (Smith et al., 2015).

A canonical function of Sema4D is as a repulsive guidance signal for neurites via induction of growth cone collapse (Tasaka et al., 2012). Sema4D is also involved in forming inhibitory synapses (Frias et al., 2019; Adel et al., 2023). Both functions are medicated by signaling cascades activated by Sema4D leading to actin cytoskeletal rearrangement. The extent to which these roles are involved in

neuroprotection or neurodegenerative disease are not known, though there are some theories. For instance, it is hypothesized that the cytoskeletal rearrangement signaling cascade started by Sema4D is at play in the cytoskeletal rearrangements seen in reactive astrocytes that were activated by Sema4D (Evans et al., 2022). Some reports indicate that Sema4D expression is increased in both HD and AD, though this has not been replicated in larger studies, and the exact cause and effect of this increase in expression is not yet clear (Evans et al., 2022).

Multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system, is characterized by demyelination of axons. Sema4D and Plexin-B1 interactions are thought to promote demyelination and axonal degeneration (Vogler et al., 2022). Moreover, Sema4D signaling inhibits the migration and differentiation of oligodendrocyte precursor cells, which are involved in proper myelination (Smith et al., 2015). Sema4D and Sema4D receptor knockout animals are resistant to the most common experimentally-induced model of MS, and Sema4D blockade treatment in animal models of MS mitigated the MS phenotype (Kumanogoh et al., 2002; Okuno et al., 2010; Smith et al., 2015; Vogler et al., 2022).

The increase of migration and differentiation of oligodendrocyte precursor cells that results from blockade of Sema4D may be beneficial for other conditions; for instance, blocking Sema4D with a monoclonal antibody increased the white matter volume in an animal model of HD. Blocking Sema4D also mitigated gray matter loss (Southwell et al., 2015).

APOE4 interactions:

Whether pepinemab or SEMA4D blockade interacts with APOE4 status is not yet known.

Aging and related health concerns: Very early trials hint at potential benefit of pepinemab in cancer treatment, and preclinical work demonstrates rationale for testing pepinemab for other indications.

Types of evidence:

- 1 meta-analysis and systematic review
- 1 open label trial
- 2 observational studies
- 3 reviews

- 6 laboratory studies

The efficacy of Sema4D blocking therapy, such as with pepinemab, has been investigated in health-related conditions such as cancer and multiple sclerosis in humans. In preclinical models, modulation of Sema4D by genetic manipulation or antibody bocking has been explored for a variety of other conditions, such as atherosclerosis and rheumatoid arthritis (Yoshida et al., 2015; Hu & Zhu, 2018; Park et al., 2023). Sema4D binding to its receptor Plexin-B1 in bone cells can also suppress bone formation, and blocking the Sema4D-Plexin-B1 interaction via blocking antibodies improved animal models of postmenopausal osteoporosis (Vogler et al., 2022).

Conversely, increasing levels of Sema4D such as via direct injection have been suggested to be involved in wound repair, such as by promoting angiogenesis and reducing inflammation in animal models (Wang et al., 2018).

Cancer: POTENTIAL BENEFIT

Sema4D is involved in several oncologically-relevant processes, such as immune cell regulation, tumor cell proliferation and migration, and vascular growth. It is thought to be upregulated in several tumor types and has been suggested as a prognostic biomarker, though this is still in the early stages of exploration. It is thought that blockade of Sema4D may increase immune cell presence in tumors and improve patient response to immunotherapies, as well as modulate tumor progression and angiogenesis (Yang et al., 2019; Lu et al., 2021). Preclinically, reducing Sema4D expression and/or action has also been suggested as a potential route to avoid skeletal metastases, based on the role of Sema4D in bone reabsorption and formation (Yang et al., 2016).

Pepinemab treatment has been tested in two completed cancer trials. One trial explored the use of pepinemab in patients with advanced solid tumors. This open label, multiple dose, dose escalation trial enrolled 42 patients with advanced tumors who were relapsed or not responding to standard treatment and for whom no curative therapy was available. The researchers tested seven doses: 0.3, 1, 3, 6, 9, 15, and 20 mg/kg, with dose escalations approved based on safety data. Patients received pepinemab treatment weekly in 28-day cycles. Patients could receive further cycles at the same dose level as long as they did not experience a dose limited toxicity or had disease progression. No complete responses were seen; the median duration of stable diseases and profession free survival was 7.8 weeks (range, 0.57 to 54.8 weeks). Of the 42 patients, 19 (45.2%) showed no sign of disease progression for at least 8 weeks.

Patients with higher B- and T-cells at baseline and who received higher doses of drug appeared to have longer progression free survival. While this would need to be confirmed in a controlled trial, this hints at the potential efficacy of pepinemab treatment in combination with other therapies that enhance the immune response (Patnaik et al., 2016).

A phase Ib/II open-label combination trial of pepinemab and avelumab, an immune checkpoint blockade therapy, was tested in 62 patients with advanced non-small cell lung cancer (NSCLC). Avelumab, a PD-L1 blocking antibody, is designed to enhance the immune response to cancer cells; while this drug is approved for treatment of certain cancer subtypes, durable responses to avelumab and other anti-PD-1/L1 therapies are not seen in the majority of patients with NSCLC. The phase Ib portion of the study enrolled 12 total patients who were treated with 10 mg/kg of avelumab and 10, 15, or 20 mg/kg of pepinemab. The phase II portion of the study enrolled a total of 50 patients who were given 10 mg/kg of avelumab and 10 mg/kg of pepinemab based on other ongoing pepinemab preclinical and clinical trials. Of the total 62 patients in the trial, 30 were immunotherapy naïve (ION) – that is, they had never received immunotherapy before – and 32 had previous PD-1/L1 monotherapy that failed (IOF). Patients received doses every two weeks until disease progression, intolerable toxicity, patient withdrawal, or patient death. While it is difficult to compare results between trials, the data hinted at improved performance of the combination therapy compared to avelumab alone, particularly in immunotherapy naïve patients. This is not unexpected; a group that contains people who previously failed any immunotherapy but especially an immunotherapy blocking one of the same targets as the new combination therapy may well be enriched for non-responders. Some of the efficacy results are below. It should be noted that the disease control rate appears to be driven by stable disease as opposed to partial or complete responses.

Group	Disease Control Rate	Objective Response Rate	Median Progression-Free Survival
Immunotherapy Naïve	81% (17 of 21 evaluable patients)	24% (5 of 21 evaluable patients)	11.6 weeks
Prior PD-1/L1 Monotherapy Failure	59% (17 of 29 evaluable patients)	7% (2 of 29 evaluable patients)	8.4 weeks

Disease control rate: patients with stable disease, partial response, or complete response
Objective response rate: patients with partial or complete response
(Shafique et al., 2021).

Safety: Preliminary results from trials indicate that headache, nausea, vomiting, and potentially pain and/or fatigue are possible side effects of pepinemab. Further work is needed to assess immunogenicity and the potential consequences of anti-drug reactions.

Types of evidence:

- 2 randomized controlled trials
- 2 open label studies

Feigin et al., 2022 detail the result s of SIGNAL-HD, a randomized controlled trial that tested the effects of 18 months of treatment with 20 mg/kg pepinemab vs. placebo in 256 patients with either prodromal or early manifest HD. After the end of treatment, patients were followed for at least 2 more months and up to 6 months for safety and laboratory assessments. There was no statistically significant difference between placebo group and pepinemab group in terms of frequency of treatment-emergent adverse events or frequency of serious adverse events. There appeared to be more treatment-emergent adverse events that were probably or definitely related to study drug in the pepinemab group compared to placebo (25% vs. 14%, respectively); this difference was driven by mild or moderate adverse events. No serious adverse events were judged to be probably or definitely related to study drug, and no adverse events lead to study discontinuation. The authors did not discuss statistical analysis of the individual adverse events, but most occurred at similar rates in placebo and pepinemab groups. The most common adverse event was headache (19% in placebo, 38% in pepinemab). Other adverse events that occurred in at least 10% of patients and were numerically different between placebo and pepinemab, respectively, included falls (17% vs. 25%), vomiting (8% vs. 15%), pain (7% vs. 11%), and back pain (6% vs. 11%). There was one death by suicide in the study in an early manifest patient in the pepinemab group. This event was ruled to not be related to the study drug. Suicidal ideations are a known symptom of HD, along with other psychiatric symptoms such as anxiety. There was no increase in measures of anxiety or suicidal ideation between the placebo and pepinemab groups.

A subset of the study group (n=42) was treated for a further 18 months for a total of 36 months of safety follow up; there were no significant differences between frequency or severity of treatment emergent adverse events.

Immunogenicity was also investigated in the study by looking for presence of anti-pepinemab antibodies; it was found that 8 of 133 participants in the pepinemab group had these antibodies, though the responses were transient, low titer, and there was no association between immunogenicity status

and safety outcomes. The authors report that there were no clinically meaningful changes in any laboratory or physical examinations between groups over the course of the trial.

A randomized, placebo-controlled trial of pepinemab in patients with multiple sclerosis was published in 2017. This study tested single ascending doses of pepinemab, with ten participants assigned to each of five dose cohorts: 1, 3, 6, 10, or 20 mg/kg. The goal of the study was to determine safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics. Treatment-emergent adverse events were observed for 4 of 10 (40%) placebo treated participants and 26 of 40 (65%) pepinemab treated patients. There was no dose-dependent pattern of adverse events in the pepinemab group. The most common treatment-emergent adverse events were urinary tract infection, muscular weakness, contusion, and insomnia. Overall, three participants, all in a pepinemab arm, experienced a serious adverse event. Of these three events, only one was judged to be possibly related to pepinemab treatment. The patients had a grade 3 increase in MS-related brain lesions from baseline to day 29 after treatment. This patient experienced an MS relapse 3 months before trial enrollment and showed signs of active disease at baseline. The adverse event was judged as possibly related to pepinemab treatment. There were no clinically significant changes in physical or laboratory assessments. Many the patients (29 out of 40) did develop anti-drug antibodies, but most were low-titer and none showed fully neutralizing antibodies (LaGanke et al., 2017).

Pepinemab has also been trialed in patients with cancer. One open label study examined the safety and tolerability of weekly doses of pepinemab in 42 patients with advanced solid tumors. Participants received variable number of doses (median = 8 doses) and concentrations of drug (escalating from 0.3 up to 20 mg/kg in successive cohorts). Nausea (14.3% of participants) and fatigue (11.9% of participants) were the two most common treatment-related adverse events. Joint stiffness, decreased appetite, infusion related reaction, and fever were each observed in 7.3% of participants. No dose-related safety trends were observed, whether of incidence or severity of adverse event. All treatment related events were grade 1 or grade 2, except for one grade 3 event that was considered a dose limiting toxicity and severe. The event was an elevated liver enzyme (gamma- glutamyltransferase). Twenty three of the 42 patients developed anti-drug antibody responses; the response of one patient was neutralizing, and led to study discontinuation. There were twelve deaths in the study, though none were considered to be treatment related (Patnaik et al., 2016).

An open label combination trial testing pepinemab and avelumab in patients with advanced non-small cell lung cancer (NSCLC) enrolled 62 patients. Patients received 10, 15, or 20 mg/kg of pepinemab and

10 mg/kg avelumab. Without an avelumab-only or placebo group it is difficult to fully assess the safety signal of pepinemab alone. However, it appeared that the combination therapy was well-tolerated. No safety signals outside of those expected for avelumab were seen. There were nine grade 3 (14.5%) and three grade 4 (4.8%) treatment-related adverse events. Fatigue was the most common adverse event (Shafique et al., 2021).

Drug interactions:

The drug interactions of pepinemab are not yet known.

Research underway:

There are seven ongoing trials of pepinemab. There are no other ongoing trials that mention Sema4D. Six of the pepinemab trials are investigating the use of pepinemab as a treatment for different kinds of cancer; one ongoing trial is testing the effects of pepinemab in Alzheimer's disease.

NCT04381468, called SIGNAL-AD, is a randomized, blinded trial that has recruited 50 individuals with mild dementia. Participants will receive either 40 mg/kg pepinemab or placebo via IV infusion once every 4 weeks for 44 weeks for a total of 12 infusions. The final trial assessment will take place at 52 weeks. The primary outcome of the trial is the number of treatment emergent adverse events, including events that onset after treatment and medical conditions present at baseline that increase in severity after dosing begins. A key secondary outcome measure is changes in brain metabolism over the course of the study as measured by FDG PET. Other secondary outcomes include measures of cognition such as change in MMSE, CDR, and ADAS-cog13, measures of function such as the Alzheimer's disease Cooperative Study - Activities of Daily Living (ADCS-ADL), and readouts of behavior such as the Neuropsychiatric Inventory (NPI). The frequency and titer of anti-drug antibodies will also be assessed as a secondary outcome measure. Other outcome measures include pharmacodynamic measures such as half-life, drug levels in CSF, and target engagement, and biomarker assessments such as levels of tau, Aβ, and brain volume as measured by MRI.

Search terms:

Pubmed, Google: pepinemab, semaphorin 4D, Sema4D

- Huntington's disease, Alzheimer's disease, dementia, cancer, cardiovascular, multiple sclerosis, osteoporosis, stroke

Websites visited for pepinemab:

- Clinicaltrials.gov
- PubChem
- DrugBank.ca