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DRUG EVALUATION

Pepinemab: a SEMA4D antagonist for treatment of Huntington's and other neurodegenerative diseases

Andrew Feigin[a,b], Elizabeth E. Evans[c], Terrence L. Fisher[c] and Maurice Zauderer[c]

[a]NYU Langone Health, New York, NY, USA; [b]Rho, Inc., Durham, NC, USA; [c]Vaccinex, Inc, Rochester, NY, USA

ABSTRACT

Introduction: Huntington's Disease (HD) is a progressive fatal neurodegenerative disease with an unmet need for disease-modifying therapies. Neuroinflammation, particularly astrogliosis, plays a crucial role in the pathogenesis of HD and modulation of this damaging activity and its downstream effects presents a promising therapeutic avenue. Pepinemab, a semaphorin 4D (SEMA4D) blocking antibody, has the potential to serve this purpose.

Areas covered: We review the proposed mechanisms of action of pepinemab, published safety and efficacy results from the 'SIGNAL' Phase 2 trial in HD and supporting data from a Phase 1 trial in multiple sclerosis (MS).

Expert opinion: Pepinemab's potential to reduce reactive gliosis and inflammation is a novel mechanism of action (MOA) that may be effective as a standalone therapy as well as one that may complement other strategies to reduce toxic disease associated processes. Pepinemab has demonstrated a favorable safety profile and treatment benefits in fluid biomarkers, imaging endpoints, and measures of cognitive function that encourage continued development in HD and other neurodegenerative diseases.

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Huntington's disease; astrocytes; glial cells; neuroinflammation; pepinemab; SEMA4D; SIGNAL; Alzheimer's disease

1. Introduction

Huntington's disease (HD) is a distinct neurodegenerative disorder with underlying pathophysiological mechanisms and clinical presentations, of which some features are common to other neurodegenerative and neuroinflammatory diseases. HD is an autosomal dominant disorder caused by a trinucleotide CAG expansion in the HTT gene on chromosome 4 [1]. The clinical presentation has an average age of onset around age 40 (this can vary from early childhood to more advanced age) and is characterized by the triad of a movement disorder (chorea, parkinsonism, dystonia, gait impairment), cognitive disorder (a 'subcortical dementia' with executive dysfunction), and psychiatric changes (depression, apathy, irritability, psychosis). The underlying pathology initially involves striatal medium spiny neuronal loss but spreads to involve both subcortical and widespread cortical neuronal loss [2]. Despite clear differences in pathology and clinical presentation from other neurodegenerative diseases such as Alzheimer's (AD), these neurodegenerative disorders share characteristics of neuroinflammation, contributing to significant brain damage that aggravates disease progression [3] and cognitive decline. It is of considerable interest that several such diseases appear to be triggered by misformed, albeit distinct, protein aggregates, e.g. mutant huntingtin protein (mHTT), amyloid beta protein (Aβ) or α-synuclein.

Current therapeutic approaches to HD and AD largely focus on pathophysiology of these disorders resulting from their characteristic toxic protein aggregates. In HD, genetic based therapies such as antisense oligonucleotides, RNA interference, and small molecule RNA splice modulators that aim to lower the production of the mutant huntingtin protein have entered human trials. These early studies have had mixed results, suggesting that these approaches may be complicated by potential lowering of the normal huntingtin allele and other issues [4]. Three drugs have received regulatory approval for HD, all of which are limited to providing symptomatic improvements of chorea via inhibition of vesicular monoamine transporters, with no impact on cognitive or behavioral deficits. In AD, many trials of therapies aimed at lowering Aβ amyloid or tau have also had mixed results but moderate cognitive benefits, especially early in disease, have led to regulatory approval of three monoclonal antibodies to date [5]. These therapies are, however, associated with potential risks (e.g. brain hemorrhaging and inflammation detected as amyloid-related imaging abnormalities, ARIA) that require continued monitoring. While targeting disease-specific mechanisms remains important, therapies that target common disease pathologies such as neuroinflammation may also offer broad and meaningful benefits.

Neuroinflammation appears to play an important role in many if not all neurodegenerative disorders [3,6]. Semaphorin 4D (SEMA4D) is a key modulator of neuroinflammation, contributing to reactive transformation of astrocytes and microglia that appears to aggravate and accelerate neurodegenerative processes. Antibody blockade of SEMA4D with a specific monoclonal antibody (pepinemab) has been shown to ameliorate the inflammatory and neurodegenerative processes in animal models of HD and AD, and this has led to several promising trials of this drug. This article will briefly review the mechanism of action of pepinemab, the preclinical

CONTACT Terrence L. Fisher tfisher@vaccinex.com Vaccinex, Inc, 1895 Mt Hope Ave, Rochester, NY 14612

Article highlights

- Neuroinflammation, mediated by astro- and microgliosis, plays an important role in the pathogenesis of HD and AD.
- SEMA4D is a key modulator of neuroinflammation leading to pathogenesis and progression in neurodegenerative diseases including HD and AD.
- Antibody blockade by pepinemab ameliorates the damaging effects of reactive gliosis in both preclinical models and clinical studies.
- Pepinemab has been very well-tolerated in clinical trials of patients with MS, HD, and AD.
- The largest clinical trial of pepinemab in HD (n=301) showed beneficial treatment effects on cognition, brain metabolism, brain atrophy, and astrocyte reactivity.
- Pepinemab has the potential to be a promising therapeutic for HD and AD due to its unique MOA, benign safety profile, and the demonstration of important treatment and biomarker effects in Phase 2 clinical trials.

Box1. Drug summary box.

Drug name: Pepinemab
Phase: Phase 2
Indication: Huntington's Disease and other neurodegenerative diseases
MOA: Blocks binding of SEMA4D to its receptors to reduce reactive gliosis and neuroinflammation, promoting brain health and metabolism
Route of administration: Intravenous infusion
Structure: Humanized IgG4 monoclonal antibody
Key Trials: Phase 2 SIGNAL-HD (NCT02481674) and SIGNAL AD (NCT04381468)

data supporting its efficacy, and importantly, the results from human clinical trials.

2. Pepinemab and its mechanism of action

Pepinemab (VX15/2503; MAb 2503; VX15) is a humanized IgG4 monoclonal antibody that binds specifically to semaphorin 4D (SEMA4D; CD100) [7]. SEMA4D is a member of a large family of semaphorin proteins initially recognized as axonal guidance factors involved in neuronal development [8]. SEMA4D was the first semaphorin discovered to also have a role in the immune system [9,10]. This multifunctional protein is a novel therapeutic target in a variety of immune, oncologic, and neurological indications [11]. SEMA4D is expressed as a transmembrane 300 kDa disulfide-linked homodimeric protein and is also expressed in a physiologically active, 240 kDa, homodimeric, soluble form (sSEMA4D) that results from proteolytic cleavage of the extracellular domain [12,13]. Pepinemab blocks the binding of both cellular and soluble forms of SEMA4D to its two high-affinity receptors, plexin-B1 (PLXNB1) and plexin-B2 (PLXNB2), as well as to a low-affinity receptor, CD72.

SEMA4D and its plexin receptors are upregulated during brain injury or disease [14–18], for example, as might be caused by stress due to accumulation of toxic protein aggregates. We have reported that SEMA4D is upregulated predominantly in neurons [16] in diseased HD and AD brains of both mice and postmortem human tissues. Others have also described upregulation of the SEMA4D/PLXNB signaling pathway in microglia [15] and oligodendrocytes [19]. SEMA4D signals through PLXNB1 receptors on astrocytes and possibly also PLXNB2 receptors expressed on microglia [15] to (i) promote reactive gliosis [16,20,21] (ii) to disrupt normal astrocyte functions that support brain metabolism and neuronal activity [16], (iii) to inhibit migration and differentiation of oligodendrocyte precursor cells (OPC) that could repair damage to white matter [22–25], and (iv) to disrupt endothelial tight junctions that are required for the vascular integrity of the brain [20].

Astrogliosis, or astrocyte reactivity, serves as a major pathological hallmark of neuroinflammatory and neurodegenerative diseases and is characterized by changes in gene expression and morphology, including retraction of astrocyte dendritic processes. In contrast, under normal homeostatic conditions, astrocytes extend these processes to interact with capillaries to facilitate glucose transport and to cradle synapses to recycle neurotransmitters. In preclinical studies using purified human astrocyte cultures, SEMA4D induced morphologic and physiologic reactive changes in astrocytes that reduced their ability to support energy metabolism in the brain and to control levels of neurotransmitters required for efficient signaling. SEMA4D-blocking antibody inhibited these reactive changes of astrocytes and preserved normal homeostatic astrocyte functions [16].

We previously demonstrated in multiple preclinical disease models that antibody neutralization of SEMA4D ameliorates neuroinflammatory and neurodegenerative processes characteristic of neurological diseases [14,20]. We and others have reported a key role for SEMA4D/PLXN signaling in promoting pathogenic activities in mouse EAE models of multiple sclerosis [15,20,26]. Inactivation or blockade of this signaling pathway can inhibit interactions between astrocytes, microglia, neurons and oligodendrocytes so as to reduce damaging neuroinflammation, improve remyelination of damaged neurons and ameliorate EAE. In mouse models of HD (zQ175 [16] and YAC128 [14]), upregulation of SEMA4D in neurons was associated with reactive astrogliosis and anti-SEMA4D treatment ameliorated neuropathological signatures, including striatal and cortical atrophy, as well as reducing anxiety-like behavior and rescuing cognitive deficits. In CVN mice, a disease model that appears to reproduce many features of AD-like pathology including neuroinflammation, SEMA4D antibody treatment reduced the presence of reactive astrocytes, prevented characteristic loss of GABAergic synapses, and restored spatial memory and learning [16]. Significant upregulation of SEMA4D was also observed in postmortem human HD and AD brain tissue, increasing with progressive pathological stages of HD. Data from these preclinical disease models elucidated mechanisms of action and activity of SEMA4D antibody blockade.

Overall, SEMA4D appears to play multiple roles in the pathogenesis and progression of several neurodegenerative diseases (Figure 1), and this provides a strong rationale for blocking the binding of SEMA4D to its receptors to treat such diseases. Nonclinical GLP toxicology studies in rats and non-human primates demonstrated pepinemab was well-tolerated and produced no clinical or toxicological findings of

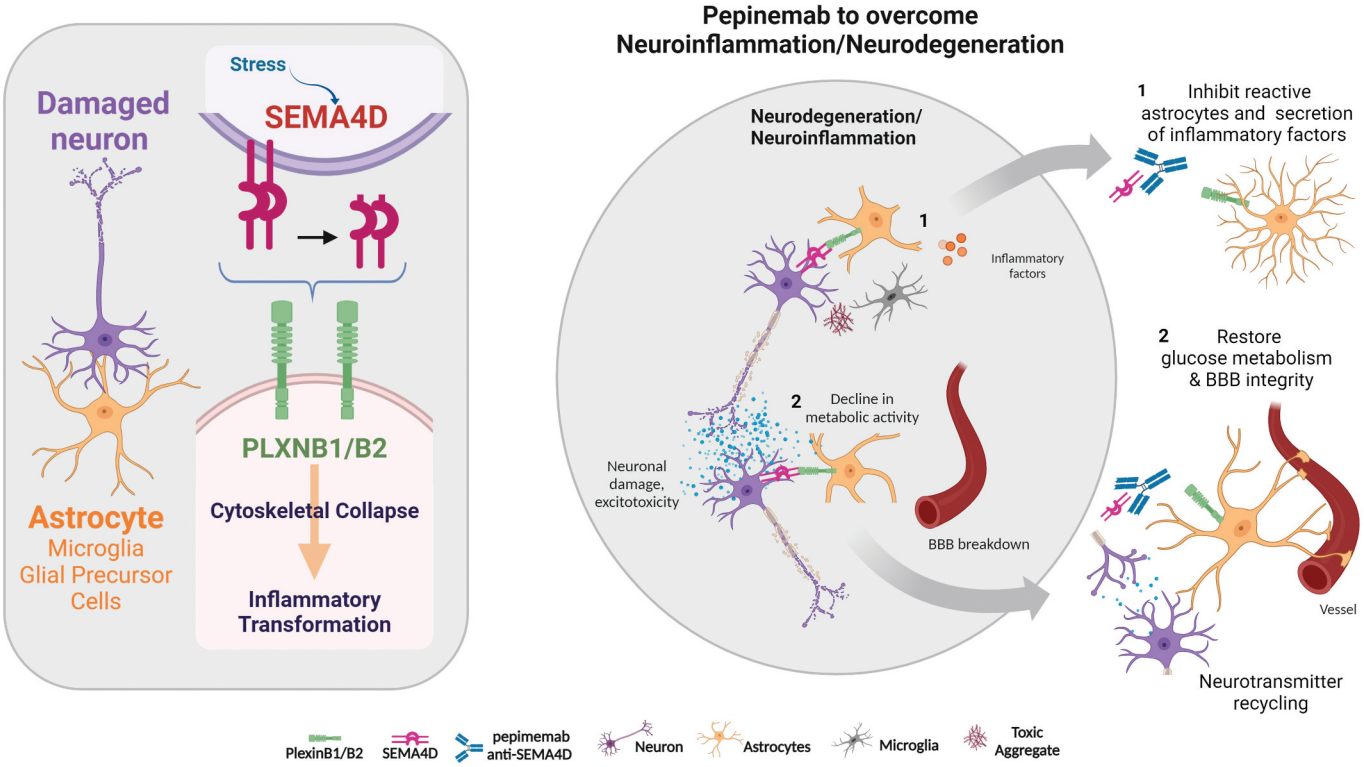

Figure 1. Proposed mechanism of action for pepinemab in neurodegenerative disease. Semaphorin 4D (SEMA4D), the major ligand of plexin B1/B2 receptors expressed on astrocytes, is upregulated in diseased or damaged neurons during Huntington's and Alzheimer's disease (HD and AD) progression and triggers astrocyte reactivity, leading to loss of homeostatic support functions, including downregulation of glutamate receptors and glucose transporters that, respectively, recycle excitatory transmitters and support energy metabolism [16]. In parallel, morphogenic and functional changes lead astrocytes to gain inflammatory processes, e.g. secretion of inflammatory mediators that can further exacerbate damaging neuroinflammation and neurodegeneration. Pepinemab is a humanized, high affinity monoclonal antibody that blocks the binding of SEMA4D to its receptors and inhibits activation of this signaling pathway.

consequence [27], providing further support for initiating clinical trials.

3. Pepinemab clinical studies

Table 1 provides a summary of completed and ongoing clinical trials evaluating pepinemab in neurodegenerative diseases.

3.1. Phase 1 MS

A Phase 1 single-dose, randomized, placebo controlled study was completed to assess safety and tolerability of pepinemab in adult patients with MS [28]. Ten patients each were randomized into five ascending dose cohorts of 1, 3, 6, 10, or 20 mg/kg delivered by intravenous infusion. All dose levels were determined by a Dose Escalation Safety Committee to be well-tolerated. No treatment-related serious adverse events (SAEs) or dose-limiting toxicities were observed, and a maximum tolerated dose (MTD) was not determined. The study was not designed for formal evaluation of efficacy.

3.2. SIGNAL: a phase 1/2 huntington's disease trial

The 'SIGNAL' study was a Phase 1/2, multi-center, randomized, double-blind, placebo-controlled study in individuals with late prodromal and early manifest Huntington's Disease (HD) to assess the safety, tolerability, PK, and efficacy of pepinemab [29]. The adaptive study design (Figure 2) employed two cohorts and enrolled at 30 clinical sites (27 US and 3 Canada). All patients enrolled had confirmed CAG repeat length of ≥ 36. Patients in the phase 1 Cohort A (Figure 2(a)) of this study were randomized 1:1 to receive monthly infusions of either placebo or pepinemab (at 20 mg/kg) for the first 6 months, and then all patients received pepinemab for the remaining 6 months. The results of Cohort A ($n = 36$) informed expansion and design of phase 2 Cohort B ($n = 265$). Cohort B was further divided into Cohort B1 composed of patients diagnosed with early symptoms of manifest disease and Diagnostic Confidence Level (DCL) = 4, (Figure 2(b), $n = 179$), and Cohort B2, a late prodromal population with DCL = 2 or 3, (Figure 2(b), $n = 86$). Cohorts B1 and B2 were independently randomized 1:1 to receive infusions of placebo or pepinemab for up to 36 months, and the study was completed [29] in August 2020.

The SIGNAL clinical study established the safety and tolerability of pepinemab immunotherapy in individuals with HD and no concerning clinically relevant safety issues were identified. The Phase 2 Cohort B study did not meet its prespecified primary efficacy endpoint, consisting of coprimary efficacy outcome measures in patients with early manifest disease ($n = 179$) of (1) a two-item HD cognitive assessment family comprising one-touch stockings of Cambridge (OTS) and paced tapping (PTAP) and (2) clinical global impression of change (CGIC). No significant benefit was detected in patients with

Table 1. Summary of pepinemab clinical trials in patients with neurodegenerative disease.

Alias/NCT #	Description	Design	Summary of Results
Phase 1 MS (NCT01764737)	Phase 1, randomized, double-blind, placebo-controlled, dose-escalation safety and pharmacokinetic/pharmacodynamic study of pepinemab in adults with multiple sclerosis	$N = 50$ Single dose, Dose escalation 1 to 20 mg/kg Key Endpoints: Safety, PK, PD	Well tolerated at all dose levels in MS patients Receptor occupancy sustained at saturating levels for ≥155 days after 1 dose at 20 mg/kg, lower limit of pepinemab in serum needed for target saturation was approximately 0.1 to 0.3ug/ml. Half-life increased with dose level, and was approximately 20 days at 20 mg/kg
SIGNAL **Cohort A** **Cohort B** (NCT02481674)	Phase 2, randomized, double-blind, placebo-controlled, safety and efficacy study of pepinemab in adults with early manifest and late prodromal HD with confirmed CAG repeat score ≥ 36.	$N = 301$ (Cohort A, 36; Cohort B, 265) Q4W, 20 mg/kg Key Endpoints: Safety, cognition via HD-CAB, brain metabolism via FDG-PET	Well tolerated in HD patients Positive treatment effects observed in individuals with early manifest HD (Diagnostic Confidence Level = 4) and especially those with evidence of cognitive impairment at baseline (MoCA score 18–25), including, cognitive ability (HD-CAB), clinical global impression of change (CGIC), brain metabolism (FDG-PET), brain atrophy (MRI), and the astrocyte activation marker GFAP
SIGNAL AD (NCT04381468)	SEMA4D blockade safety and brain metabolism activity in AD: A Phase 1b/2, multi-center, randomized, double-blind, placebo-controlled safety and biomarker study of pepinemab anti-SEMA4D Antibody in MCI and mild dementia due to AD (MMSE 17–26, CDR-GS 0.5–1)	$N = 50$ Q4W, 40 mg/kg Key Endpoints: Safety, brain metabolism via FDG-PET, biomarkers including GFAP, p-tau 217 and clinical scales including cognitive testing, and prespecified subgroup analysis (baseline MMSE and CDR-GS)	Completed, July 2024 (manuscript in preparation, also www.vaccinex.com, see 'News,' 'Presentations')

NCT: National Clinical Trial; MS: multiple sclerosis; PK: pharmacokinetics; PD: pharmacodynamics; HD: Huntington's Disease; CAG: cytosine, adenine, guanine; Q4W: monthly; HD-CAB: Huntington's Disease Cognitive Assessment Battery; FDG-PET: [18F]-Fluoro-2-Deoxy-D-Glucose positron emission tomography; MoCA: Montreal Cognitive Assessment; CGIC: clinical global impression of change; MRI: magnetic resonance imaging; GFAP: glial fibrillary acidic protein; AD: Alzheimer's Disease; SEMA4D: semaphorin 4D; MCI: mild cognitive impairment; MMSE: mini-mental state examination; CDR-GS: Clinical Dementia Rating Global Score; p-tau 217: phosphorylated tau at threonine 217.

late prodromal HD. Nevertheless, several findings from the SIGNAL trial suggested meaningful treatment effects in this population and provide rationale and direction for the continued development of pepinemab in neurodegenerative disease. These are discussed below.

3.2.1. Cognition: HD-CAB

In multiple surveys, HD patients and their families have identified cognitive decline as their major concern during disease progression [30,31]. The Huntington's Disease Cognitive Assessment Battery (HD-CAB) is based on six different measures of change in different cognitive domains (One Touch Stockings of Cambridge (OTS), Paced Tapping Test (PTAP), Symbol Digit Modalities Test (SDMT), Trail Making Test-B (TMT-B), Hopkins Verbal Learning Test (HVLT), and Emotion Recognition Test (EMO)) and was designed by HD investigators to assess overall cognitive decline [32]. Importantly, the development and validation of the HD-CAB demonstrated that each of the six included tests independently contributed to the overall assessment of cognitive function. The SIGNAL Phase 2 study of pepinemab antibody in HD was initially designed to employ HD-CAB composite as a primary cognitive endpoint for Cohort B1. We were, however, encouraged by FDA to instead adopt a novel two-item cognitive family from the HD-CAB to avoid the use of a composite score which might theoretically be skewed by the impact of only one or two of the constituent elements. Based on prior data from SIGNAL Cohort A, OTS and PTAP were selected for the two-item cognitive family. Unfortunately, the SIGNAL study was not designed to be powered for this substitute endpoint and, although all six assessments showed numerical improvement in their respective scores, the effect of pepinemab treatment on OTS narrowly missed statistical significance (one-sided $p = 0.028$) and for PTAP showed a trend in the direction of benefit ($p = 0.06$). As originally planned, however, the study was well-powered for the full composite HD-CAB, which was retained as an exploratory endpoint and indicated a highly significant treatment effect ($p = 0.007$).

The data from this study suggests that, for regulatory purposes, it will be important to define a comprehensive, clinically meaningful measure of cognitive decline in HD. As described below, post-hoc analysis supported HD-CAB as 1) a useful measure of disease progression [33], that 2) correlates with clinically meaningful measures of disease burden. To determine if pepinemab treatment had an effect on delaying disease progression, we employed an exploratory analysis of changes in the HD-CAB composite over time. Figure 3(a) shows the point estimates and standard error bars (fitted and extrapolated) from the exploratory MMRM model of change from baseline in the HD-CAB composite scores up to 18 months of treatment in patients with early manifest HD (Cohort B1). The observed pattern of change is consistent with a compound effect (per apparent piece-wise linear trend) in which one or more components increase during the first six months of treatment, possibly related to a symptomatic treatment effect, after which the rate of change appears to normalize to a linear decline with separation between groups that appears to increase with treatment duration. Treatment with placebo had an annualized decline in LS mean from month 6 to month 18 in the HD-CAB composite of −0.139 compared to −0.089 for pepinemab, which is a treatment benefit of 0.05 per year (36% improvement). The dashed lines extrapolate the trend observed between month 6 and month 18. The separation between pepinemab and placebo steadily increases during this time and, assuming continued linear progression, is mathematically projected to continue to increase.

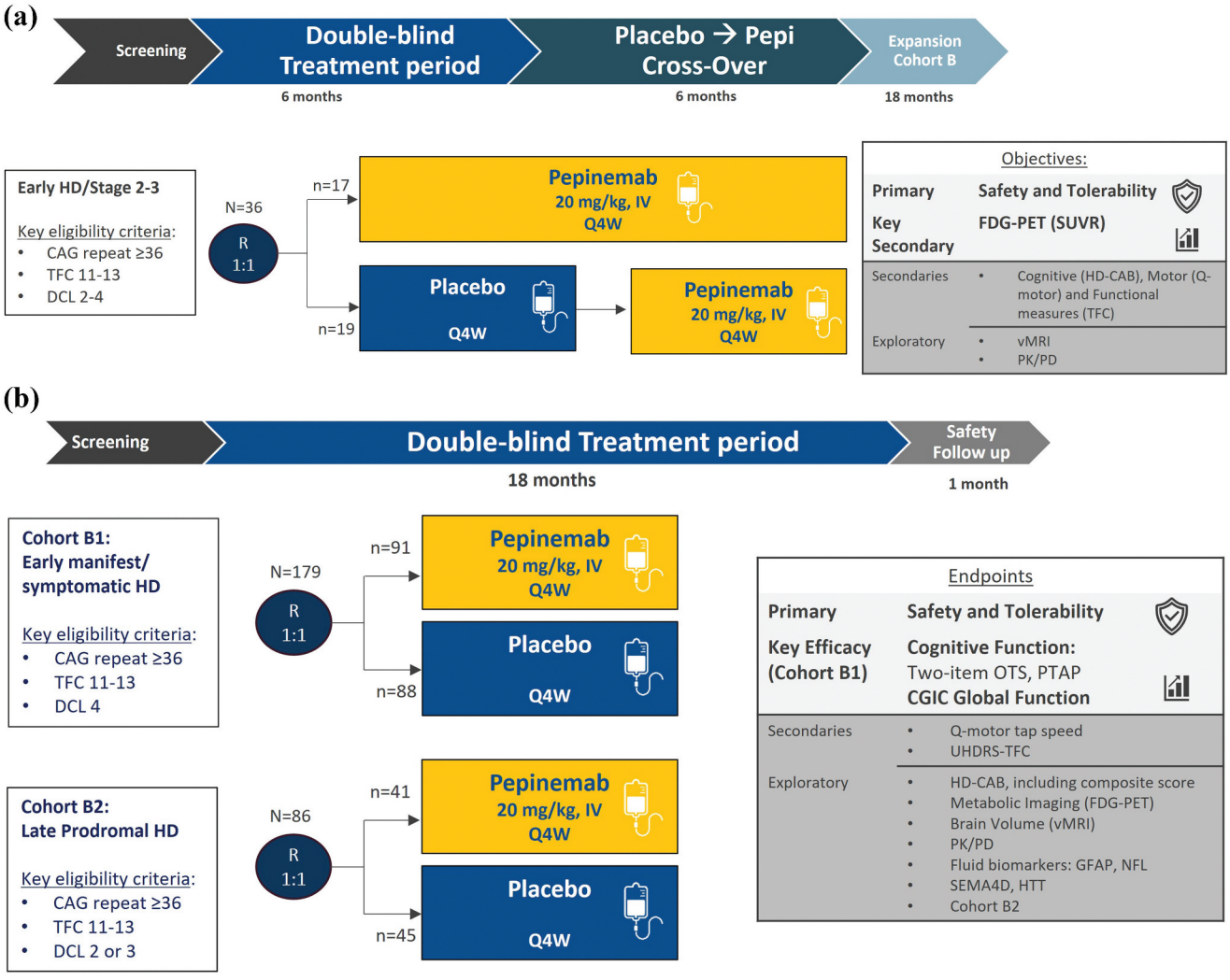

Figure 2. SIGNAL study designs for HD. (a) Cohort A; (b) Cohort B.

These findings show an estimated and extrapolated delay in cognitive decline after Month 6 in the pepinemab group relative to the placebo group in Cohort B1. The predicted delay in disease progression was projected to increase from 11.2 months (after 17 months of pepinemab treatment) to 17.4 months (after approximately 35 months of treatment), a projected further improvement over an additional 18-month span of treatment. In early manifest HD, a slowing of cognitive decline of this magnitude, reflecting approximately half a year of delay in clinical progression, could be considered clinically meaningful.

To further support the relationship between HD-CAB and disease progression, a post-hoc analysis was performed to determine if changes in the HD-CAB were correlated with CAP scores at baseline in pepinemab-treated patients with early manifest HD. The CAP score is a widely employed age-adjusted measure of disease burden in HD that, in contrast to CAG repeat length alone which is not adjusted for patient age, has been reported to correlate positively with multiple other measures of HD progression, including age of disease onset, motor dysfunction, cognitive deficits, compromised daily living capacity, and neurodegeneration [34–36]. The CAP score is an index of the length and severity of the individual's exposure to the effects of the mutant HTT gene [37]. Indeed, changes in the HD-CAB were correlated with CAP scores at baseline in pepinemab-treated patients with early manifest HD (Figure 3(b), Pearson $R^2 = 0.33$, $p < 0.0001$), further supporting the relationship between HD-CAB and disease progression.

The change in HD-CAB composite was also compared to a global assessment of function, Clinical Global Impression of Change (CGIC). Figure 3(c) shows that the empirical cumulative distribution functions of HD-CAB composite scores were consistently separated for the CGIC worsen and not worsen categories ($p = 0.017$), and that the magnitude of the difference increased as improvement on the HD-CAB composite increased. This observation that improvement in cognition as detected by the HD-CAB is associated with improvement or stabilization in global functioning detected by cumulative distribution analysis is additional support for the HD-CAB composite as a clinically meaningful outcome.

3.2.2. *Brain metabolism: FDG-PET*

[^{18}F]-Fluoro-2-Deoxy-D-Glucose positron emission tomography (FDG-PET) neuroimaging was employed to evaluate regional cerebral glucose metabolism as a marker of glial and neuronal competency and synaptic function and to determine whether there was a treatment effect on preserving neuronal

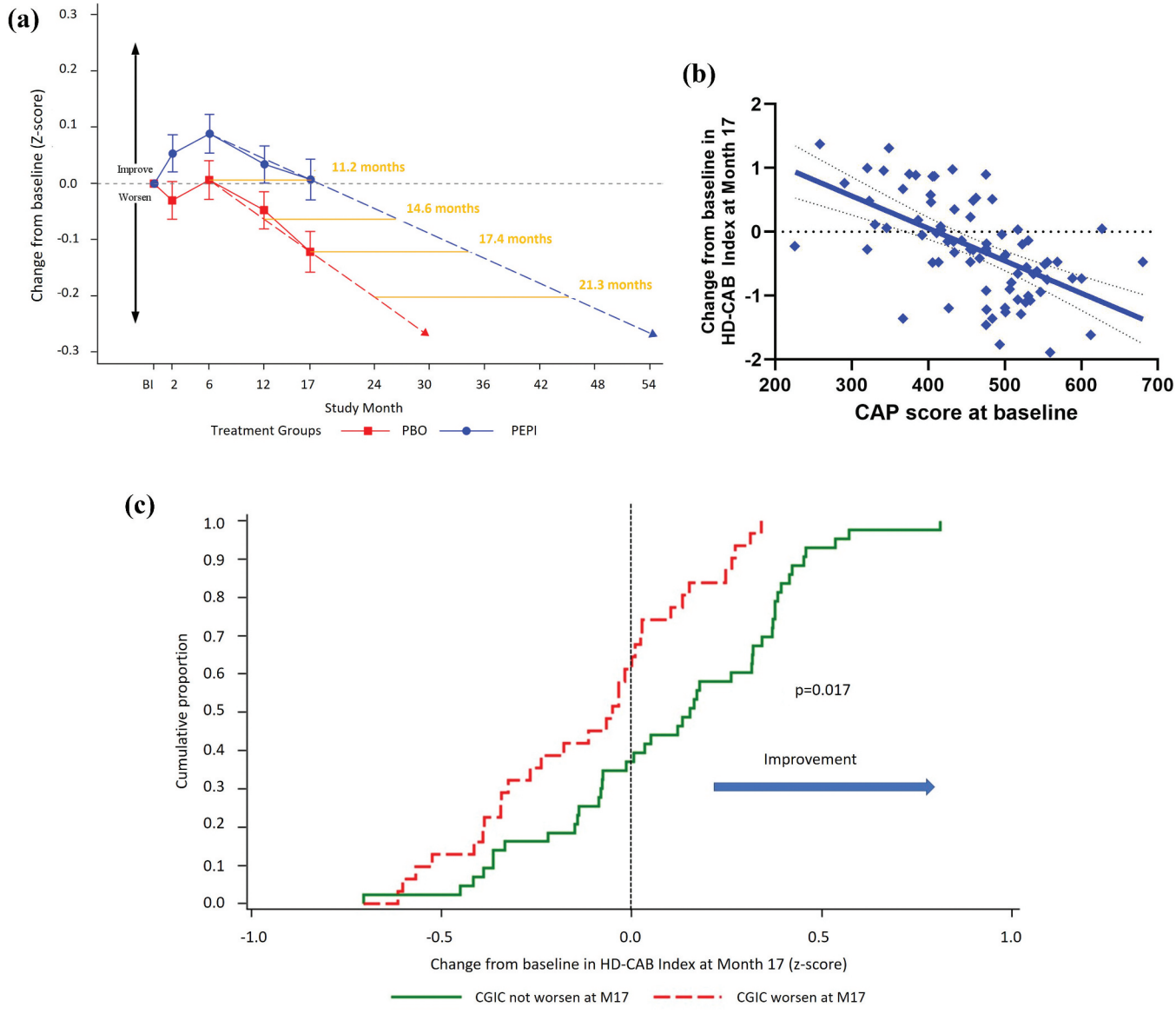

Figure 3. Clinical meaningfulness of pepinemab treatment effect in SIGNAL-HD. (a) The change in HD-CAB composite over time in cohort B1; point estimates and standard error bars (fitted and extrapolated) are from the MMRM model of change from baseline in HD-CAB values up to month 17. The dashed lines extrapolate the trend from month 6 to month 17. The orange lines represent the delay in disease progression for pepinemab compared with placebo. (b) Correlation between CAP score at baseline and 17-month change in HD-CAB composite score in pepinemab-treated patients with early manifest HD; the correlation between CAP score at baseline and change in HD-CAB composite score was statistically significant in patients ($N = 79$) with early manifest HD (Pearson $R^2 = 0.33$, $p < 0.0001$). (c) HD-CAB composite score correlates with clinician global impression of change; cumulative distribution function analysis, p-value generated from a Kolmogorov – Smirnov two-sample test used to analyze differences in CGIC categories (not worsen [$n = 43$] and worsen [$n = 31$]) at month 17.

activity and synaptic function. As has been previously reported for HD and other slowly progressive neurodegenerative diseases, brain metabolic activity detected by FDG-PET declines with underlying disease progression [38–40].

In Cohort A, FDG-PET data were available for a total of only 19 participants (pepinemab (PEPI) [$n = 11$] and placebo (PBO) [$n = 8$]). Despite the low n in this cohort, a numerically positive treatment effect was observed in brain FDG-PET Standard Uptake Value Ratio (SUVR) in numerous regions of interest (ROI). Double-blind treatment with PEPI for six months led to statistically significant LS mean increases ($p < 0.05$) from baseline compared to PBO (effect size) in 10 ROI of the frontal and parietal lobes and 4 ROI of the temporal and cingulate lobes. Importantly, this treatment effect was observed in two separate cohorts of patients in Cohort A, both in patients that received 6 months of double-blind treatment initially, as well as a separate group of patients that received placebo for the first 6 months and then crossed over to receive pepinemab during the final 6 months of the study in a staggered start design.

While the group sizes were small in Cohort A, the results motivated and informed the FDG-PET assessments conducted in patients with early manifest disease in Cohort B1. Figure 4 depicts both the mean change from baseline (Figure 4(a)) as well as difference in the % change between the PEPI and the PBO groups (Figure 4(b)), with an effect size greater than zero suggesting a positive treatment effect. Strikingly, in the larger groups and longer treatment duration of Cohort B1 ($n = 31$ PBO and $n = 28$ PEPI), 26/26 brain ROI showed a positive PEPI

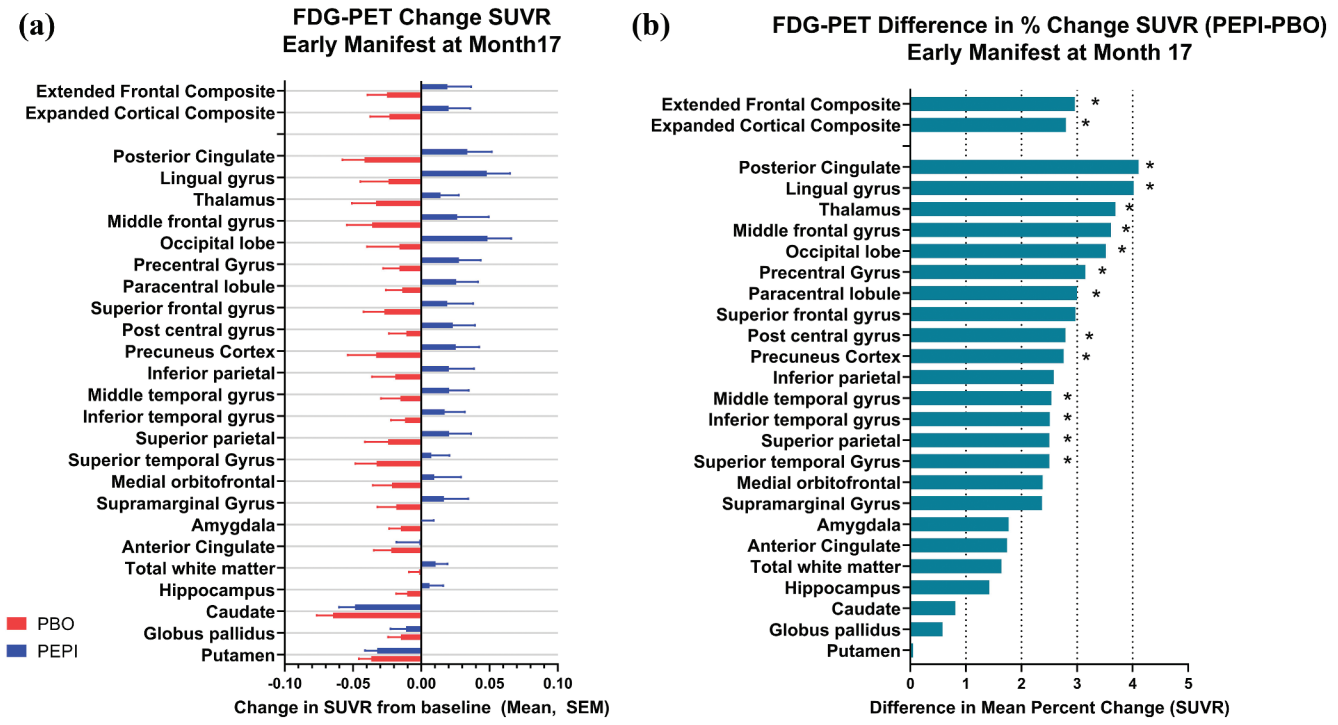

Figure 4. Pepinemab restores loss of metabolic activity in EM subjects. (a) FDG – PET SUVR change from baseline to month 17 for each treatment group (mean, SEM) in each brain ROI for EM cohort B1. (b) Treatment effect at month 17 calculated as difference between pepinemab ($n = 40$) and placebo groups ($n = 36$) as mean percentage change in SUVR for 24 individual brain regions and 2 composite brain regions. *$p \leq 0.05$; exact two-sided p values for 15 brain regions (listed from top to bottom) are: extended frontal composite, 0.031; expanded cortical composite, 0.028; posterior cingulate, 0.008; lingual gyrus, 0.014; thalamus, 0.011; middle frontal gyrus, 0.033; occipital lobe, 0.029; precentral gyrus, 0.010, paracentral lobule, 0.014; post central gyrus, 0.028; precuneus cortex, 0.048; middle temporal gyrus, 0.044; inferior temporal gyrus, 0.033; superior parietal, 0.050; superior temporal gyrus, 0.037. Reproduced from [29] under CC-BY license.

treatment benefit with 15/26 ROI indicating a p-value <0.05 [29]. These data suggest that pepinemab prevents and/or reverses the decline in metabolic activity in the majority of brain regions evaluated, particularly in the frontal and cortical regions of patients with early manifest HD represented in Cohort B1. We did not observe a significant treatment effect in brain ROI of late prodromal patients evaluated in Cohort B2 (not shown).

Decline in FDG-PET SUVR during progression of HD and other neurodegenerative diseases has been variously attributed to reduced metabolic activity of reactive astrocytes and microglia as compared to normal physiological levels of glucose uptake and metabolism. This is a particularly appealing hypothesis in view that astrocytes are the most numerous cells in brain, and under normal homeostatic conditions, extensive interactions form between astrocytes and endothelial cells such that brain capillaries are 100% covered by normal astrocytic cytoplasmic projections that express glucose transporter and facilitate glucose uptake. When activated by damage and disease-associated signals, astrocytic cytoplasmic projections contract while expression of glucose transporters and other enzymes involved in glucose metabolism are known to be downregulated. This is, therefore, a likely contributor to metabolic decline during disease progression. In addition, extensive crosstalk between astrocytes and microglia is known to coordinate their activity and could further amplify decline in FDG-PET signal. However, it is also reasonable to expect that neurodegeneration and loss of synaptic activity impact glucose metabolism. Indeed, we consistently observed that pepinemab treatment appears to have only a relatively modest effect in preventing decline of FDG-PET signal in putamen and caudate, striatal regions that are often among the first to undergo neurodegenerative effects in HD, suggesting that early decline of FDG-PET signal in striatum is due to an independent process that may not depend on astrocyte reactivity. It is likely, therefore, that a combination of reactive gliosis and neurodegeneration in different brain regions account for the correlation between FDG-PET decline and disease progression.

3.2.3. Biomarker of astrocyte reactivity: GFAP

Glial fibrillary acidic protein (GFAP) is a biomarker that is more specifically associated with astrocyte reactivity than FDG-PET. Plasma levels of GFAP have been reported to increase with progression of disease and cognitive decline in both HD and AD [41,42]. Strikingly, as shown in Figure 5, pepinemab treatment significantly reduced plasma GFAP levels as compared to placebo at both 12 and 18 months ($p < 0.05$).

In other structural MRI imaging studies, pepinemab treatment was shown to also reduce brain atrophy and to prevent expansion of ventricular volume as compared to placebo [29]. This is further evidence that reduction of glial activation and inflammation may slow progression of pathologic features associated with the natural history of disease.

3.3. Overall pepinemab safety, tolerability, PK-PD

Pepinemab has, to date, been well-tolerated in multiple clinical trials. In the Phase 1 MS study [28] ($n = 50$), there were no

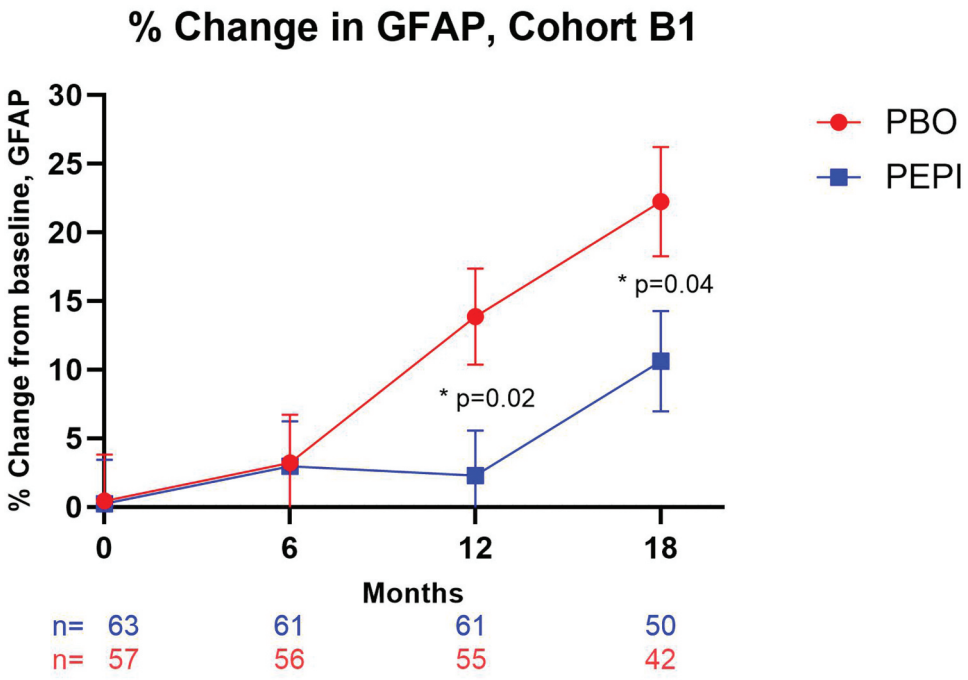

Figure 5. Pepinemab reduced GFAP increase in cohort B1; % change from baseline (ng/ml) over time was analyzed in plasma via MMRM model after adjusting for baseline value and age. *p* values represent t-tests for significant difference (PEPI-PBO) at each timepoint.

reports of treatment-related SAEs, no dose-limiting toxicities were observed, and an MTD was not determined. Immunogenicity was detected, but mainly with low titer (<100) and in the lower-level dose groups (1,3,6 mg/kg). No patients exhibited infusion reactions. In the Phase 2 SIGNAL study [29] ($n = 301$), pepinemab was well-tolerated in patients with HD, no concerning safety signals were identified, discontinuation rate was low (3%) and immunogenicity was again not a concern. Pepinemab has also been well tolerated in several oncology studies, both as a single agent in a Phase 1 trial [43] and in several Phase 1/2 immunotherapy combination trials [44].

Pepinemab half-life values measured in serum increased with dose level across the range of 1 mg/kg to 20 mg/kg, ranging from 3.9 days at the 1 mg/kg dose level to approximately 20 days at the 20 mg/kg dose level [28]. C_{max} and AUC $_{0-\infty}$ values increased linearly with increasing dose level. PK analysis of CSF from the SIGNAL study showed that pepinemab crossed the BBB at an average CSF/serum concentration ratio of 0.39%, suggesting saturating levels of pepinemab were present after repeated monthly dosing at 20 mg/kg [29]. Evidence of target engagement was also demonstrated by an increase in the concentration of antibody/soluble SEMA4D complexes in CSF post dosing, believed to be due to extended half-life of antibody/ligand complexes.

PD analysis in all trials included a flow cytometry-based assay to assess receptor occupancy ('saturation') of pepinemab bound to cellular SEMA4D (cSEMA4D) on peripheral T cells [45]. Cellular SEMA4D saturation occurred in all patients at all dose levels after a single dose and persisted for ≥155 days in the 20 mg/kg group. The minimum amount of pepinemab needed in the serum to achieve saturation was approximately 0.1 to 0.3 ug/ml and desaturation occurred as pepinemab was cleared. Cellular levels of SEMA4D expression decrease after dosing due to internalization of the pepinemab/cSEMA4D complex [7]. As expected, levels of the pepinemab/sSEMA4D complex increase in serum after dosing due to the increased half-life of the drug/soluble target complex.

Overall, throughout clinical development, pepinemab has demonstrated a favorable safety and tolerability profile and relatively consistent PK and PD parameters [46].

4. Conclusion

A neuroinflammatory response is believed to aggravate and accelerate neurodegenerative processes in HD and inflammatory mediators may represent novel therapeutic targets. In human clinical trials, pepinemab has been observed to be well-tolerated in several populations including patients with MS and HD. Furthermore, the randomized, double-blind, placebo controlled, phase 2 SIGNAL trial of pepinemab treatment in HD, demonstrated compelling evidence of improved regional brain metabolism and reduced brain atrophy over the course of 18 months treatment, as well as a strong suggestion of improved cognitive function across several domains (though the study failed to achieve statistical significance for the primary outcome measure). Given the many physiological parallels between glial activation and inflammatory processes in HD and AD, results from the SIGNAL-HD trial suggest that preventing astrocyte reactivity and reducing brain inflammation with pepinemab treatment could be an attractive alternative or complement to anti-Aβ antibodies as treatment for AD. An ongoing trial in AD will be reporting imaging and clinical results in Q3 2024 (manuscript in preparation). Positive results in this study would further support

the mechanism of action of pepinemab in progressive neurodegenerative diseases.

5. Expert opinion

Development of experimental therapeutics for HD, AD, and other neurodegenerative disorders have focused on reducing the toxic proteins associated with these disorders (e.g. mHTT in HD and Aβ and tau in AD). In HD, this focused strategy has not resulted in approved therapies. So, while these protein lowering approaches have produced some successes and certainly deserve continued attention and improvement, restoring glial health and reducing neuroinflammation may provide additional clinical benefit.

Indeed, the contribution of the SEMA/PLXN signaling pathway to activation of astrocytes and neuroinflammation represents a common therapeutic target for several slowly progressive neurodegenerative diseases. SEMA/PLXN mediated reactive astrocytes may lead to loss of normal homeostatic support functions for neurons, while pleiotropic effects, including cross-talk with microglia, may significantly contribute to inflammation-related disease pathology and dysfunction. For example, Huang et al [47] recently reported that the PLXNB1 pathway governs astrocyte and microglia crosstalk, such that cytoskeletal changes in reactive astrocytes control cell distancing in peri-amyloid plaque glial nets, which restricts microglial access to amyloid deposits. Observations from successful treatment strategies in oncology and HIV suggest that combination therapies targeting multiple discreet mechanisms may be needed to combat complicated multifaceted neurodegenerative disorders (e.g. knockdown of toxic disease-specific proteins combined with anti-inflammatory therapies common to these disorders).

Pepinemab is a first-in-class SEMA4D blocking monoclonal antibody that reduces damaging effects of neuroinflammation. Importantly, pepinemab has been found to be safe and well-tolerated; as of 16 January 2025 approximately 650 patients have been enrolled in seven Phase 1 clinical trials and six Phase 2 clinical trials of pepinemab in separate indications and no concerning safety patterns have emerged. Notably, for HD, concerns regarding potential toxicity associated with knockdown of the normal HTT allele do not apply. Furthermore, many of the potential disease modifying therapies being pursued in HD, such as RNAi and ASO's, require either neurosurgical delivery or multiple intrathecal administrations, which may involve surgical risks or risks associated with repeated lumbar punctures (e.g. meningeal inflammation, headaches). The favorable safety profile of pepinemab is also an important potential advantage in AD, given that the approved anti- Aβ therapies, lecanemab and donanemab, have demonstrated potential serious safety concerns involving bleeding and swelling of the brain known as ARIA (amyloid-related imaging abnormalities). The approval pathway in Europe for these drugs has proven to be challenging given this risk-reward balance. Furthermore, unlike protein-lowering therapeutics that require disease specificity, inhibition of the SEMA/PLXN pathway via pepinemab offers the advantage of being potentially applicable to a range of neurodegenerative diseases, including HD, AD, MS, PD, vascular dementia, and others.

A large Phase 2 trial of pepinemab in 301 early HD patients (SIGNAL) has demonstrated both biomarker and clinical evidence of benefit. Specifically, regional brain metabolism measured with FDG-PET and MRI measures of brain volume were improved in patients following 17 months of treatment with pepinemab compared to those treated with placebo. As reported herein, pepinemab also significantly reduced levels of plasma GFAP, an astrocytic protein and biomarker of reactive astrocytes and inflammation in brain diseases including HD and AD [48,49]. Sensitive assays for blood-based biomarkers are now available and represent useful objective measurements to precisely evaluate disease progression and efficacy of therapeutic interventions. In patients with HD, reactive astrocytes are strongly related to disease progression. Consistently, plasma GFAP significantly correlated with HD disease severity and clinical stages, as well as other biomarkers including neurofilament light protein [41]. In the SIGNAL study, biomarker effects were also associated with benefits on a multi-domain HD cognitive assessment battery (HD-CAB) in patients randomized to pepinemab. This and potentially consistent findings in the ongoing SIGNAL-AD trial would lend strong support to the concept that SEMA4D targeted therapies may be useful, alone or potentially in combination with disease specific therapies, in the treatment of neurodegenerative disorders.

The comprehensive data package for pepinemab warrants further clinical development and the next milestone for HD is a larger Phase 3 study. The Phase 2 SIGNAL study provided valuable insights that will guide the design of this study, although final details will be collaboratively discussed with industry partners, key opinion leaders (KOLs), patient advocacy and regulatory agencies.

First, regarding patient selection, no significant treatment effects were observed in individuals with late prodromal HD (patients that are mutant HTT gene-positive but do not yet show signs of manifest disease). In contrast, there was evidence of cognitive benefit in individuals with early manifest HD, with an even greater treatment effect in individuals with early evidence of cognitive decline (MoCA <26). Biomarker imaging endpoints supported this pattern of cognitive improvement in the early manifest HD cohort; pepinemab treatment significantly reduced caudate atrophy (volumetric MRI) and significantly increased brain metabolism (FDG-PET) in most brain regions. This suggests that an ideal population would be patients who are somewhat more advanced in disease progression, and have manifest HD as defined by DCL 4 and MoCA scores between 19–25 consistent with Mild cognitive impairment (early Integrated Staging System (ISS) Stage 3 HD). Recruitment and enrollment timelines might be improved by the inclusion of HD patients with more advanced disease, but whether these patients could benefit from pepinemab remains uncertain as patients in the SIGNAL trial had TFC > 10. Results of the AD trial of pepinemab may help to address this question.

Second, regarding the dosage of pepinemab, the 20 mg/kg Q4W dose of pepinemab demonstrated its ability to penetrate

the BBB and achieve a CSF concentration that exceeded the threshold required for biological activity (100% receptor occupancy in the periphery). The dose employed in the SIGNAL-AD study was double that used in the HD study (40 mg/kg Q4W) and proved to be well-tolerated. Consequently, the PK/PD data from both studies will be taken into consideration when selecting the final dose for a future Phase 3 HD study.

Lastly, SIGNAL HD provided important data to help select the Phase 3 clinical endpoints. The SIGNAL Cohort B study was originally designed to employ the HD-CAB composite score as a primary cognitive endpoint; however, FDA objected to use of a composite cognitive score and encouraged the sponsor to instead adopt a novel cognitive family comprised of a subset of measures from the HD-CAB as a co-primary endpoint together with a global or functional measure of clinical progression. The study was powered for the original HD-CAB composite but not for the alternative coprimary endpoints, and the overall treatment effects did not reach the critical pre-specified p-values, although the HD-CAB composite score did indeed demonstrate significant beneficial treatment effects. It is notable that in the SIGNAL trial the six items in the HD-CAB all trended toward treatment benefit to contribute to the overall statistical significance of the composite score as predicted by early HD-CAB development and validation studies [32]. Additional discussions with the FDA and other regulatory agencies will be needed to align on the final endpoints to be used to assess cognition and function. Amelioration of cognitive decline will remain a crucial foundation for establishing a primary endpoint for future clinical trials.

Pepinemab is an ideal candidate for combination therapy in HD given its safety profile and independent MOA as compared to protein-lowering approaches. However, in the absence of an HTT-lowering agent with demonstrated benefit, the Phase 3 would likely concentrate on single agent pepinemab, perhaps with the flexibility of including an HTT-lowering agent via adaptive design at a later stage of the trial. For AD, given the approval of lecanemab and donanemab, it may be possible to include a combination arm in the next trial for that indication.

Overall, pepinemab could be a promising therapeutic for a variety of neurodegenerative diseases due to its unique MOA, benign safety profile, and the demonstration of important treatment and biomarker effects in Phase 2 clinical trials.

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Declaration of interest

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