WHITE PAPER

NEFLAMAPIMOD: Targeting Basal Forebrain Cholinergic Dysfunction and Degeneration to Treat Dementia with Lewy Bodies

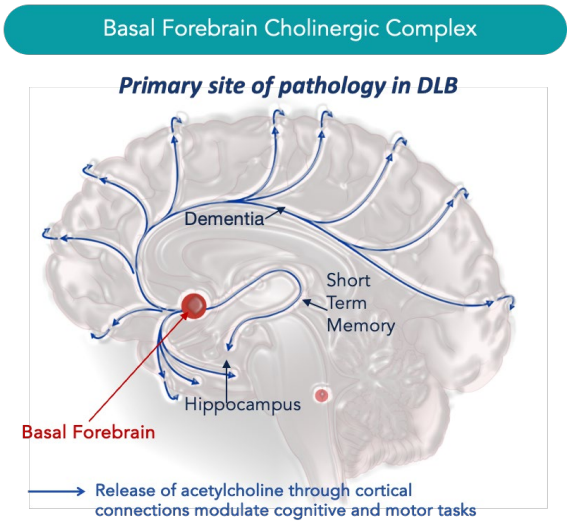
SUMMARY

Dementia with Lewy bodies (DLB) is the third most common chronic age-related degenerative disease of the brain, trailing only Alzheimer's disease (AD) and Parkinson's disease (PD). In the US, it is estimated that 700,000 individuals have DLB, representing approximately 15% of the dementia population.

DLB is a serious disease that impacts both cognitive and motor function. Patients with DLB have lower functional capacity, greater caregiver burden, and report lower quality of life than patients with AD and, also, their caregivers have higher levels of distress.

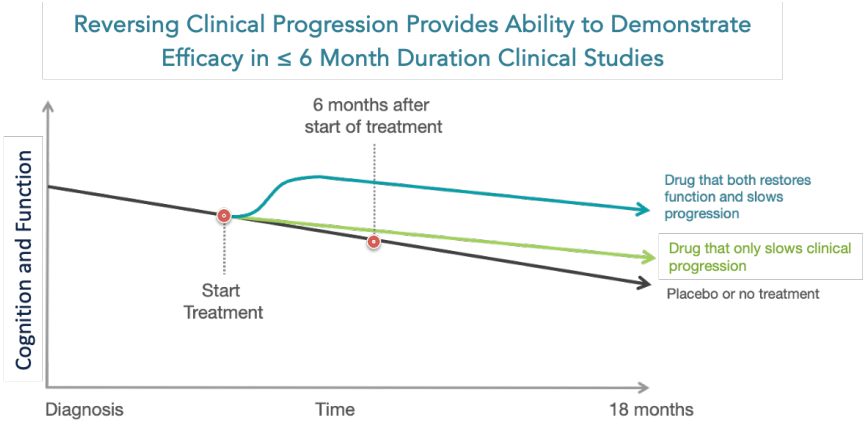
There are no disease-modifying treatments available for DLB. The primary available therapy, cholinesterase inhibitors, are not approved in this indication and only provide transient, limited improvement in cognitive function, with no effects on motor function. There is no available therapy for patients already receiving cholinesterase inhibitors.

Despite the severity of its clinical presentation, compared to that seen in AD, DLB is characterized by less cortical neurodegeneration, i.e., frank neuronal loss, particularly in the medial temporal lobe region of the brain. Pathologically DLB is characterized by atrophy, and not cell death, of the basal forebrain cholinergic system, the primary source of the neurotransmitter acetylcholine in the brain. As a result, the primary driver of clinical disease expression and progression in the early stages of disease cholinergic dysfunction and loss of synaptic terminals of the basal forebrain cholinergic neurons. In this early stage, when patients are considered to have "pure DLB", the disease is limited to the basal forebrain cholinergic system and there is limited neurodegeneration (i.e., neuronal loss), both in the basal forebrain and in the cortex, with the medial temporal lobe (i.e., the hippocampus) being particularly spared.



Accordingly, pure DLB is a disease of synaptic dysfunction in the basal forebrain cholinergic system, rather than neuronal loss, has a significant reversible component. This provides the potential for

treatments targeting the underlying disease process in the basal forebrain cholinergic system to reverse clinical disease progression and restore cognition and function. As the disease progresses, in association with the development of elevated biomarkers (e.g., plasma phosphorylated tau) of AD-related (amyloid and tau) pathology, patients develop progressive cortical neurodegeneration, including in the hippocampus, leading to fixed, less reversible, and progressive deficits. From a clinical development standpoint, the ability to reverse clinical disease progression enables demonstration of clinical efficacy with shorter duration (e.g., 3 to 6 months treatment duration) than would be required in the more advanced patient population that have AD co-pathology and hippocampal neurodegeneration.



Neflamapimod (aka, VX-745) is an oral small molecule inhibitor of p38α kinase, acting on specific pathophysiologic aspects of basal forebrain cholinergic degeneration. Based on the biological rationale and phase 2a clinical results, neflamapimod is being developed as a treatment of patients with pure DLB, i.e., those who meet the consensus criteria for DLB *and* do not exhibit biomarker and/or neuroimaging evidence of temporal lobe tau pathology.

Neflamapimod reversed pathological and clinical disease progression in an animal model (Ts2 mice) that develops a DLB-like phenotype, i.e., basal forebrain cholinergic degeneration and behavioral deficits consistent with cholinergic deficits. Specifically, in a vehicle-controlled study in Ts2 mice, neflamapimod restored the numbers of cholinergic neurons in the basal forebrain, reduced tau hyperphosphorylation, and reversed behavioral deficits that are seen in this model, i.e., the drug demonstrated effects on the underlying disease process driving cholinergic dysfunction and degeneration, the primary pathophysiologic defect in DLB. Importantly, these results are consistent with the scientific literature indicating that correcting the physiologic defect within the basal forebrain cholinergic system would have a more profound beneficial effect than would compensating for this defect with cholinesterase inhibitors.

Preliminary clinical evidence to support that neflamapimod may demonstrate substantial improvement over available therapy on clinically significant endpoint(s) is provided by findings in the AscenD-LB clinical study, an exploratory double-blind placebo controlled 16-week treatment phase 2a study in 91 patients with predominantly mild DLB receiving cholinesterase inhibitor therapy. In the trial, in the primary modified intention-to-treat population (all patients randomized with ≥ 1 efficacy endpoint evaluation), significant improvement relative to placebo was seen with neflamapimod on two clinically significant endpoints that measure distinct aspects of DLB that

represent irreversible morbidity – the Clinical Dementia Rating Scale Sum-of-Boxes (CDR-SB, measure of cognition and function) and the Timed Up and Go (TUG, measure of functional mobility) test.

Furthermore, within the AscenD-LB study, 54% of the patients did not have evidence of AD co-pathology (i.e., pre-treatment level of plasma ptau181 < the pre-specified cutoff of 2.2 pg/mL), consistent with having pure DLB. Within this pure DLB patient population being evaluated in an ongoing phase 2b clinical trial and the intended patient population for first NDA filing, the following treatment effects of neflamapimod were demonstrated:

- *Consistent with treating the underlying disease process, 16 weeks of treatment with neflamapimod led to a substantial restoration of cognition and function, with Cohen's d treatment effect size compared with placebo ≥ 0.7 on cognition & function (CDR-SB), functional mobility (TUG test), cognitive tests of attention, and working memory (International Shopping List Test, ISLT, Recognition)*. From an MMRM (Mixed Model for Repeated Measures with baseline as a covariate) analysis of the effects of neflamapimod 40mg TID (n=11) vs. the matched placebo TID (n=14) in patients with pure DLB, significant improvement over placebo with neflamapimod was seen in CDR-SB (–0.93, 95%CI:-1.61,-0.25, p=0.009, d=0.98), change in the TUG test (–3.6 sec, 95%CI:-6.1,-0.9, p<0.010, d=0.70), in cognitive tests that measure Attention (+0.46, 95%CI: 0.04–0.88, p=0.034, d=0.70), and ISLT-Recognition (+0.9, 95% CI: 0.1–1.7, p=0.035, d=1.17; there were also trends on a cognitive test battery assessing attention and executive function (p=0.12) and ISLT Immediate Recall (p=0.067).
- *Significant reduction compared with placebo in plasma levels of biomarker of the underlying disease process, glial fibrillary acidic protein (GFAP), with the effects on GFAP being correlated to the clinical outcome, as assessed by change in CDR-SB.* From baseline to week 16, in the pure DLB patients in the study there was a mean 14.1 pg/mL increase in placebo vs. mean 10.6 pg/mL reduction in neflamapimod recipients (p=0.045 for the difference). In participants treated with neflamapimod there was a significant correlation (r=0.542, p=0.036) between the effects of GFAP and clinical outcomes assessed by change from baseline to week 16 in CDR-SB, with increased GFAP being associated with worsening CDR-SB, while reduction in GFAP was associated with either no change improvement on CDR-SB. The correlation was not seen in placebo-recipients (r=0.31, p=NS).

The clinical results from patients with DLB in the AscenD-LB study, are supported by CSF and MRI data from prior phase 2 trials in biomarker-confirmed Early AD, a disease which, like DLB, is associated with cholinergic degeneration in the basal forebrain, likely by the similar pathogenic mechanisms (note: lumbar puncture and MRI studies were not performed in the AscenD-LB study):

- *In a 161-patient 24-week placebo-controlled study in CSF-biomarker confirmed patients with Early AD, neflamapimod reduced CSF levels of phosphorylated-tau and total tau, considered to be biomarkers of basal forebrain cholinergic degeneration*. Specifically, there were statistically significant effects with neflamapimod treatment, with a reduction relative to placebo, in the change from baseline to week 24 in CSF protein levels of phosphorylated tau (p-tau181, p=0.012 vs. placebo) and total tau (p=0.031 vs. placebo). Tau pathology has been shown in the scientific literature to be a downstream consequence of p38α kinase-related tau phosphorylation, and inhibition of aberrant tau phosphorylation by neflamapimod is associated with its effects on cholinergic degeneration in the Ts2 mouse model. Thus, the

effect of neflamapimod on CSF levels of ptau181 and total tau demonstrates "target engagement" within the brains of subjects, i.e., demonstrating that neflamapimod has the intended pharmacological action on the underlying disease process.

- *In a pilot, phase 2a, 12-week treatment study in Amyloid PET confirmed (PiB+) Early AD, neflamapimod increased the volume of the basal forebrain and its functional connectivity by MRI.* Basal forebrain volumetry has emerged as a very robust assessment of disease of the basal forebrain cholinergic system, with atrophy of the basal forebrain by MRI being correlated to cognition and function, as well clinical disease progression in both AD and DLB. Structural and MRI assessments were conducted at baseline and following 12 weeks of treatment with neflamapimod in 15 patients. Analysis of those MRI data that demonstrated that the volume of the NbM (nucleus basalis of Meynert, largest cholinergic cluster in the basal forebrain) was statistically significantly higher at the end of treatment [EOT, mean 3.1% (95% CI: 0.8% to 5.6%) higher vs. baseline, p=0.026]. Treatment with neflamapimod was also associated with a statistically significantly higher functional dynamic connectivity between the NbM and deep grey matter (DGM) at EOT [mean 10.8% (95% CI: 1.5% to 20.1%) higher vs. baseline, p=0.043]. As natural history studies indicate that biomarker confirmed AD patients show an approximately 2% annual decline in NbM volume by MRI, the potential regression of atrophy and recovery of function in neflamapimod-treated patients in this study suggests a neflamapimod treatment driven restoration of cholinergic neuronal health in the NbM, consistent with neflamapimod treatment having a beneficial effect on the underlying disease process in the basal forebrain cholinergic system.

Taken the together, the evidence suggests that neflamapimod treats the underlying disease process in the basal forebrain cholinergic system for the following reasons:

- The substantial effects of neflamapimod treatment across multiple, uncorrelated clinical outcomes (e.g., dementia severity, gait, attention, working memory), all assessing deficits that have been linked to the basal forebrain. For the neuropsychiatric component, the deficits (i.e., the signal) at baseline was too low to evaluate the effects of neflamapimod on this aspect of the disease in the pure DLB patient population.
- The preclinical mechanistic data showing that neflamapimod reverses atrophy and dysfunction of cholinergic neurons in the basal forebrain, while in the clinic its treatment effect is specific to DLB patients whose disease is relatively confined to the basal forebrain cholinergic system.
- The demonstrated ability of neflamapimod to decrease plasma levels of a biomarker of disease activity in DLB, glial fibrillary acidic protein (GFAP), an effect correlated to the effects to the clinical outcome, as assessed by change in CDR-SB.
- The demonstrated effects of neflamapimod on tau pathology, considered to be a major driver of cholinergic degeneration in the basal forebrain. In the clinic, neflamapimod reduced CSF levels of total tau and phosphorylated tau, the latter reported to be associated with basal forebrain atrophy by MRI (i.e., CSF phosphorylated tau may be a biomarker of cholinergic degeneration in the basal forebrain).
- The demonstrated effect of neflamapimod in patients with early AD, who develop basal forebrain cholinergic degeneration in a similar fashion as do those with DLB, to increase the

volume and functional connectivity by MRI of the nucleus basalis of Meynert (NbM), the major cholinergic nucleus in the basal forebrain.

The mechanism of action, together with preclinical and clinical findings suggest that neflamapimod through acting on the underlying disease process in the basal forebrain cholinergic system has the potential to be a transformative therapy for patients with pure DLB, a serious, rapidly progressing and devastating disease for which there is no approved therapies.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
AUC	Area Under the Curve
BFC	Basal Forebrain Cholinergic
CDR-SB	Clinical Dementia Rating-Sum Of Boxes
CSF	Cerebrospinal Fluid
DLB	Dementia with Lewy Bodies
DLB-AD	DLB with AD co-pathology
DS	Down Syndrome
LMMRM	Linear Mixed Effects Model for Repeated Measures
MAPK	Mitogen-activated protein kinase
MMSE	Mini Mental Status Examination
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental-Status Examination
NFMD	Neflamapimod
NPI	Neuropsychiatric Inventory
NTB	Neuropsychological Test Battery
PET	Positron Emission Tomography
PD	Parkinson's Disease
TUG	Timed Up and Go Test

1. INTRODUCTION

CervoMed is targeting molecular mediators of basal forebrain cholinergic neuron (BFC) neuronal health and synaptic function to develop therapeutics for age-related neurologic disorders. The latter includes multiple well known neurodegenerative diseases, including dementia with Lewy bodies (DLB), Alzheimer's disease (AD), frontal temporal dementia (FTD) and recovery after ischemic stroke.

The purpose of this document is to provide a concise, non-confidential summary of the rationale for and data supporting the development of CervoMed's lead asset, Neflamapimod (aka, VX-745), an oral small molecule, blood-brain-barrier penetrating inhibitor of p38αlpha kinase, as a treatment for DLB. Neflamapimod is currently being evaluated in a Phase 2b trial of patients in the "pure DLB" stage of the disease, i.e., patients diagnosed with DLB who do not show evidence of having developed AD-related co-pathology, as evaluated by a blood-based biomarker of such pathology, plasma ptau181, a marker of having advanced disease.

As described in the following sections, DLB as the lead indication is based on recent advancements in the understanding of the molecular mechanisms that leads to BFC system dysfunction and degeneration (see Figure 1. Timeline of published translational research that has advanced neflamapimod's potential as a disease-modifying drug for DLB. for timeline). This includes non-clinical data demonstating that neflamapimod reverses pathological disease progression in BFC neurons in a transgenic DS mouse model (Ts2 mouse) (Jiang, et. al, 2016) , and section 5 of this document]. Clinically, results from a placebo-controlled phase 2a study in patients with DLB (Study EIP19-NFD-501, aka, "The AscenD-LB study" or AscenD-LB) (Prins, et al., 2021), in which the primary objective was to evaluate the effects of neflamapimod on the cognitive domains impacted by the disease, showed outcomes consistent with a pharmacological effect on the BFC system. All these data have been detailed in translational publications in major journals including *Nature Communications* (Jiang, et al., 2022), *Neurology* (Alam, et al., 2023) and *Molecular Neurodegeneration* (Alam & Nixon, 2023), authored by members of the EIP Pharma/CervoMed team in conjunction with various academic collaborators and summarized in section 6 of this document.

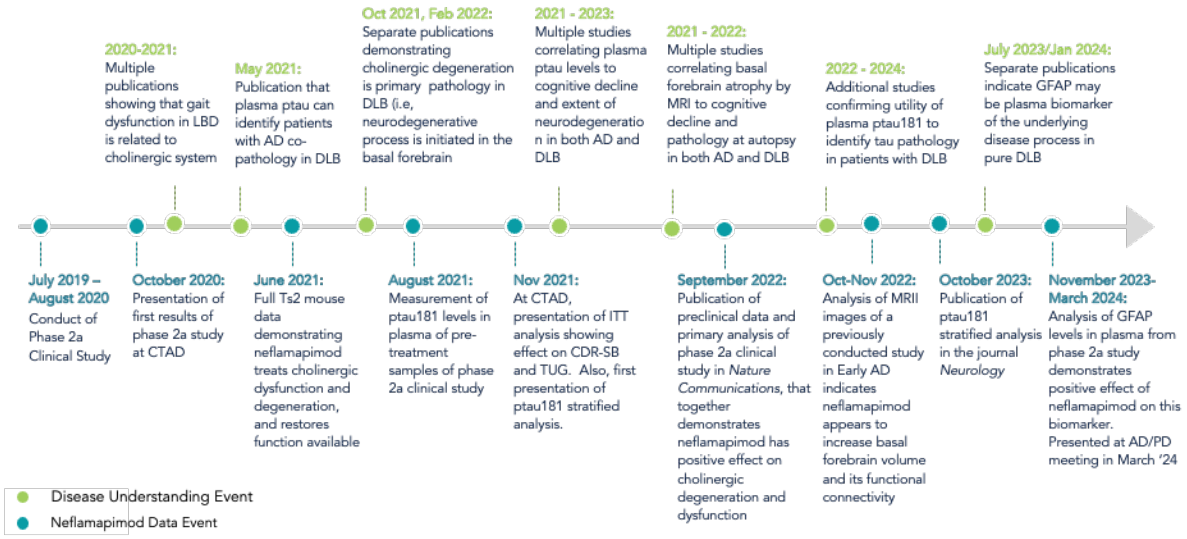


Figure 1. Timeline of published translational research that has advanced neflamapimod's potential as a disease-modifying drug for DLB.

The evidence provided in this document and the supporting publications demonstrates that neflamapimod has the potential to be a transformative therapy for patients with DLB, particularly when treatment is initated ahead of the development of AD co-pathology, i.e., when patients have pure DLB:

- *Clinically meaningful substantial restoration of cognition, function, and motor function in patients receiving cholinesterase inhibitors, observed in patients with Pure DLB in The AscenD-LB study with a treatment effect size compared to placebo ≥ 0.7 on cognition & function (CDR-SB), functional mobility (TUG), attention and working memory (International Shopping List Test, ISLT, Recognition.* Importantly, these beneficial clinical effects inherently represent improvement over currently available therapies because all the patients in The AscenD-LB study were receiving and obtaining the benefit of stable doses of the current standard of care, cholinesterase inhibitors. Further, that standard of care, has not demonstrated effects on function or motor function, while neflamapimod demonstrated positive (vs. placebo) treatment effects on the cognition and function, assessed by the CDR-SB, and motor function (specifically functional mobility), assessed by the TUG test.

- *Neflamapimod has demonstrated the potential to treat the underlying disease process in the basal forebrain cholinergic system, dysfunction of which is the primary driver of disease expression and progression in DLB, while current therapies are not intended to, and do not treat the underlying disease process.* An effect on the cholinergic degenerative disease process is clearly demonstrated in the Ts2 mouse model (see Section 5), including effects on functioning cholinergic neuron numbers and morphology, as well on tau pathology in the basal forebrain. In the clinic, neflamapimod demonstrated reduction compared to placebo of a potential biomarker of the underlying disease process in DLB, glial acidic fibrillary protein (GFAP). Notably, the treatment effects on GFAP were correlated with clinical outcomes, assessed by CDR-SB, directly supporting the thesis that the clinical effects of neflamapimod occur via its effects on the underlying disease process. In another clinical trial, though not obtained in patients with DLB (rather in patients with early AD, where basal

cholinergic degeneration is also prominent), neflamapimod demonstrated positive treatment effects on CSF biomarkers (ptau181 and total tau) associated with basal forebrain atrophy, as well on basal forebrain volume and its functional activity by MRI; further demonstrating effects of neflamapimod on the underlying disease process that leads to basal forebrain cholinergic degeneration.

Given the data obtained to date with neflamapimod, and in recognition of the potential for neflamapimod to make a difference in the lives of patients living with DLB, as well as their caregivers, CervoMed was awarded a $21M grant from the U.S. National Institute on Aging to support the trial to support a Phase 2b confirmatory proof-of-concept (POC) study was initiated in patients with pure DLB (aka, "Study 504", or RewinD-LB) from which topline data will be available during Q4 2024.

2. BASAL FOREBRAIN CHOLINERGIC SYSTEM DYSFUNCTION

The basal forebrain cholinergic (BFC) system is the primary source of cholinergic innervation to the cortex, and has been identified as a key contributor to disease expression and progression in dementia with Lewyb bodies (Grothe, et al., 2014; Duda, 2003; Schumacher, et al., 2021; Schumacher, et al., 2022). Further, BFC neuron dysfunction has been proposed as a major driver of dementia due to loss of cholinergic innervation of the hippocampus, as seen in Alzheimer's disease (Schmitz, et al., 2016; Hampel, et al., 2019; Fernandez-Cabello, et al., 2020) and also contributes to loss of motor function as evidence in Parkinson's disease (Wilson, et al., 2021; Wilkins, et al., 2020; Dalrymple, et al., 2021). Importantly, a recent neuroscience publication (Jarzebowski, et al., 2021) indicates correcting the underlying pathologic defect within the BFC neuron function though leading to physiologic pulsatile acetylcholine release would be expected to lead to substantially greater benefit than the cholinesterase inhbitors, which attempt to compensate for reduced physiologic release by decreasing the clearance in the synapse of residually released acetylcholine.

Nerve growth factor (NGF) is required for cholinergic neuron survival and proper function (Counts & Mufson, 2005). At a high level, NGF is secreted by the target cells of BFC neurons, binds to its cognate receptor tyrosine kinase, TrkA, on the BFC neuron axonal terminal, and this NGF-TrkA complex is then taken up into the BFC neurons via endocytosis into Rab5 (Ras analog in brain, a guanosine triphosphatase or 'GTPase')-positive early endosomes (Bucci, et al., 2014). Depending on numerous intra- and extracellular factors, these internalized NGF-TrkA complex-containing Rab5-positive early endosomes can mature and be degraded by the endolysosomal pathway or retrogradely transported along the considerable distance of the BFC neuron axons to the nucleus where it is involved in transcriptional regulation required for proper function and survival of of the neuron (Counts & Mufson, 2005; Bucci, et al., 2014; Nixon, 2017). Given the significant complexity of the process, the retrograde translocation of NGF along the BFC neurons' long axonal projections to the cortex is particularly vulnerable to disruption.

Rab5 has been identified as a master signaling molecule that regulates endocytosis and endosomal transport and function in neurons and other cell types. Both Rab5 hyper-activation and lowered endosome recycling rates impair NGF signaling, due at least in part to enlargement of endosomes, which slows or impedes their retrograde transport and trophic signaling (Kim, et al., 2015; Salehi, et al., 2000). This effect has been shown to result in cholinergic atrophy in Down syndrome (DS) mouse models (Holtzman, et al., 1996; Kim, et al., 2015; Salehi, et al., 2000; Cataldo, et al., 2008),

which recapitulate adult-onset BFC neurodegeneration (Jiang, et al., 2016). Further, Rab5 hyperactivation in vivo in Rab5 overexpressing transgenic mice causes BFC neuron degeneration (Jiang, et al., 2016). These findings have established Rab5 as a therapeutic target for BFC neuron dysfunction.

Importantly, results from the aforementioned animal studies indicate that the degeneration of BFC neurons is reversible, as the loss of cholinergic phenotype and functional properties can be reversed by direct NGF infusion to the basal forebrain (Cooper, et al., 2001; Chen & Mobley, 2019). Thus, pharmacologically restoring NGF signaling, by targeting Rab5, has the potential to provide symptomatic benefit as well as reverse disease progression by increasing the numbers of functional BFC neurons. This therapeutic hypothesis has led to CervoMed's development of the alpha isoform of p38 MAPkinase (p38α) inhibitor, neflamapimod (NFMD) (Alam, 2015; Alam, et al., 2017; Prins, et al., 2021), as a pharmacological approach to treating diseases associated with Rab5-mediated BFC neuron dysfunction.

The molecular biology of p38α signalling and its potential as a pharmacologic target capable of modulating Rab5-mediated neurodegeneration are detailed in a comprehensive review article published by members of the CervoMed team (Germann & Alam, 2020). In summary, p38α has been long understood as a key upstream regulator of both basal and pathologically-induced activity of Rab5 and its effectors. p38α expression in neurons is associated with formation of pathological Aβ-, inflammation- (e.g., IL-1β) and tau-induced impairment of synaptic plasticity as well dendritic spine loss (Lynch, 2010; Li, et al., 2011; Birnbaum, et al., 2015; Koppensteiner, et al., 2016; Bhaskar, et al., 2010). Furthermore, studies in animal models driven by these molecular mechanisms of pathology indicate that spatial learning and working memory deficits can be reversed using small molecule inhibitors of p38α kinase activity (Alam J. , 2015; Roy, et al., 2015; Maphis, et al., 2016).

A summarized in Section 5 of this document, members of the CervoMed team and our academic collaborators have published data providing direct evidence that the therapeutic effects of p38α inhibition are mediated via Rab5 (Alam, et al., 2017; Jiang, et al., 2019), including studies in which inhibition of p38α with neflamapimod blocked Rab5 overactivation (Alam, et al., 2017; Duffy, et al., 2011), reversing Rab5-positive-endosomal enlargement and cholinergic neurodegeneration in a mouse model of DS (Ts2) as effectively as reducing APP-β-CTF levels (Jiang, et al., 2016).

Taken together these data suggest that normalizing dysregulated Rab5 activity via inhibition of p38α is a viable therapeutic target for the modification of the early stages of the neurodegenerative disease process.

3. DEMENTIA WITH LEWY BODIES

DLB is the third most common chronic age-related degenerative disease of the brain, trailing only AD and PD. In the US, it is estimated that 700,000 individuals have DLB, representing approximately 15% of the dementia population (Karantzoullis & Galvin, 2013; Outeiro, et al., 2019; Surendranathan, et al., 2020).

DLB is characterized by progressive dementia and fluctuating cognition (particularly deficits in attention), visual hallucination, motor dysfunction (disturbances in gait and balance), and sleep disturbances. Having both cognitive and motor deficits (McKeith, et al., 2006; Fritz, et al., 2016),

as well as the neuropsychiatric component, patients with DLB have lower functional capacity, greater caregiver burden and distress, and report lower quality of life than patients with Alzheimer's disease (AD) (Karantzoullis & Galvin, 2013; Mueller, et al., 2017). In addition, people with DLB progress from mild to severe dementia more rapidly than people with AD, with nursing home admission occurring nearly two years earlier in DLB than in AD (Rongve, et al., 2013), and the median survival is approximately half that for AD patients (3.7 years for DLB, 7.0 for AD) (Price, et al., 2017).

There are no disease-modifying treatments available for DLB, so current management focuses on relief of symptoms, including its cognitive and functional (e.g., parkinsonian bradykinesia) manifestations. Further, the therapies that are utilized for symptom management in DLB are the cholinesterase inhibitors (e.g., donepezil, rivastigmine), which are not approved for use in DLB, though they are approved for treatment of AD, and in the case of rivastigmine, also for Parkinson's disease dementia.

The cholinesterase inhibitors represent the current standard of care and lead to limited improvement in cognition (Tahami Monfared, et al., 2020). However, cholinesterase inhibitors do not, are and are not intended to treat the underlying disease process, and even the limited benefits are transient. In addition, they have been evaluated for effects on motor function in DLB and have not demonstrated any effects (Matsunaga, et al., 2015; Tahami Monfared, et al., 2020). As a result, despite the availability of cholinesterase inhibitor therapy there is substantial unmet medical need in DLB.

Another type of therapy occasionally used in DLB patients are dopaminergic medications that some patients receive for their parkinsonism. However, in contrast to patients with PD, who generally have a sustained beneficial response to dopaminergic medications such as carbidopa/levodopa, patients with DLB are dose-limited due to side effects of confusion and hallucinations and often have a limited response to such medications (Gomperts, 2016). This is consistent with the fact that DLB is a disease of cholinergic neurons and not dopaminergic neurons. In fact, in the PD population while some aspects of gait are improved with dopaminergic medications, gait variability and balance tend to be resistant to dopaminergic therapy (Wilson, et al., 2021; Wilkins, et al., 2020), an observation that is consistent with the fact that balance and quality of gait are related to the cholinergic system rather than the dopaminergic system. Therefore, dopaminergic therapies do not constitute available therapy for patients with DLB.

From a pathogenesis standpoint, at disease inception and through the early and mid-stages of its course, DLB is primarily a disease of the BFC system (Schumacher, et al., 2021; Ferreira, et al., 2022) which is the primary source of the neurotransmitter acetyl choline in the brain. This system has long been known to modulate a range of cognitive tasks, particularly around attention and memory, but is increasingly understood to play a major role in the control of voluntary movement (e.g., gait). Dysfunction and loss of cholinergic neurons is more prominent in the basal forebrain in DLB (Grothe, et al., 2014) compared to AD, where neuronal loss is more focused in the hippocampus. Importantly, the disease in the basal forebrain is due to pre-synaptic alpha-synuclein toxicity that leads to cholinergic synaptic dysfunction and degeneration (i.e., synaptic terminal loss) (Okkels, et al., 2023; Frigerio, et al., 2024).

An extensive literature exists that demonstrates that the disease in the cholinergic system is reversible. This was shown very clearly in animals, and good evidence indicates it is likely true in patients as well (Mufson, et al., 2003). As the disease advances, degeneration of cholinergic neurons leads to loss of cholinergic neuron input to the cortex, including and particularly in the

medial temporal lobe (including specifically in the hippocampus). Ahead of, or coincident with, development of medial temporal atrophy and hippocampal neurodegeneration patients develop biomarker evidence of amyloid and/or tau pathology (Abdelnour, et al., 2020), including elevation of plasma phosphorylated tau levels (Hall, et al., 2021). Based on autopsy studies, this cortical atrophy is only seen in patients who also have AD-like neuropathologic changes (Hansen, et al., 1998) with increase in plasma phosphorylated tau levels correlating with disease progression, cognitive decline, AD co-pathology (particularly tau pathology) and neurodegeneration (Gonzalez, et al., 2022). The elevation of biomarkers of AD co-pathology (i.e., biomarkers of both amyloid and tau) is seen in 40-50% of patients (Alam & Nixon, 2023).

As shown in Figure 2, the DLB patient population broadly includes two distinct populations of roughly equal size: (1) patients with pure DLB, whose disease is limited to the BFC system and therefore have a reversible component of disease; and (2) patients with DLB with biomarker evidence of AD (i.e., patients with DLB-AD), who have extensive neurodegeneration in the medial temporal lobe (including an particularly within the hippocampus) and therefore have primarily fixed, or less reversible disease. Importantly, from a clinical development standpoint, the ability to reverse clinical disease progression in patients with pure DLB provides the ability to demonstrate clinical efficacy in the DLB population with shorter treatment durations (e.g., 3 to 6 months treatment duration) than would be required in the more advanced patient population who have AD co-pathology and evidence of hippocampal neurodegeneration.

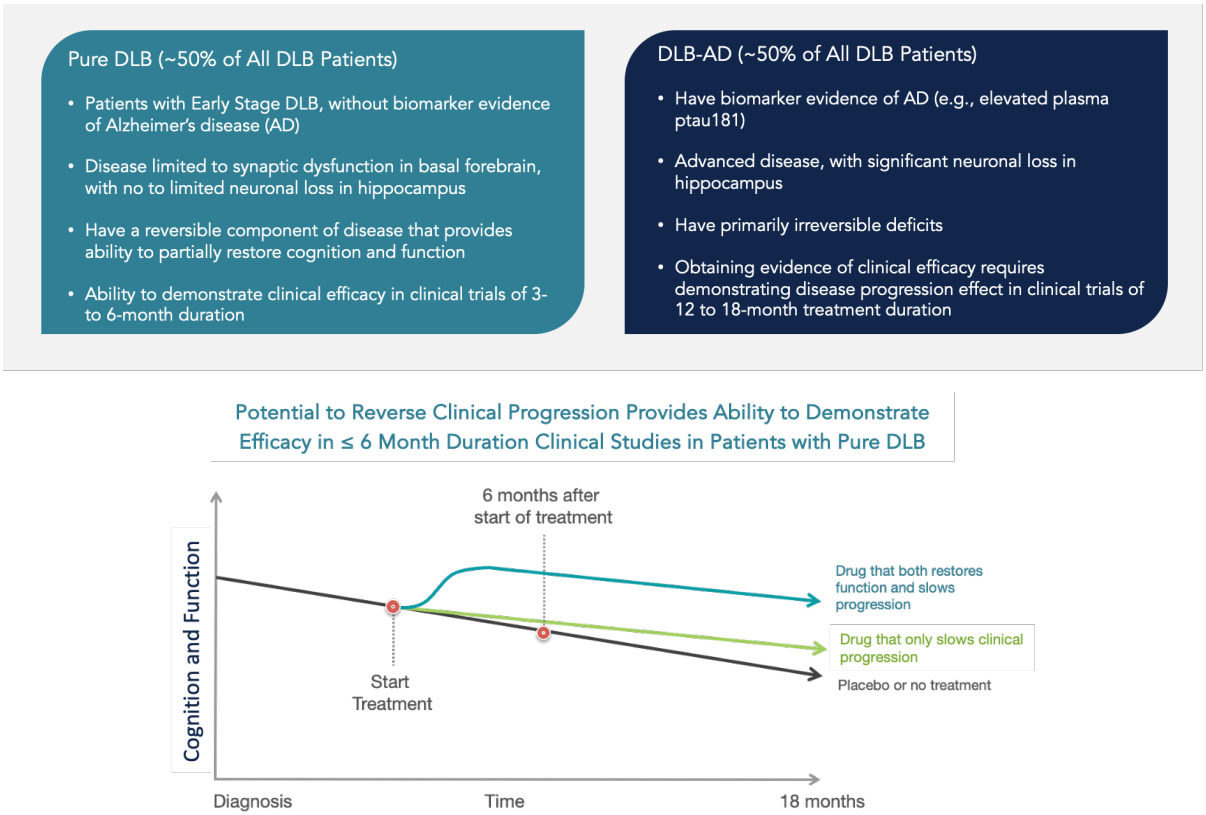


Figure 2. Distinctions Between "Pure DLB" and "DLB-AD".

The ability to target reversal of BFC neuron dysfunction and consequently clinical disease progression in patients without biomarker-based evidence of AD co-pathology enables demonstration of clinical efficacy with shorter duration clinical trials (e.g., 3 to 6 months treatment duration) than would be required in a more advanced patient population where AD co-pathology would be indicative of hippocampal neurodegeneration. Further, this provides the potential for the development of treatments targeting the underlying disease process in the BFC system that not only reverse clinical disease progression but also effect symptomatic improvement through the restoration of cognition and function, a key set of outcomes for patients and care-givers that has not previously been realized in neurodegenerative disease.

Due to evolving diagnostic criteria, first established only in 1996 (with subsequent revisions in 2005 and 2017), there are a limited number of prevalence and incidence studies for DLB in the literature, and none utilizing the 2017 diagnostic criteria. Approximately 5% of dementia cases are diagnosed to be DLB (Surendranathan, et al., 2020; Vann Jones & O'Brien, 2013; Walker, et al., 2015), while 7.5% of dementia cases diagnosed in secondary care are diagnosed as DLB (Vann Jones & O'Brien, 2013); the latter reflects a more accurate diagnosis rate. These reports are likely to be underestimates as autopsy studies indicate 15%–20% of dementia is due to DLB (Surendranathan, et al., 2020) and the majority of these cases are not diagnosed in-life to be DLB. Consistent with that assertion, in a recent publication applying all available clinical and imaging technologies with machine-learning based diagnostic algorithms, approximately 15% of all dementia was found to be due to DLB (Tolonen, et al., 2018). Applying this 15% rate to the estimated 5 million individuals living with dementia in the US suggests there are upwards of 750,000 people in the US who have DLB, as noted at the beginning of this section.

With respect to life expectancy, in a large cohort of DLB and AD cases (251 DLB, 222 AD), after controlling for age at diagnosis, comorbidity, and antipsychotic prescribing, the median survival for DLB was 3.3 years (95% CI 2.88 to 3.83) for males and 4.0 years (95% CI 3.55 to 5.00) for females, while that for AD was 6.7 years (95% CI 5.27 to 8.51) for males and 7.0 years (95% CI 5.92 to 8.73) for females (Price, et al., 2017). The authors concluded that "the survival from first presentation with cognitive impairment was markedly shorter in DLB compared with AD".

Separate from survival and progression to severe disease, even in the mild-to-moderate stages, the disease burden with respect to quality of life and caregiver burden, is greater in DLB than in AD (McKeith, et al., 2006; Mueller, et al., 2017; van de Beek, et al., 2021). Furthermore, patients with DLB are more frequently admitted to general hospitals and utilize inpatient care to a substantially higher degree than do those with AD or the general elderly population (Mueller, et al., 2018). Most importantly, in a large prospective study, mild dementia patients with DLB were admitted to a nursing home after only a median of 1.8 years from presentation and diagnosis, nearly 2 years shorter than the 3.7 years in the AD group (Rongve, et al., 2013).

Regarding the pure DLB patient population, while they have less advanced disease than those with DLB-AD, by definition, they have dementia, i.e., progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities (McKeith, et al., 2017). In addition, DLB disease progression invariably results in disease progressing in terms of hippocampal neurodegeneration (Ferreira, et al., 2022).

4. NEFLAMAPIMOD

As previously noted, neflamapimod (aka, VX-745) is an oral small molecule, blood-brain-barrier penetrating, highly specific ATP-competitive inhibitor of the intracellular enzyme p38 mitogen activated protein kinase alpha (p38α).

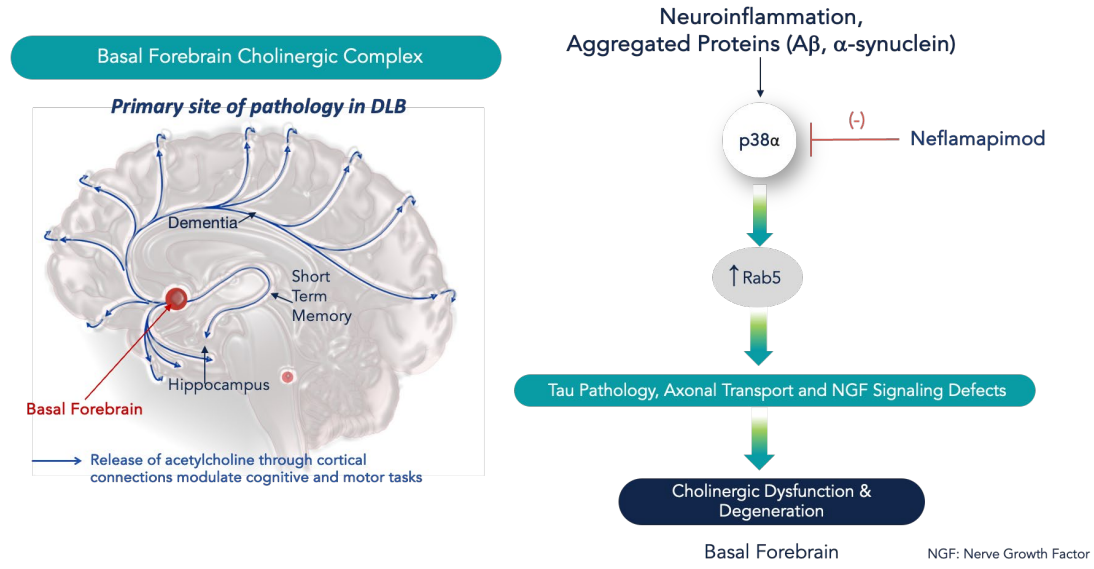
The conceptual framework for the action of neflamapimod in DLB is unique and novel based on it therapeutically targeting the pathogenic mechanisms underlying cholinergic neuronal dysfunction and loss in the basal forebrain (Alam & Nixon, 2021). Preclinical studies have shown that neflamapimod acts on specific mechanisms related to cholinergic dysfunction (*i.e.,* aberrant Rab5 activation, leading to defective endosomal signaling). *In vivo*, in a robust animal model of BFC neurodegeneration, the Ts2 transgenic mouse, neflamapimod reduced Rab5 activity and significantly increased the number of functioning cholinergic neurons to levels seen in wild-type (non-diseased) mice, demonstrating its potential to modify the underlying disease process in a relevant animal disease model (see Section 5 for more information).

Neflamapimod has been administered to greater than 300 clinical study participants, at doses up to 1500mg BID for 10 days, 750mg BID for four weeks, and 250mg BID for 12 weeks. The AscenD-LB study was the first study of neflamapimod in patients with DLB. It was a 91-patient, 16-week, double-blind placebo-controlled phase 2a clinical study in patients with probable DLB as defined by the 2017 consensus criteria (McKeith, et al., 2017) [dementia, with at least one core clinical feature of DLB and demonstrated abnormality in dopamine uptake by DaTscan™ (Ioflupane I123 SPECT)], receiving cholinesterase inhibitor therapy (>3 months, stable dose for >6 weeks), and having a Mini-Mental Status Examination (MMSE) score between 16 and 28.

Prior to the conduct of a Phase 2a clinical trial in patients with DLB, neflamapimod was evaluated in three studies in Early AD, two pilot phase 2a studies of 6- and 12-weeks duration, respectively, and a 24-week placebo-controlled study; the latter demonstrating target engagement, with significant reduction vs. placebo of CSF levels of total tau and ptau.

5. PRE-CLINICAL DATA SUPPORTING USE OF NEFLAMAPIMOD TO TREAT DLB

The animal pharmacology results obtained with neflamapimod, to date, provide evidence of its activity against specific pathophysiologic aspects of DLB regarded as the most important drivers of disease expression. These are, specifically, synaptic dysfunction and degeneration in the cholinergic neuronal system of the basal forebrain, the brain region considered to underlie the dementia in DLB (Ferreira, et al., 2022). As noted in Section 2, the mechanistic rationale for the activity of neflamapimod in protecting BFC neurons has been reviewed (Germann & Alam, 2020; Alam & Nixon, 2021; Alam & Nixon, 2023); a rationale that is based on p38α being an activator of a protein called Rab5, while aberrant activation of Rab5 plays a critical role in cholinergic dysfunction and degeneration (Pensalfini, et al., 2020). Towards the mechanism of action depicted in Figure 3, neflamapimod through inhibiting p38α kinase activity reduces Rab5 activity to reverse defects in axonal transport and nerve growth factor (NGF) signalling that lead to cholinergic dysfunction and degeneration (Alam & Nixon, 2023; Jiang, et al., 2022).



Alam & Nixon, *Molecular Neurodegeneration, 2023;* Jiang et al, *Nature Communications*, 2022

Figure 3. Mechanism of Action of Neflamapimod with Respect to Cholinergic Degeneration.

To address its ability to inhibit the progression of cholinergic degeneration in the basal forebrain, neflamapimod was tested in Ts2 transgenic mouse model, which develop basal forebrain cholinergic degeneration. This pathology is particularly relevant to DLB, as it is a disease of forebrain cholinergic neuronal dysfunction and loss (Grothe, et al., 2014).

Ts2 mice were treated with either neflamapimod (3 mg/kg, twice per day (BID) or vehicle by oral gavage for 28 days, beginning at ~ 6 months of age, by which time cholinergic neuronal loss and endosomal pathology has already developed. At the end of the treatment period, the Ts2 mice had a significant 30% reduction in the number of choline acetyltransferase positive (ChAT+) neurons in the basal forebrain compared to in wild-type (2N, healthy) mice. Neflamapimod treatment significantly increased the number of functioning cholinergic neuron counts in the basal forebrain to levels comparable to those in wildtype mice. In addition, ChAT-positive neurons exhibited a more normal morphology in neflamapimod-treated mice compared with those in vehicle-treated mice (see Figure 4). These findings were conducted in the laboratory of Prof. Ralph Nixon at NYU Langone Medical Center and have been published in a high impact factor journal (Jiang, et al., 2022).

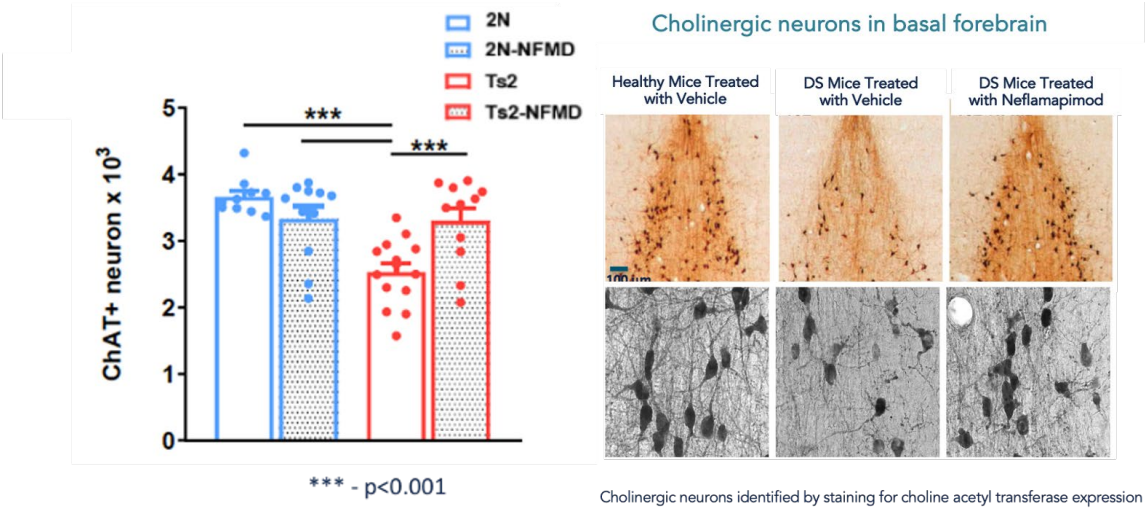


Figure 4. Neflamapimod restores numbers and morphology of cholinergic neurons in basal forebrain (i.e., reverses disease progression) in Ts2 transgenic mouse.

Figure Notes: Quantitated numbers of cholinergic neurons and morphology, as assessed after staining positive for choline-acetyltransferase (ChAT+) in the medial septal nucleus of the basal forebrain, in healthy wild-type ("2N") or Ts2 transgenic mice after treatment for four weeks with either vehicle or neflamapimod (NFMD) 3 mg/kg BID via oral gavage.

The finding of restoration of cholinergic neuron numbers (i.e., reversal of disease progression) is consistent with animal studies, as well as studies of early AD pathology samples (Mufson, et al., 2003) that show the apparent "degeneration" and loss of BFC neurons does not reflect cell death; rather, there is a loss of cholinergic phenotype and functional properties, and neuronal shrinkage, all of which can be reversed with direct infusion of nerve growth factor to the basal forebrain (Cooper, et al., 2001; Niewiadomska, et al., 2002). There is also evidence from studies in early AD, that cholinergic phenotype loss, rather than frank neuronal death and loss, occurs in the basal forebrain of humans as well (Mufson, et al., 2003).

To further understand the impact of neflamapimod on the underlying disease process, the Nixon lab also evaluated the effects of neflamapimod on tau phosphorylation in the medial septal nucleus of the mice in the Ts2 mouse study. This analysis was conducted because tau pathology, specifically pathologically phosphorylated tau, is considered to play a critical role in the pathogenesis of basal forebrain cholinergic degeneration (Geula, et al., 2021). As shown in Figure 5, from quantitation of western blot analysis of protein levels, neflamapimod treatment leads to a significant reduction compared to vehicle treatment in total tau protein levels and in levels of tau phosphorylated at the pathologic epitope, serine 202. Along with providing mechanistic insight on the effects of neflamapimod, these result provide the rationale for measuring effects on total tau and phosphorylated tau as a biomarker in clinical studies to demonstrate both that neflamapimod has the intended pharmacological effect in humans and that neflamapimod impacts the underlying disease process in patients.

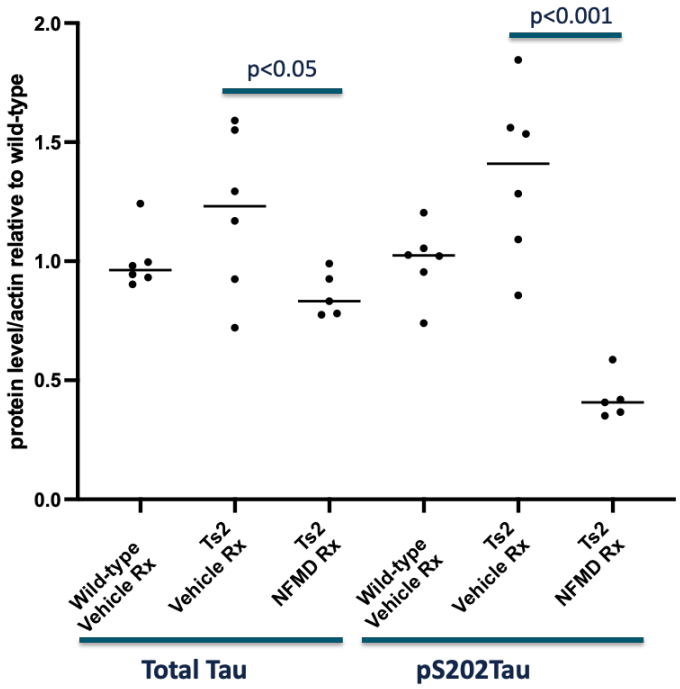


Figure 5. Neflampimod reduces total tau and phosphorylate tau levels in Ts2 Mice.

Figure Notes: Quantitation of western blot analysis for total tau and tau phosphorylated at serine 202 (pS202Tau) in medial septal nucleus of vehicle treated wild-type and Ts2 mice treated with either vehicle or neflamapimod (NFMD) 3 mg/kg BID for one month. Protein levels normalized to mean level in wild-type mice is shown. Neflamapimod treatment of Ts2 mice significantly reduced total tau levels ($p<0.05$ vs. vehicle) and levels of pS202Tau ($p<0.001$ vs. vehicle).

Along with the pathologic effects, neflamapimod treatment led to reversal of deficits in the Novel Object Recognition (NOR) and the Open Field Test tests which were performed in a separate group of animals (Figure 6). These behavioural tests are considered to specifically assess cholinergic function because lesions of the basal forebrain are known to result in specific deficits in these two tests.

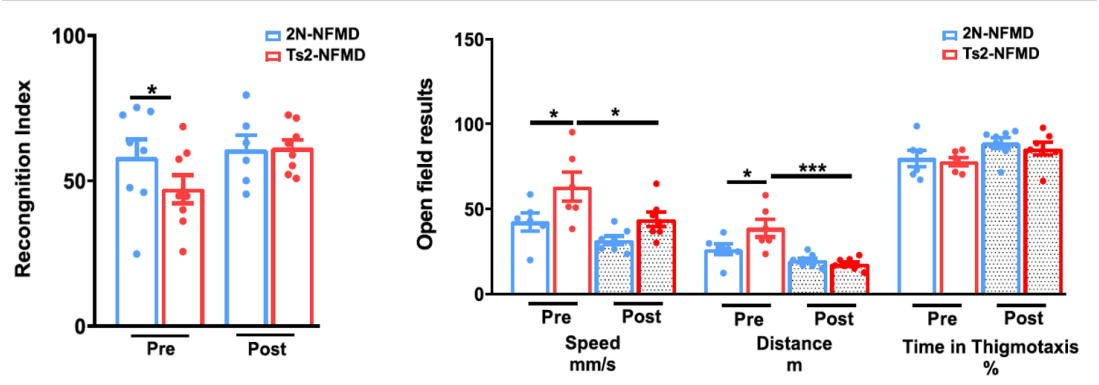


Figure 6. Novel Object Recognition (NOR) test at 24 h.

Figure Notes: Novel Object Recognition (NOR) test at 24 h after familiarization session, represented by recognition index (left panel) and Open Field Test results, including speed, distance and percentage of time in thigmotaxis (right panel), for 2N (healthy/wild-type, n = 8) and Ts2mice (n = 8) Pre and Post 4 weeks of neflamapimod (3 mg/kg BID) treatment. Statistical significance represented by asterisks *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

6. CLINICAL EVIDENCE DEMONSTRATING POTENTIAL OF NEFLAMAPIMOD TO BE A TRANSFORMATIVE THERAPY FOR DLB

Neflamapimod has been administered to greater than 300 participants, at doses up to 1500mg BID for 10 days, 750mg BID for four weeks, and 250mg BID for 12 weeks. Prior to conducting a trial in patients with DLB, neflamapimod was evaluated in three studies in Early AD, including two pilot phase 2a studies of 6- and 12-weeks duration, respectively, and a 24-week placebo-controlled study; the latter demonstrating target engagement, with significant reduction vs. placebo of CSF levels of total tau and ptau.

AscenD-LB Clinical Trial Design

Clinical evidence to support that neflamapimod may demonstrate substantial and clinically meaningful benefit is provided by the results of the AscenD-LB phase 2a study design, which was the first study of neflamapimod in patients with DLB, and thus an exploratory study.

As described in the Nature Communication paper (Jiang, et al., 2022), 91 patients were enrolled in the AscenD-LB study across 22 centers in the United States and two centers in the Netherlands (n=91; 76 in the US, 15 in the Netherlands). This was an phase 2a, double-blind placebo-controlled 16-week treatment clinical study designed to evaluate the effects of neflamapimod in patients with mild-to-moderate dementia with Lewy bodies by consensus criteria (McKeith, et al., 2017), including a positive demonstrated abnormality in dopamine uptake by DaTscan™ (Ioflupane I^{123} SPECT).

Enrolled patients were randomized to receive 40mg neflamapimod capsules or matching placebo capsules (randomized 1:1), taken at mealtime with food, for 16 weeks. All patients had to have already been receiving oral cholinesterase inhibitor therapy for at least 3 months (stable dose for greater than 6 weeks) and continued such therapy without dose modification during the study. Based on body weight, patients were assigned to either a BID [weight <80 kg; 40mg BID neflamapimod or placebo BID] or thrice-daily (TID) [weight ≥80 kg; 40mg TID neflamapimod or placebo TID] regimen. This dosing regimen was utilized because, based on available preclinical and clinical data at the time the study was initiated, the target for therapeutic efficacy was a 12-hour plasma drug exposure of 100 ng*hr/mL; and, the pharmacokinetic data available at the time predicted that 40mg BID would achieve the drug exposure target, but only in patients weighing less than 80kg (thus requiring 40mg TID in the higher weight range). In addition, the available clinical pharmacokinetic data suggested that there was an effect of weight on clearance and that a dose of 40mg TID in patients weighing <80kg would exceed the limit imposed by the US FDA through a Partial Clinical Hold on the IND which is intended to provide a ten-fold safety margin to the no-adverse-effect-level (NOAEL) observed in chronic repeat dose toxicity studies in the dog. To the latter, it is important to note that the pharmacokinetic data and a fully developed population model that became available after the AscenD-LB study was fully enrolled indicated the weight-related effect was limited to patients with weights less than 60kg, and was most prominent in patients weighing less than 50kg. As a result, the estimated plasma drug exposure with the 40mg BID dose was approximately 30% less than expected; and, as discussed below, the BID dose was ineffective

in the study. Accordingly, to evaluate the full potential of neflamapimod, the analyses presented herein for the AscenD-LB study are focused on the clinically active dose, 40mg TID, and compared to the matched (patients with weight ≥ 80kg) placebo-recipients.

The AsenD-LB was an exploratory clinical trial in that it did not have a pre-specified hypothesis for treatment effects. It was the first clinical trial of neflamapimod in DLB, and used many endpoints that had never been utilized in a therapeutic clinical trial in that disease. As such, the primary and secondary objectives of the study were to "evaluate" the effects of neflamapimod against a range of clinical endpoints in patients with DLB, and NOT to demonstrate that neflamapimod treatment significantly improved outcomes relative to placebo.

Prior to the AscenD-LB study there was no precedent for specific endpoints to be used in trials measuring the impact of disease-modifying approaches in DLB. Moreover, the disease has cognitive, motor and neuropsychiatric manifestations. Accordingly, in designing the trial we incorporated multiple measures that would evaluate potential therapeutic effects on multiple aspects the disease, with endpoints assessing cognition, cognition and function, motor function and neuropsychiatric outcomes. With the limited information available both in terms of how these endpoints would perform in DLB, as well with this being the first study of neflamapimod in DLB, a priori there was no means to know against which endpoints neflamapimod would show the most robust clinical activity. However, because there was evidence with cholinesterase inhibitors that cognitive testing could detect treatment effects in DLB, a six cognitive test Neuropsychological Test Battery (NTB) designed to evaluate deficits in attention and executive function (the deficits specific to DLB), was chosen as a primary outcome measures. Although we understood from trials in AD that CDR-SB was a validated, and clinically meaningful measure of cognition and function in dementia patients, it was not chosen as the primary endpoint because there was no published CDR-SB data from therapeutic clinical trials in DLB and longitudinal natural history CDR-SB data were published only after our study was initiated. Instead, the CDR-SB was considered an important endpoint and put as a major secondary endpoint. Secondary endpoints also included the Timed Up and Go (Test) to evaluate effects on motor function (specifically, functional mobility), the International Shopping List Test (ISLT) to evaluate effects on memory, the Mini-Mental-Status-Examination (MMSE) to evaluate effects on global cognition, and the certain domains of the Neuropsychiatric Inventory (NPI) to evaluate effects on the neuropsychiatric component of DLB.

At the time the protocol for the AsenD-LB study was written, there were preliminary data available that indicated that patients with AD co-pathology were likely to have a more aggressive clinical course, and so potentially a lower response to neflamapimod treatment. As such, the original protocol indicated that randomization would be stratified by amyloid biomarker status, based on either historical PET or CSF results (neither one of which was available in any of the patient randomized) or by screening plasma Ab42/40 result (which at the time was the most advanced blood-based biomarker in terms of validation for determining amyloid status in patients with AD). However, there was no validated commercially available Ab42/40 assay available at the time the study was conducted. Instead, the pre-treatment plasma was obtained and stored with the intent of determining AD co-pathology status once a plasma biomarker with a cut-off was available and conducting a stratified analysis utilizing such data. Of note, for both AD and DLB, in the intervening years, plasma Ab42/40 has been supplanted by plasma phosphorylated tau assays.

After the AscenD-LB study was completed, it was reported (Hall, et al., 2021) that in patients with DLB, levels of plasma phosphorylated tau, either ptau181 (tau phosphorylated at position 181, a

serine) or ptau217 (tau phosphorylated at position 217, a threonine) could be utilized to predict the presence of concomitant AD pathology, assessed by either abnormal tau PET scan in temporal cortex or abnormal CSF Aβ42 /Aβ40 ratio [area under the curve (AUC) > 0.78 and > 0.81,respectively]. In addition, plasma ptau181 or ptau231 concentrations were reported to be associated with cognitive decline in a long-term (minimum 5 years' follow-up) longitudinal cohort study in patients with DLB (Gonzalez, et al., 2022). In the latter study, similarly to the findings of Hall et al., the patients with abnormal CSF Aβ42 levels had higher plasma concentrations of both p-tau markers than did those with normal CSF levels and the AUC for plasma ptau181 predicting reduced CSF Aβ42 was 0.62.

Based on these developments in the literature regarding plasma ptau as a biomarker in patients with DLB, and on the assumption that the effects of neflamapimod would be dependent on the presence of AD co-pathology (specifically, medial temporal lobe tau pathology and/or neurodegeneration), plasma levels of ptau181 in the stored pre-treatment samples from the AscenD-LB study were determined utilizing the Simoa® HD-X platform (Quanterix) and the efficacy outcomes were analysed after stratifying patients by whether pre-treatment plasma ptau181 level was elevated above an a priori defined cut-off of 2.2 pg/mL. The cut-off 2.2 pg/mL was utilized because in an independent patient cohort it was the optimal ptau181 level to differentiate CSF biomarker-confirmed (i.e., abnormal CSF markers for both amyloid and tau pathology) AD dementia from healthy controls (Bayoumy, et al., 2021).

[Note: no cut-off data with the Simoa-based ptau181 assay in a DLB patient population was available at the time the analysis was conducted. In a more recent publication, the Simoa-based plasma ptau181 assay appears to correlate best with either tau pathology or combined amyloid and tau pathology by PET scan (Diaz-Galvan, et al., 2024), rather than amyloid pathology alone. In addition, in unpublished findings from the VU Medical Center in Amsterdam, 2.2 pg/mL as a cutoff in that assay correlates best with either tau pathology by CSF or medial temporal lobe atrophy by MRI in the Amsterdam DLB patient cohort (personal communication, Prof. Charlotte Teunissen, Amsterdam Medical Center).]

The main results of the ptau181 stratified analysis, which was based on the comparison of neflamapimod 40mg TID compared to placebo in patients with or without elevated plasma ptau181, were recently published (Alam & Nixon, 2023). In this document, we provide the results of a supplementary analysis, which is based on the comparison of neflamapimod 40mg TID with the matched, higher weight (≥ 80kg) placebo TID patients. The baseline data for this comparison, which we believe is the most appropriate for the purposes of assessing the probability of success in phase 2b, indicates that the two groups of patients were well matched at study entry (Table 1).

Table 1. Baseline Data in Patients with Pre-Treatment Plasma ptau181 < 2.2 pg/mL.

	Placebo TID (N=14)	Neflamapimod 40mg TID (N=11)
Age (y)	69.5 (5.7)	69.3 (5.5)
Male	93%	100%
CDR Sum of Boxes	4.1 (2.4)	4.3 (1.7)
MMSE	24 (4.7)	25.2 (2.2)
ISLT-Immediate	15.4 (6.9)	16.4 (4.8)
ISLT -Delayed	4.6 (2.6)	5.0 (2.4)
ISLT-Recognition	10.6 (1.4)	10.3 (1.4)
Timed Up and Go	13 (6.2)	12.8 (4.0)
NTB *z*-score	0.11 (0.82)	0.22 (0.74)
NPI-10	8.7 (8.6)	9.3 (10.2)
Fluctuating cognition	50%	45%
Visual hallucinations	64%	64%
REM sleep disorder	79%	73%
Parkinsonism	79%	82%

Neflamapimod Demonstrates Substantial Improvement Over Placebo on Multiple Clinical Outcome Measures in Patients with Pure DLB

The major clinical efficacy findings from the patients with Pure DLB included in AscenD-LB study are shown in Table 2. As per the protocol, all the endpoints were analysed as change from baseline utilizing a mixed model for repeated measures (MMRM) utilizing all time points on study (weeks 8 and 16 for CDR-SB and TUG, weeks 4, 8 and 16 for the other endpoints). That is, the analysis was conducted to evaluate neflamapimod treatment to restore function starting early in the treatment period and so included all time points on study. In contrast, if the objective had been to evaluate an effect on disease progression the analysis would have been focused on the last time point on study, i.e., at week 16 only. The results demonstrate substantial improvement with neflamapimod treatment (Cohen's *d* effect size > 0.7), compared to placebo, across multiple endpoints that collectively comprehensively assess cognition and function. Of note, consistent treatment effects of moderate to large magnitude effect size are seen on a diverse set of endpoints that utilize very different assessment approaches (e.g., structured questionnaire for CDR-SB vs. computerized cognitive tests for attention composite), and therefore would be otherwise considered to be uncorrelated. The only endpoint that did not show any difference from placebo is the ISLT delayed recall, which showed the least deficit at baseline relative to age-adjusted norms, and as a measure of episodic memory is the least specific for DLB and the cholinergic system. For CDR-SB, the endpoint that would generally be considered as most relevant clinically in patients with DLB, the magnitude of the treatment effect is large (by convention > 0.8) (Sullivan & Feinn, 2012). Furthermore, the mean difference in change of CDR-SB between neflamapimod 40mg TID and placebo TID of 0.93 points in exceeds the 0.5 points in the CDR-SB which by the nature of the CDR-SB scoring in the early stages (increases in 0.5-point increments when global CDR scores are 0.5 or 1.0) is inherently clinically meaningful (Tarawneh & Pankratz, 2024).

The findings that neflamapimod both has clinical effects not seen with cholinesterase inhibitors and provides additional benefit in relation to effects seen with such therapy is consistent with a recent report that optogenetic enhancement in mice of BFC neuron function leads to physiologic release patterns that compensate more effectively for basal forebrain cholinergic dysfunction than the continuous elevation induced by cholinesterase inhibitors (Jarzebowski, et al., 2021). While similar effect size has been reported in some clinical trials of cholinesterase inhibitors (Tahami Monfared, et al., 2020; Mori, et al., 2012), those same trials did not evaluate, and so did not report results on functional impairment (e.g., on CDR-SB) and did evaluate effects on motor function, for which the cholinesterase inhibitors proved ineffective. That is, correcting the physiologic defect within BFC neurons results in a therapeutic effect not achieved by compensating for that defect with cholinesterase inhibitors. In addition, the results we report are in patients who were already being treated with cholinesterase inhibitors, indicating the treatment with neflamapimod substantially adds to the pro-cognitive effects associated with cholinesterase inhibitors.

Table 2. Clinical Outcomes for Neflamapimod 40mg TID vs. Placebo TID in Patients with Pure DLB (pre-treatment ptau181 < 2.2 pg/mL) in The AscenD-LB study.

		Mixed Model for Repeated Measures Analysis		
Endpoint	N= NFMD 40mg TID, Placebo TID	Difference[1] (95% CI)	p-value	Cohen's d Effect size
NTB z-score	11,13	+0.25 (-0.07,0.52)	0.12	0.61
Attention z-score	11,13	+0.46 (0.04,0.88)	0.034	0.70
CDR-SB	11,14	-0.93 (-1.61, -0..25)	0.009	0.98
TUG	11,13	-3.5 (-4.7, -1.6)	0.010	0.70
ISLT Total Recall	11,14	+2.3 (-0.1,4.7)	0.063	0.66
ISLT Delayed Recall	10,13	-0.2 (-1.5, 1.1)	0.7	-0.07
ISLT- Recognition	10,21	+0.9 (0.1,1.7)	0.035	1.17

NTB – Neuropsychological Test Battery, ISLT – International Shopping List Test. Improvement reflected by negative sign for CDR-SB and TUG and positive sign for other measures.

The results obtained with the cognitive tests are less robust than those with the CDR-SB and the TUG. This finding could be because that, as compared with AD, DLB presents with disproportionately greater functional impairment for given levels of cognitive impairment (Galvin, et al., 2021). That is, in an early patient population such as those in the current analysis, there is inherently more deficit (signal) against functional endpoints compared to cognitive endpoints. Specifically, the effects on the NTB were diluted because the mean result at baseline in the overall study on two of the six cognitive tests (category fluency test and letter fluency test) was ≤ 1 standard deviation (SD) below the age-adjusted norm (i.e., effectively no deficit) and was 1.1 SD below the adjusted norm for a third test, the one-card learning test (Prins, et al., 2024) (the deficits will be even less in the pure DLB patients). In contrast, the one cognitive endpoint that demonstrated the most robust effect was ISLT recognition, a measure of working memory, which is a cognitive domain that is prominently

impacted in DLB (Calderon, et al., 2001; Kemp, et al., 2017). Consistent with that expectation, within the NTB, at baseline the mean in the test that evaluated working memory, the one back accuracy, was 2.6 SD below the age-adjusted norm.

Given the robust effects on the CDR-SB and TUG, an endpoint analysis was conducted to assess the statistical robustness of the result. The results shown in Figure 7 demonstrate significant improvement for the change from baseline to week 16 in the CDR-SB [mean (median) change 1.28 (0.5) in placebo, -0.18 (0.0) in neflamapimod 40mg TID] utilizing either a parametric (p=0.012, unpaired t-test) or non-parametric (p=0.008, Mann-Whitney test) statistical test. For the TUG, there was improvement as well, but it did not reach statistical significance (p=0.066, unpaired t-test; p-0.059, Mann-Whitney test).

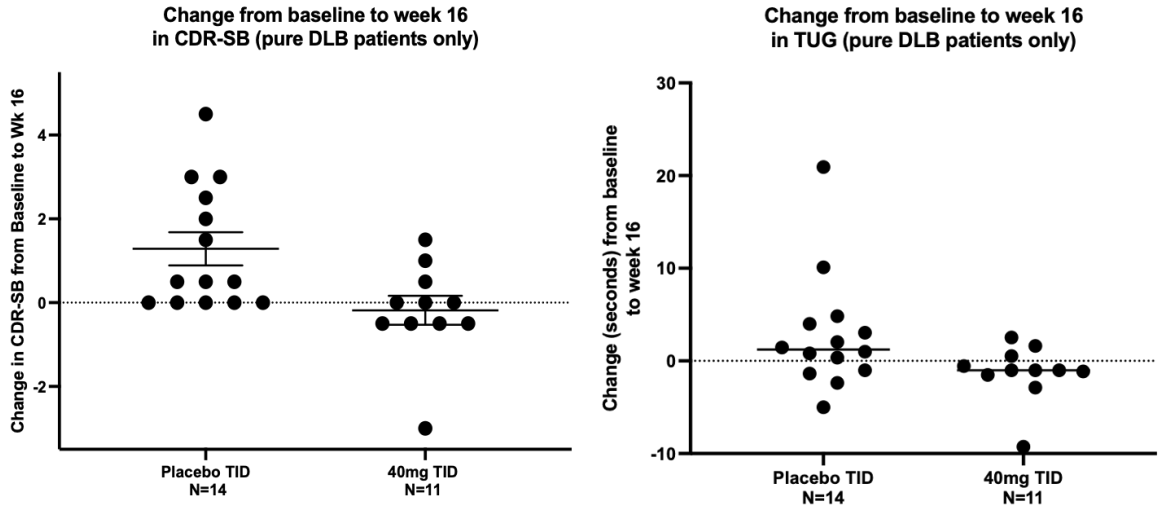


Figure 7. Change from baseline to week 16 in CDR-SB or TUG in patients with pure DLB (pre-treatment plasma ptau181 < 2.2 pg/mL.

Figure Notes: For change in CDR-SB, neflamapimod 40mg TID vs. placebo, p=0.012 (t-test) or p=0.008 (Mann-Whitney test). For change the TUG, neflamapimod 40mg TID vs. placebo, p=0.060 (t-test) or p=0.067 (Mann-Whitney test)

As noted, the above pure DLB patient-specific analysis was conducted after the study was completed, but was contemplated in the study protocol which stated that randomization would be stratified by screening amyloid status (which eventually could not be done at the time of patient enrollment because the assay was not available). Further, amyloid biomarker status was the only sub-group for stratification and analysis identified in the original protocol (i.e., AD co-pathology status was the only prospectively defined sub-group analysis). The analysis was only conducted post-hoc because the plasma assay to identify AD co-pathology was not available and validated in the literature against PET and CSF assessment of AD co-pathology until after the study was completed. In addition, the cutoff of 2.2 pg/mL was taken from the literature, based on an independent cohort of patients with AD, and was prospectively defined before the analysis was conducted. That is, the results were not based on assessing multiple cut-offs and then reporting the one that demonstrated the best result. Instead, the cut-off level, having been independently validated for CSF amyloid and tau pathology status, aligns the result with the biological rationale

for why AD co-pathology and associated hippocampal neurodegeneration would impact treatment response to agent such as neflamapimod that targets the BFC system.

The effects on cognition and function, including specifically on motor function (specifically, gait) particularly with the magnitude of the effect argues that the neflamapimod impacts the underlying disease process. Moreover, the specificity of the effect with respect to the basal forebrain (Alam & Nixon, 2023) suggests that the effect of neflamapimod is through acting on the BFC system, as demonstrated in the preclinical studies. The rationale for this argumentation is that the patients with pure DLB have disease have confined to the cholinergic system, while those with DLB-AD have, along with disease in the cholinergic system, neurodegeneration in the hippocampus. That is, because the cholinergic system only modulates hippocampal function, the prediction would be that a drug directed against cholinergic function would inherently be less effective in the DLB-AD patient population, while being very active in the pure DLB patient population.

MMRM analyses in the pure DLB patient population were conducted for all primary and secondary measures included in The AscenD-LB study, except for the MMSE and the NPI-10. MMRM analyses were not conducted for the MMSE because COVID-19 pandemic restrictions prevented many visits to the clinical research centers, resulting in more than third of on-study MMSE evaluations being missed or conducted remotely by video, an as-yet unvalidated approach (note: the CDR-SB as a semi-structured questionnaire is easily administered remotely). In addition, within the pure DLB patients, reflecting the poor sensitivity of the MMSE in the early stages of DLB (Rodriguez-Porcel, et al., 2022), the MMSE score was high (mean 24.5), which would have in any case led to ceiling effects and inability to discern treatment effects. For the NPI-10, in the overall analysis, while there were trends on certain domains (e.g., decreased hallucination severity), the overall score at baseline was low (Mean 11.0, with range of 0 to 120), as patients predominantly reported symptoms in one of only four domains (Hallucinations, Agitation/Aggression, Depression/Dysphoria, or Anxiety), with no domain being reported in more than 50% of patients at baseline. As the NPI-10 at baseline was even lower in patients (mean 9.0) with pure DLB, and were in a range considered normal (Nunes, et al., 2019), we did not believe there would be sufficient signal to evaluate treatment effects.

Neflamapimod Demonstrates Substantial Improvement Over Placebo in The AscenD-LB study on a Biomarker of DLB Disease Activity, Glial Fibrillary Acidic Protein

Plasma Glial Fibrillary Acidic Protein (GFAP), produced in astrocytes, has emerged as an important biomarker of disease activity and neurodegeneration in a range of neurologic disorders (Abdelhak, et al., 2022; Chatterjee, et al., 2023). In the dementia context, GFAP proved superior to plasma neurofilament light (NfL) and plasma ptau181 in discriminating AD dementia from healthy controls, as well MCI from healthy controls (Ally, et al., 2023). Importantly, in the same study (Ally, et al., 2023) plasma GFAP "was associated with worse dementia severity and worse performance on 11 of 12 neuropsychological tests". Further, in a separate report (Tang, et al., 2023), GFAP levels were elevated in patients with PD dementia and PD-MCI and were negatively correlated with the MMSE scores. In DLB, plasma GFAP differentiated Prodromal DLB (aka DLB-MCI) from healthy controls and was more discriminant than NfL in this context (Hamilton, et al., 2023), suggesting that GFAP is an early marker of the disease process in DLB.

Baseline and Week 16 plasma samples were available in 57 patients in The AscenD-LB study. These samples were analyzed for GFAP utilizing the Simoa platform (Quanterix, Inc.). Consistent with the scientific literature, at baseline there was a significant correlation between plasma GFAP levels and dementia severity assessed by the CDR-SB (Figure 8).

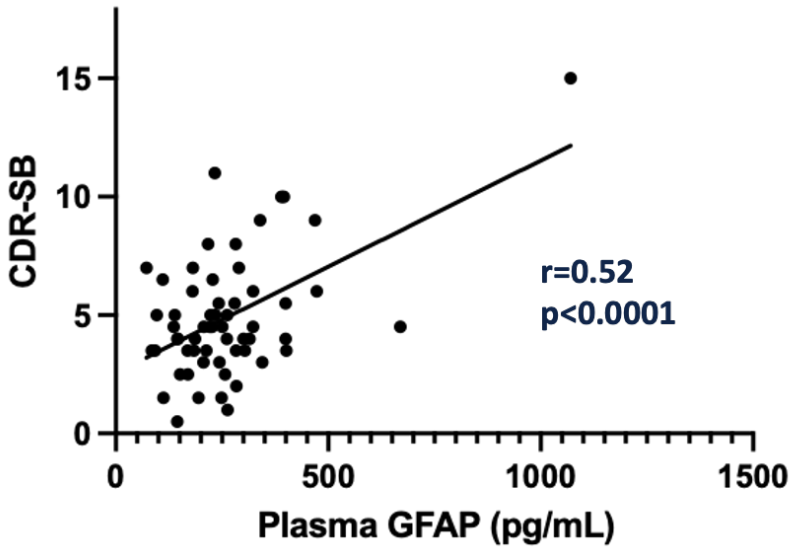


Figure 8. Baseline plasma GFAP level and CDR-SB score are correlated in The AscenD-LB study.

Figure Notes: Baseline (pre-treatment) level of plasma GFAP in patients with DLB (in The AscenD-LB study) is correlated to cognition and function, assessed by CDR-SB (r=0.52, p<0.001). The correlation remains significant (p=0.04, r=0.27) when the outlier participant with CDR-SB=15 is removed from the analysis.

On treatment, neflamapimod recipients demonstrated a trend towards reduction and significant reduction, compared to placebo, in the overall patient population and pure DLB patients, respectively (Figure 9). Specifically, in the overall population (i.e., without stratification for baseline plasma ptau181), there was a mean 3.7±7.8 pg/mL *increase* in GFAP levels from baseline to week 16 in placebo vs. mean 12.3±6.8 pg/mL *reduction* with NFMD (p=0.13 for difference). In pure DLB patients (i.e., patients with pre-treatment plasma ptau181 below the cutoff for AD-related co-pathology), there was a mean 14.1±10.2 pg/mL *increase* in placebo from baseline to week 16 vs. mean 10.6±6.4 pg/mL *reduction* with NFMD (p=0.045 for the difference).

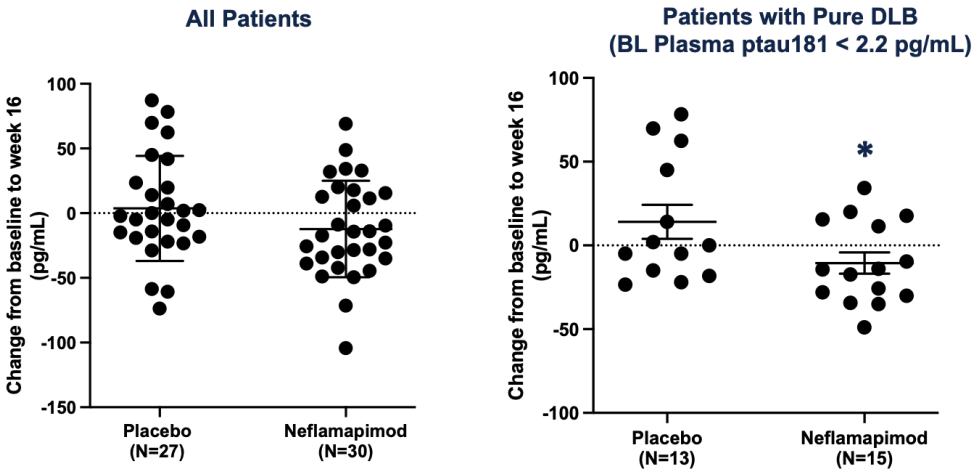


Figure 9. Neflamapimod reduces plasma GFAP levels in patients with pure DLB.

Figure Notes: Change in plasma GFAP levels from baseline to week 16 in placebo-recipients and neflamapimod-treated patients in all patients (left panel) and patients with pure DLB (right panel). * p=0.045 change in GFAP in neflamapimod-treated patients vs. placebo-recipients in patients with pure DLB (baseline plasma ptau181 < 2.2 pg/mL).

Given the correlation between baseline GFAP levels and CDR-SB, as well the literature showing an association with dementia severity/cognition with GFAP levels, the association between on-treatment effects of neflamapimod treatment on GFAP and change in CDR-SB was evaluated. As shown in Figure 10, among neflamapimod recipients with pure DLB, increased GFAP associated with worsening CDR-SB, reduction in GFAP associated with improvement on CDR-SB (r=0.542, p=0.036). The correlation was not seen in placebo-recipients with pure DLB (r=0.31, p=NS). Because correlations between biomarker and clinical effects generally require robust, high magnitude clinical efficacy, the demonstrated correlation between the effects of neflamapimod on GFAP and clinical outcome, as assessed by change in CDR-SB, further supports that neflamapimod is clinically efficacious in pure DLB. In addition, the association with a disease biomarker and clinical outcomes argues that the positive effects of neflamapimod on dementia severity (i.e., CDR-SB) are mediated by an effect on the underlying disease process.

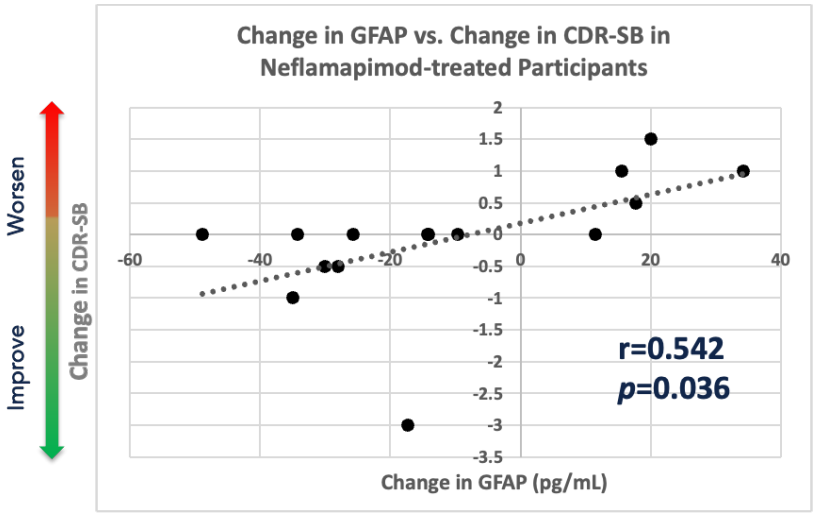


Figure 10. Change in plasma GFAP levels and change in CDR-SB are correlated.

Figure Notes: Change on-treatment in plasma GFAP is Correlated to the Clinical Outcome (Change in CDR-SB from Baseline to Week 16)

Supportive Data from Patients with Early AD

CSF and MRI studies were not obtained in The AscenD-LB study. However, such studies were obtained in clinical trials obtained previously in patients with biomarker confirmed patients with Early AD. While neurodegeneration in the hippocampus is clearly the driver of disease expression and progression in patients with AD dementia, more recent evidence indicates BFC degeneration is a major driver of disease in early AD (Schmitz, et al., 2018; Fernandez-Cabello, et al., 2020). Moreover, a range of evidence indicates that AD and DLB share common pathogenic mechanisms that lead to BFC degeneration (summarized and further referenced in (Alam & Nixon, 2023)).

Neflamapimod Demonstrated Significant Reduction on CSF levels of Biomarkers of Basal Forebrain Atrophy in Patients with Early AD

As discussed previously, tau pathology (i.e., neurofibrillary tangles) within neurons in the basal forebrain is considered to be critical in the pathogenesis of cholinergic degeneration (Geula, et al., 2021). Consistent with the role tau pathology plays in BFC degeneration, CSF levels of phosphorylated tau have been correlated to BFC atrophy by MRI (Cantero, et al., 2019). Further, in association with the positive treatment effects on the BFC system, neflamapimod treatment led to decreased total tau and phosphorylated tau (ptau202) in Ts2 mice. In addition, p38α kinase, the molecular target of neflamapimod is well understood to be a mediator of tau aggregation and phosphorylation (Chen & Yu, 2023). Combined, the literature and our preclinical data suggest that positive clinical effects of neflamapimod are mediated by an effect on the underlying disease process in the BFC and should read through as positive effects on CSF markers of tau pathology, e.g., protein levels total tau and phosphorylated tau in the forebrain.

While CSF was not collected in DLB patients in The AscenD-LB study, they were collected in EIP-VX17-745-304 (Study 304), which was a Phase 2b clinical trial in subjects with Early AD (Prins, et al., 2021). In Study 304, 161 subjects were enrolled at 38 sites in the Czech Republic (5 sites),

Denmark (3 sites), Netherlands (3 sites), United Kingdom (11 sites) and United States (16 sites) and were randomized 1:1 to receive neflamapimod 40 mg capsules or matching placebo capsules twice daily (BID) with food for 24 weeks. Inclusion criteria were as follows: men and women aged 55 to 85 years, with CDR-Global score of 0.5 or 1.0 (i.e., with mild AD); CDR memory sub-score of at least 0.5; MMSE score of 20 to 28, inclusive; positive biomarker for AD, as defined by CSF Aβ1-42 <1000 pg/mL and phospho-tau/Aβ1-42 >0.024 in the Roche Eclesys® immunoassay (which was also platform utilized to evaluate on-treatment effects).

As shown in Figure 11, in the analysis of CSF biomarkers, there were statistically significant effects of neflamapimod treatment, with a reduction relative to placebo, in the change from baseline to week 24 in CSF protein levels of phosphorylated tau (p-tau181, p=0.012 vs. placebo) and total tau (p=0.031 vs. placebo).

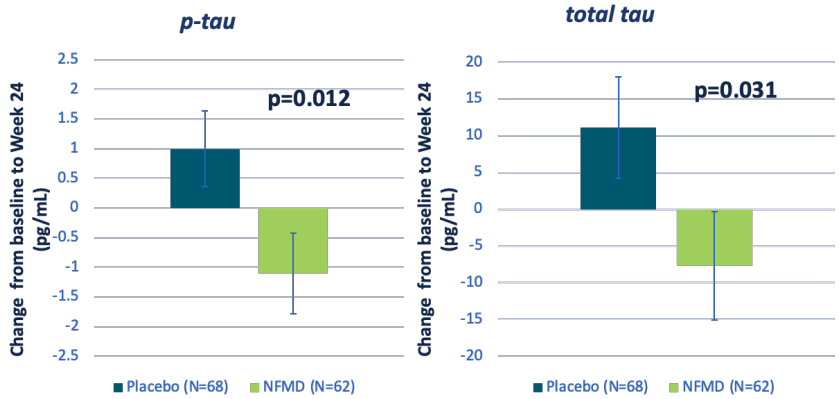


Figure 11. Neflamapimod reduces CSF levels of ptau181 and total tau, relative to placebo, after 24 weeks of treatment in patients with Early AD.

Figure Notes: Least square mean (SEM) change from baseline to week 24 in Study 304 in patients with Early AD. For ptau181,95% CI for difference: -3.6, -0.5; mean= -2.0. For total tau, 95% CI for difference: -36.0, -1.0; mean= -18.9.

With respect to the clinical outcome of this study, there was no evident difference between the neflamapimod and placebo groups in the primary clinical efficacy endpoint, the combined change from baseline to week 24 in the z-scores of HVLT (Hopkins Verbal Learning Test) of Total Recall and Delayed Recall. As a single dose of neflamapimod was utilized in the trial, pre-specified pharmacokinetic pharmacodynamic analyses were conducted to evaluate the results for potential dose-dependency. These analyses showed improvement, relative to the placebo group, in tests of episodic memory in neflamapimod-treated subjects with the highest (top quartile) trough plasma drug concentrations; with positive trends evident both for the primary endpoint (combined change in z-scores of HVLT total recall and delayed recall) and the major secondary endpoint of change in Wechsler Memory Scale Combined Immediate and Delayed Recall composites. Prior to the obtaining the The AscenD-LB study results, this analysis provided critical dose-response information as it indicated that 40mg BID was too low a dose, but that a dose of 40mg TID would achieve therapeutically effective drug concentration levels in the blood.

With the recent finding that elevated plasma ptau181 in patients with DLB (i.e., in The AscenD-LB study) is associated with lessened response to neflamapimod, in retrospect, an additional reason why a clinical effect was not evident against the primary endpoint in Study 304 is that one of the

inclusion criteria in Study 304 was elevated CSF levels of ptau181. That is, given the findings in The AscenD-LB study with respect to the impact of including patients with elevated levels of ptau181, a reasonable inference is that while neflamapimod in Study 304 demonstrated a biomarker effect that is consistent with improving BFC function, the patients could not improve clinical outcomes because the extent of neurodegeneration in the hippocampus was too far advanced.

Neflamapimod Increases the Basal Forebrain Volume and Its Functional Connectivity by MRI in Patients with Early AD

With the development and availability of analytic MRI-based techniques to evaluate potential treatment effects on the basal forebrain, the MRI images (n=15) from Study EIP-VX00-745-303, a phase 2a study in neflamapimod in patients (n=15) with amyloid PET (PiB) positive Early AD, were reanalyzed by a specialized neuroimaging group at the Amsterdam Medical Center (Lin, et al., 2022). The goal of this exploratory analysis, which was presented at the AD/PD meeting in Gothenburg, Sweden in April 2023, was to assess by MRI the treatment effects of neflamapimod on the NbM, the largest cluster of cholinergic neurons in the basal forebrain. Structural and MRI assessments had been conducted as part of the study at baseline and following 12 weeks of treatment with neflamapimod. The additional analysis demonstrated that the NbM volume was statistically significantly higher at the end of treatment [EOT, mean 3.1% (95% CI: 0.8% to 5.6%) higher vs. baseline, p=0.026], with eight of 15 subjects with greater than 3% NbM higher volume at EOT, as compared to baseline. Treatment with neflamapimod was also associated with a statistically significantly higher functional dynamic connectivity between the NbM and deep grey matter (DGM) at EOT [mean 10.8% (95% CI: 1.5% to 20.1%) higher vs. baseline, p=0.043], with six of 13 subjects showing a greater than 10% higher dynamic NbM-DGM connectivity at EOT, as compared to baseline (Figure 12). As natural history studies indicate that AD patients with elevated amyloid PET signal show an approximately 2% annual decline in NbM volume by MRI (Xia, et al., 2023), the potential regression of atrophy and recovery of function in neflamapimod-treated patients in this study suggests a neflamapimod treatment driven restoration of cholinergic neuronal health in the NbM, and are consistent with neflamapimod treatment having a beneficial effect on the underlying disease process in the BFC system.

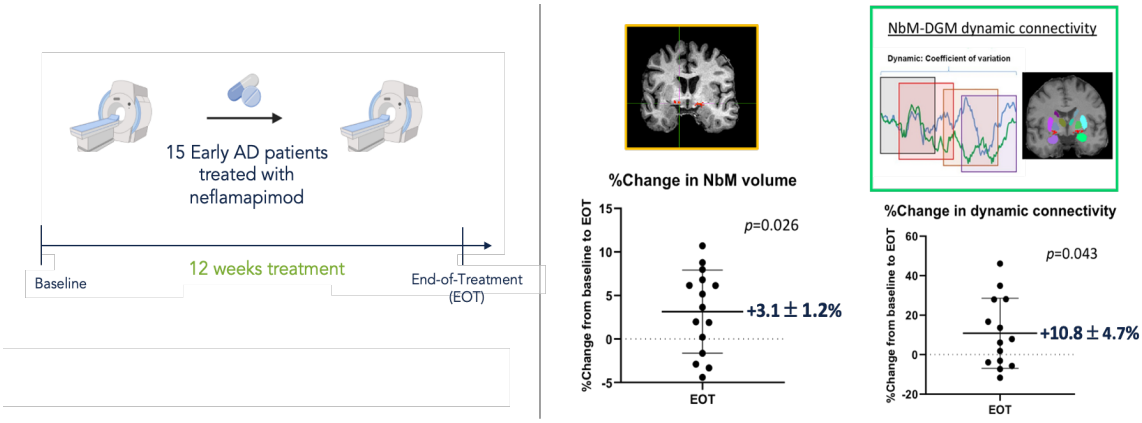


Figure 12. Neflamapimod treatment is associated with a significant increase of basal forebrain volume and functional connectivity.

Figure Notes: Structural (3D T1 Isotropic) MRI and resting-state fMRI (TR=2225, 200 volumes) were obtained at baseline and end-of-treatment (n=15 participants). In the retrospective analysis, NbM volume and functional connectivity of the NbM were assessed at Amsterdam UMC using established methods (Lin, et al., 2022).

7. SUMMARY AND CONCLUSIONS

The evidence accumulated to date, including that from The AscenD-LB study, suggests that neflamapimod treats the underlying disease process in the BFC system for the following reasons:

- The substantial effects of neflamapimod treatment across multiple, uncorrelated clinical outcomes (e.g., dementia severity, gait, attention, working memory), all assessing deficits that have been linked to the basal forebrain.
- The preclinical mechanistic data showing that neflamapimod reverses the atrophy and dysfunction of cholinergic neurons in the basal forebrain, while in the clinic its treatment effect is specific to DLB patients whose disease is relatively confined to the basal forebrain cholinergic system.
- The demonstrated ability of neflamapimod to decrease plasma levels of a biomarker of disease activity in DLB, glial fibrillary acidic protein (GFAP), an effect correlated to the effects to the clinical outcome, as assessed by change in CDR-SB.
- The demonstrated effects of neflamapimod on tau pathology, considered to be a major driver of cholinergic degeneration in the basal forebrain, while in the clinic neflamapimod reduced CSF levels of total tau and phosphorylated tau, the latter reported to be associated with basal forebrain atrophy by MRI (i.e., CSF phosphorylated tau may be a biomarker of cholinergic degeneration in the basal forebrain).
- The demonstrated effect of neflamapimod in patients with early AD, who develop BFC degeneration in a similar fashion as do those with DLB, to increase the volume and function connectivity by MRI of the nucleus basalis of Meynert (NbM), the major cholinergic nucleus in the basal forebrain.

The significant, clinically meaningful effects on function and motor function are consistent with the BFC system playing a major role in modulating the cognitive aspects of ambulation and motor tasks, as well as consistent with recent literature indicating that major aspects of the motor dysfunction are due to the same pathologic processes (i.e., cholinergic dysfunction in the basal forebrain) underlying the cognitive deficits (Wilson, et al., 2021; Dalrymple, et al., 2021).

Of note, mobility is more directly linked to functional deficits and risk of dependency than cognition. In addition, mobility and balance are associated with medically important outcomes such as falls. Impairment in the TUG test has been correlated to impairment in Activities of Daily Living (ADL) and Instrumental ADL (Donoghue, et al., 2014), and to falls (Kojima, et al., 2015; Nocera, et al., 2013), which are of significant concern in patients with DLB (Allali, et al., 2017; Allan, et al., 2009).

While the pure DLB analysis performed with the data from The AscenD-LB study was conducted post-hoc, the readers is reminded that such an analysis was contemplated in the original protocol, as the final protocol stated that randomization would be stratified by screening amyloid status (which eventually was not done because the assay did not exist at the time of patient enrollment). Further, amyloid biomarker status was the only sub-group for stratification and analysis identified in the original protocol (i.e., the AD co-pathology status was the only prospectively defined sub-group analysis). The analysis was only conducted post-hoc because the plasma assay to identify AD co-pathology was not available and validated in the literature against PET and CSF assessment of AD co-pathology until after the study was completed. In addition, the cutoff of 2.2 pg/mL was taken from the literature, based on an independent cohort of patients with AD, and was prospectively defined before the analysis was conducted. That is, the results were not based on assessing multiple cut-offs and then reporting the one that demonstrated the best result. Instead, with having been validated for CSF amyloid and tau pathology status, the cut-off level aligns the result with the biological rationale for why AD co-pathology and associated hippocampal neurodegeneration would impact treatment response to agent such as neflamapimod that targets the BFC system.

Importantly, the biologic rationale for having focused on the sub-group of patients without AD co-pathology is supported by other recently reported clinical results in DLB and AB. In DLB, the PDE9 inhibitor, irsenontrine, in a 12-week placebo-controlled phase 2 study in DLB, "amyloid negative" patients (evidenced by a high plasma Ab42/40 ratio) demonstrated a strong trend (p=0.053) towards improvement in cognition, measured using the Montreal Cognitive Assessment, while no such trends were evident in "amyloid positive" patients (Irizarry, et al., 2022). Moreover, improved outcomes in patients with low levels of tau pathology, assessed by PET scan and/or plasma ptau217, compared to this with high levels of tau pathology has been reported with the anti-amyloid antibodies, donanemab and lecanemab, in the treatment of Early AD (Mintun, et al., 2023; CTAD ALZFORUM, 2023).

It should be noted that The AscenD-LB study was an exploratory study, i.e., not a hypothesis testing study, and at the time the study was initiated, in 2019, there were no precedents to inform on the choice of clinical endpoints to assess drug effects in DLB. Many of those uncertainties remain (Sabbagh, et al., 2023), in part because the cognitive tests utilized in AD are less sensitive for use in DLB (Nelson, et al., 2009), though the underlying disease is considered as severe. As a result, there is no clear consensus on choice of primary endpoint for DLB clinical trials. Moreover, most of the mechanistic understanding on the effects of neflamapimod on cholinergic degeneration, including results of the preclinical study showing effects on tau and the cholinergic pathology, were obtained after the AscenD-LB study had begun. Indeed, the primary rationale stated in the study

was around preclinical data in aged rats and clinical data in a pilot study in AD that neflamapimod had the potential to have a pro-cognitive effect. There was also much less known about dementia with Lewy bodies in 2019, including the importance the cholinergic system in the early stages of disease [the first in-life MRI studies to demonstrate basal forebrain atrophy in early-stage disease was published after the study was completed (Schumacher, et al., 2021)]. Effectively, the program went into the AscenD-LB study with the aspiration to demonstrate an isolated symptomatic effect on cognition, while, instead, the study obtained evidence of a more profound effect on cognition and function, including an effect on gait, and preclinical and clinical (primarily biomarker) data that demonstrates that neflamapimod has the potential to treat the underlying disease process in DLB.

Taken together, the pre-clinical and clinical data in DLB suggest that neflamapimod has the potential to change the course of the disease and significantly improve function and quality of life in patients with DLB. Treatment of DLB patients with neflamapimod could potentially through the demonstrated symptomatic effect reduce caregiver burden and distress in the short run and in the long run prolong independence and reduce the risk of dependency.

8. BIBLIOGRAPHY

1. Abdelhak, A., Foschi, M., Abu-Rumeileh, S., Yue, J. K., D'Anna, L., Huss, A., . . . Tumani, H. (2022). Blood GFAP as an emerging biomarker in brain and spinal cord disorders. *Nature Reviews Neurology, 18*(3), 158-172.
2. Abdelnour, C., Ferreira, D., Oppedal, K., Cavallin, L., Bousiges, O., Wahlund, L., . . . Aarsland, D. (2020). The combined effect of amyloid-B and tau biomarkers on brain atrophy in dementia with Lewy bodies. *Neuroimage. Clinical, 27*, 102333.
3. Alam, J. (2015). Selective Brain-Targeted Antagonism of p38 MAPKα Reduces Hippocampal IL-1β Levels and Improves Morris Water Maze Performance in Aged Rats. *J Alzheimers Dis, 48*(1), 219-227.
4. Alam, J., & Nixon, R. (2021). Disease-modifying pharmacological approaches to correcting basal forebrain cholinergic neuronal (BFCN) dysfunction and degeneration. *Neuropsychopharmacology, 47*(1), 405-406.
5. Alam, J., & Nixon, R. (2023). Drug development targeting degeneration of the basal forebrain cholinergic system: its time has come. *Molecular Neurodegeneration, 18*(1).
6. Alam, J., Blackburn, K., & Patrick, D. (2017). NEFLAMAPIMOD: CLINICAL PHASE 2B-READY ORAL SMALL MOLECULE INHIBITOR OF P38? TO REVERSE SYNAPTIC DYSFUNCTION IN EARLY ALZHEIMER'S DISEASE. *J Prevention Alzheimers Dis, 4*(4), 273-278.
7. Alam, J., Jiang, Y., & Nixon, R. (2017). Antagonism of p38 MAPK Alpha (p38α) Reverses APP-Induced Endosomal Abnormalities and Improves Lysosomal Function in Down Syndrome Fibroblasts. *Alzheimer's Dement., 13*, 1496-1497.
8. Alam, J., Maruff, P., Doctrow, S., Chu, H., Conway, J., Gomperts, S., & Teunissen, C. (2023). Association of Plasma Phosphorylated Tau With the Response to Neflamapimod Treatment in Patients With Dementia With Lewy Bodies. *Neurology*, e. 1708-1717.
9. Allali, G., Launay, C., Blumen, H., Callisaya, M., De Cock, A.-M., Kressig, R., . . . Beauchet, O. (2017). *Journal of the American Medical Directors Association, 18*(4), 335-340.
10. Allan, L., Ballard, C., Rowan, E., & Kenny, R. (2009). Incidence and prediction of falls in dementia: A prospective study in older people. *PLoS ONE, 4*(5), e5521.
11. Ally, M., Sugarman, M. A., Zetterberg, H., Blennow, K., Ashton, N. J., Karikari, T. K., . . . Farre. (2023). Cross-sectional and longitudinal evaluation of plasma glial fibrillary acidic protein to detect and predict clinical syndromes of Alzheimer's disease. *Alzheimer's & Dementia, 15*(4), e12492.
12. Bayoumy, S., Verberk, I., den Dulk, B., Hussainali, Z., Zwan, M., van der Flier, W., . . . Teunissen, C. (n.d.). Clinical and analytical comparison of six Simoa assays for plasma p-tau isoforms p-tau181, p-tau217 and p-tau231. *Alzheimer's Research & Therapy, 13*(1).
13. Bhaskar, K., Konerth, M., Kokiko-Cochran, O., Cardona, A., Ransohoff, R., & Lamb, B. (2010). egulation of Tau Pathology by the Microglial fRactalkine Receptor. *Neuron, 68*, 19–31.
14. Birnbaum, J., Bali, J., Rajendran, L., Nitsch, R., & Tackenberg, C. (2015). Calcium Flux-Independent NMDA Receptor Activity is Required for Abeta Oligomer-Induced Synaptic Loss. *Cell Death Dis, 6*, e1791.
15. Bucci, C., Alifano, P., & Cogli, L. (2014). The Role of Rab Proteins in Neuronal Cells and in the Trafficking of Neurotrophin Receptors. *Membranes, 4*(4), 642-677.
16. Calderon, J., Perry, R., Erzinclioglu, S., Berrios, G., Dening, T., & Hodges, J. (2001). Perception, attention, and working memory are disproportionately impaired in dementia

with Lewy bodies compared with Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 70*(2), 157-164.

17. Cantero, J., Atienza, M., Lage, C., Zaoborszky, L., Vilaplana, E., Lopez-Garcia, S., . . . Fortea, J. (2019). Atrophy of basal forebrain initiates with tau pathology in individuals at risk for Alzheimer's disease. *Cerebral Cortex, 30*(4), 2083-2098.
18. Cataldo, A., Mathews, P., Boiteau, A., Neve, R., & Gruenberg, J. (2008). Down Syndrome Fibroblast Model of Alzheimer-Related Endosome Pathology. *Am J Pathology, 173*(2), 370-384.
19. Chatterjee, P., Vermunt, L., Gordon, B. A., Pedrini, S., Boonkamp, L., Armstrong, N. J., . . . Graff-. (2023). Plasma glial fibrillary acidic protein in autosomal dominant Alzheimer's disease: Associations with AB-PET, neurodegeneration, and cognition. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 19*(7), 2790-2804.
20. Chen, X.-Q., & Mobley, W. (2019). Chen, X. Q. & Mobley, W. C. Exploring the pathogenesis of Alzheimer Disease in basal forebrain cholinergic neurons: converging insights from alternative hypotheses. *Front. Neurosci., 13*, 446.
21. Chen, Y., & Yu, Y. (2023). Tau and neuroinflammation in Alzheimer's disease: interplay mechanisms and clinical translation. *Journal of Neuroinflammation, 20*(1).
22. Cooper, J., Salehi, A., Delcroix, J.-D., Howe, C., Belichenko, P., Chua-Couzens, J., . . . Mobley, W. (2001). Failed retrograde transport of NGF in a mouse model of Down's syndrome: reversal of cholinergic neurodegenerative phenotypes following NGF infusion. *Proc Natl Acad Sci USA, 98*(18), 10439-10444.
23. Counts, S., & Mufson, E. (2005). The role of nerve growth factor receptors in cholinergic basal forebrain degeneration in prodromal Alzheimer disease. *J Neuropathol Exp Neurol, 64*(4), 263-272.
24. Dalrymple, W., Huss, D., Blair, J., Flanigan, J., Patrie, J., Sperling, S., . . . Barrett, M. (2021). Cholinergic nucleus 4 atrophy and gait impairment in Parkinson's disease. *Journal of Neurology, 268*(1), 95-101.
25. Diaz-Galvan, P., Przybelski, S. A., Algeciras-Schimnich, A., Figdore, D. J., Lesnick, T. G., Schwarz, C. G., . . . R. (2024). Plasma biomarkers of Alzheimer's disease in the continuum of dementia with Lewy bodies. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*.
26. Donoghue, O., Savva, G., Cronin, H., Kenny, R., & Horgan, N. (2014). Using Timed Up and Go and Usual Gait Speed to Predict Incident Disability in Daily Activities Among Community-Dwelling Adults Aged 65 and Older. *Archives of Physical Medicine and Rehabilitation, 95*(10), 1954-1961.
27. Duda, J. (2003). Pathology and Neurotransmitter Abnormalities of Dementia with Lewy Bodies. *Dementia and Geriatric Cognitive Disorders, 17*(Suppl. 1), 3-14.
28. Duffy, J., Harrington, E., Salituro, F., Cochran, J., Green, J., Gao, H., . . . et al. (2011). The Discovery of VX-745: A Novel and Selective p38alpha Kinase Inhibitor. *ACS Med. Chem. Lett., 2*, 758-763.
29. Fernandez-Cabello, S., Kronbichler, M., Van Dijk, K., Goodman, J., Spreng, R., & Schmitz, T. (2020). Basal forebrain volume reliably predicts the cortical spread of Alzheimer's degeneration. *Brain, 143*(3).
30. Ferreira, D., Przybelski, S. A., Lesnick, T. G., Schwarz, C. G., Diaz-Galvan, P., Graff-Radford, J., . . . Westm. (2022). Cross-sectional associations of B-amyloid, tau and cerbrovascular biomarkers with neurodegeneration in probable dementiat with Lewy bodies. *Neurology*.
31. Frigerio, I., Bouwman, M., Noordermeer, R., Podobnik, E., Popovic, M., Timmermans, E., . . . Jonkman, L. (2024). Regional differences in synaptic degeneration are linked to alpha-synuclein burden and axonal damage in Parkinson's disease and dementia with Lewy bodies. *Acta Neuropathologica Communications, 12*(1), 4.

32. Fritz, N., Kegelmeyer, D., Kloos, A., Linder, S., Park, A., Kataki, M., . . . Kostyk, S. (2016). Motor performance differentiates individuals with Lewy body dementia, Parkinson's and Alzheimer's disease. *Gait & Posture, 50*, 1-7.

33. Galvin, J., Chrisphonte, S., Cohen, I., Greenfield, K., Kleiman, M., Moore, C., . . . Tolea, M. (2021). Characterization of dementia with Lewy bodies (DLB) and mild cognitive impairment using the Lewy body dementia module (LBD-MOD). *. Alzheimer's & Dementia, 17*(10), 1675-1686.

34. Germann, U., & Alam, J. (2020). P38α MAPK Signaling—A Robust Therapeutic Target for Rab5-Mediated Neurodegenerative Disease. *International Journal of Molecular Sciences, 21*(15), 5485.

35. Geula, C., Dunlop, S., Ayala, I., Kawles, A., Flanagan, M., Gefen, T., & Mesulam, M.-M. (2021). Basal forebrain cholinergic system in the dementias: Vulnerability, resilience, and resistance. *J Neurochem, 158*(6), 1394-1411.

36. Gomperts, S. (2016). Lewy body dementias. *Continuum: Lifelong Learning in Neurology, 22*(2), 435-463.

37. Gonzalez, M. C., Ashton, N. J., Gomes, B. F., Tovar-Rios, D. A., Blanc, F., Karikari, T. K., . . . Aars. (2022). Association of Plasma p-tau181 and p-tau231 Concentrations With Cognitive Decline in Patients With Probable Dementia With Lewy Bodies. *JAMA Neurology, 79*(1), 32-37.

38. Grothe, M., Schuster, C., Bauer, F., Heinsen, H., Prudlo, J., & Teipel, S. (2014). Atrophy of the cholinergic basal forebrain in dementia with Lewy bodies and Alzheimer's disease dementia. *Journal of Neurology, 261*(10), 1939-1948.

39. Hall, S., Janelidze, S., Londos, E., Leuzy, A., Stomrud, E., Dage, J., & Hansson, O. (2021). Plasma Phospho-Tau Identifies Alzheimer's Co-Pathology in Patients with Lewy Body Disease. *Movement Disorders, 36*(3), 767-771.

40. Hamilton, C., O'Brien, J., Heslegrave, A., Laban, R., Donaghy, P., Durcan, R., . . . Thomas, A. (2023). Plasma biomarkers of neurodegeneration in mild cognitive impairment with Lewy bodies. *Psychological Medicine*, 1-9.

41. Hampel, H., Mesulam, M.-M., Cuello, A., Khachaturian, A., Vergallo, A., Farlow, M., . . . Khachaturian, Z. (2019). Revisiting the Cholinergic Hypothesis in Alzheimer's Disease: Emerging Evidence from Translational and Clinical Research. *J Prev Alzheimers Dis, 6*(1), 2-15.

42. Hansen, L., Daniel, S., Wilcock, G., & Love, S. (1998). Frontal cortical synaptophysin in Lewy body diseases: relation to Alzheimer's disease and dementia. *Journal of Neurology, Neurosurgery, and Psychiatry, 64*(5), 653-656.

43. Holtzman, D., Santucci, D., Kilbridge, J., & Mobley, W. (1996). Developmental abnormalities and age-related neurodegeneration in a mouse model of Down syndrome. *PNAS, 93*(23), 13333-13338.

44. Irizarry, M., Lai, R., Herch, S., Pinner, K., Dhadda, S., & Kramer. (2022). *Results of a Phase 2/3 Placebo-Controlled, Double-Blind, Parallel-Group, Randomized Study to Evaluate the Efficacy and Safety of 12 Week Treatment with Phosphodiesterase 9 (PDE9) Inhibitor Irenontrine (E2027) in Subjects with Dementia with Lewy Bodies.* Eisai Inc.

45. Jarzebowski, P., Tang, C., Paulsen, O., & Hay, Y. (2021). Jarzebowski, P., Tang, C. S., Paulsen, O., & Hay, Y. A. (2021). Impaired spatial learning and suppression of sharp wave ripples by cholinergic activation at the goal location. *ELife*, 10.

46. Jiang, Y., Alam, J. J., Gomperts, S. N., Maruff, P., Lemstra, A. W., Germann, U. A., . . . Gardner, A. (2022). Preclinical and randomized clinical evaluation of the p38α kinase inhibitor neflamapimod for basal forebrain cholinergic degeneration. *Nature Communications, 13*(1), 5308.

47. Jiang, Y., Rigoglioso, A., Peterhoff, C., Pawlik, M., Sato, Y., Bleiwas, C., . . . Nixon, R. (2016). Partial BACE1 reduction in a Down syndrome mouse model blocks Alzheimer-related endosomal anomalies and cholinergic neurodegeneration: role of APP-CTF. *Neurobiol Aging, 39*, 90-98.

48. Jiang, Y., Stavrides, P., Darji, S., Yang, D.-S., Bleiwas, C., Smiley, J., . . . Nixon, R. (2019). Effects of p38α MAP Kinase Inhibition on the Neurodegenerative Phenotype of the Ts2 Down Syndrome Mouse Model. *Alzheimer's Dement., 15*, 1597.

49. Karantzoullis, S., & Galvin, J. (2013). Update on Dementia with Lewy Bodies. *. Current Translational Geriatrics and Experimental Gerontology Reports, 2*(3), 196-204.

50. Kemp, J., Philippi, C., Botzung, A., & Blanc, F. (2017). Cognitive profile in prodromal disease (dementia) with Lewy bodies. *Gériatrie et Psychologie Neuropsychiatrie Du Viellissement, 15*(4), 434-442.

51. Kim, S., Sato, Y., Mohan, P., Peterhoff, C., Pensalfini, A., Rigoglioso, A., . . . Nixon, R. (2015). Evidence that the rab5 effector APPL1 mediates APP-βCTF-induced dysfunction of endosomes in Down syndrome and Alzheimer's disease. *Molecular Psychiatry, 21*, 707-716.

52. Kojima, G., Masud, T., Kendrick, D., Morris, R., Gawler, S., Treml, J., & Iliffe, S. (2015). Does the timed up and go test predict future falls among British community-dwelling older people? Prospective cohort study nested within a randomised controlled trial. *BMC Geriatrics, 15*(1).

53. Koppensteiner, P., Trinchese, F., Fa, M., Puzzo, D., Gulisano, W., Yan, S., . . . et al. (2016). Time-Dependent Reversal of Synaptic Plasticity Induced by Physiological Concentrations of OLigomeric Abeta42: An Early Index of Alzheimer's Disease. *Sci Rep, 6*, 32553.

54. Li, S., Jin, M., Koeglsperger, T., Shepardson, N., Shankar, G., & Selkoe, D. (2011). Soluble Abeta Oligomers Inhibit Long-Term Potentiation through a Mechanism Involving Excessive Activation of Extrasynaptic NR2B-Containing NMDA Receptors. *J Neurosci, 31*, 6627–6638.

55. Lin, C., Frigerio, I., Boon, B., Zhou, Z., Rozemuller, A., Bouwman, F., . . . Jonkman, L. (2022). Structural (dys)connectivity associates with cholinergic cell density in Alzheimer's disease. *Brain: A Journal of Neurology, 145*(8), 2869-2881.

56. Lynch, M. (2010). Age-Related Neuroinflammatory Changes Negatively Impact on Neuronal Function. *Front. Aging Neuroci., 1*, 6.

57. Maphis, N., Jiang, S., Xu, G., Kokiko-Cochran, O., Roy, S., Van Eldik , L., . . . Bhaskar, K. (2016). Selective Suppression of the Alpha Isoform of p38 MAPK Rescues Late-Stage Tau Pathology. *Alzheimer's Res. Ther., 8*, 54.

58. Matsunaga, S., Kishi, T., Yasue, I., & Iwata, N. (2015). Cholinesterase Inhibitors for Lewy Body Disorders: A Meta-Analysis. *International Journal of Neuropsychopharmacology, 19*(2), pyv086.

59. McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J.-P., Weintraub, D., . . . Chen-Plotkin, A. (2017). Diagnosis and management of dementia with Lewy bodies. *Neurology, 89*(1), 88-100.

60. McKeith, I., Rowan, E., Askew, K., Naidu, A., Allan, L., Barnett, N., . . . O'Brien, J. (2006). More Severe Functional Impairment in Dementia With Lewy Bodies Than Alzheimer Disease Is Related to Extrapyramidal Motor Dysfunction. *The American Journal of Geriatric Psychiatry, 14*(7), 582-588.

61. Mintun, M., Raket, L., Zimmer, J., Evans, C., Lu, M., Sparks, J., . . . Sims, J. (2023). *Predicting Efficacy in Donanemab-Treated Participants.* Eli Lilly and Company.

62. Mori, E., Ikeda, M., & Kosaka, K. (2012) Donepezil for dementia with Lewy bodies: A randomized, placebo-controlled trial. *Annals of Neurology, 72*(1), 41-52.

63. Mueller, C., Ballard, C., Corbett, A., & Aarsland, D. (2017). The prognosis of dementia with Lewy bodies. *The Lancet Neurology, 16*(5), 390-398.

64. Mueller, C., Perera, G., Rajkumar, A., Bhattaral, M., Price, A., O'Brien, J., . . . Aarsland, D. (2018). Hospitalization in people with dementia with Lewy bodies: Frequency, duration, and cost implications. *Alzheimer's & dementia (Amsterdam, Netherlands), 10*, 143-152.

65. Mufson, E., Ginsberg, S., Ikonomovic, M., & DeKosky, S. (2003). Human cholinergic basal forebrain: chemoanatomy and neurologic dysfunction. *Journal of Chemical Neuroanatomy, 26*(4), 233-242.

66. Nelson, P., Kryscio, R., Jicha, G., Abner, E., Schmitt, F., Xu, L., . . . Markesbery, W. (2009). Relative preservation of MMSE scores in autopsy-proven dementia with Lewy bodies. *Neurology, 73*(14), 1127-1133.

67. Niewiadomska, G., Komorowski, S., & Baksalerska-Pazera, M. (2002). Amelioration of cholinergic neurons dysfunction in aged rats depends on the continuous supply of NGF. *Neurobiology of Aging, 23*(4), 601-613.

68. Nixon, R. (2017). Amyloid precursor protein and endosomal-lysosomal dysfunction in Alzheimer's disease: inseparable partners in a multifactorial disease. *FASEBJ, 31*, 2729-2743.

69. Nocera, J., Stegmoller, E., Malaty, I., Okun, M., Marsiske, M., & Haas, C. (2013). Using the Timed Up & Go Test in a Clinical Setting to Predict Falling in Parkinson's Disease. *Archives of Physical Medicine and Rehabilitation, 94*(7), 1300-1305.

70. Nunes, P. V., Schwarzer, M. C., Leite, R. E. P., Ferretti-Robustini, R. E. d. L. … Suemoto, C. K. (2019) Neuropsychiatric Inventory in Community-Dwelling Older Adults with Mild Cognitive Impairment and Dementia. J Alzheimers Dis. 2019; 68(2): 669–678.

71. Okkels, N., Horsager, J., Labrador-Espinosa, M., Kjeldsen, P., Damholdt, M., Mortensen, J., . . . Borghammer, P. (2023). Severe cholinergic terminal loss in newly diagnosed dementia with Lewy bodies. *Brain: A Journal of Neurology, 146*(9), 3690-3704.

72. Outeiro, T., Koss, D., Erskine, D., Walker, L., Kurzawa-Akanbi, M., Burn, D., . . . McKeith, I. (2019). Dementia with Lewy bodies: an update and outlook. . *Molecular Neurodegeneration, 14*(1).

73. Pensalfini, A., Kim, S., Subbanna, S., Bleiwas, C., Goulbourne, C., Stavrides, P., . . . Nixon, R. (2020). Endosomal Dysfunction Induced by Directly Overactivating Rab5 Recapitulates Prodromal and Neurodegenerative Features of Alzheimer's Disease. *Cell Reports, 33*(8), 108420.

74. Price, A., Farooq, R., Yuan, J.-M., Menon, V., Cardinal, R., & O'Brien, J. (2017). Mortality in dementia with Lewy bodies compared with Alzheimer's dementia: a retrospective naturalistic cohort study. *BMJ Open, 7*(11), e017504.

75. Prins, N., Haan, W., Blackburn, K., Chu, H., Galvin, J., & Alam, J. (2024). Phase 2A Learnings Incorporated into RewinD-LB, a Phase 2B Clinical Trial of Neflamapimod in Dementia with Lewy Bodies. *Journal of Prevention of Alzheimer's Disease*.

76. Prins, N., Harrison, J., Chu, H., Blackburn, K., Alam, J., Scheltens, P., & Reverse-SD Study Investigators. (2021). A phase 2 double-blind placebo-controlled 24-week treatment clinical study of the p38 alpha kinase inhibitor neflamapimod in mild Alzheimer's disease. *Alzheimer's Research & Therapy, 13*(1), 106.

77. Rodriguez-Porcel, F., Wyaman-Chick, K. A., Abdelnour Ruiz, C., Toledo, J. B., Ferreira, D., Urwyler, P., . . . Lewis, S. J. (2022). Clinical outcome measures in dementia with Lewy bodies trials: critique and recommendations. *Translational Neurodegeneration, 11*(1).

78. Rongve, A., Soennesyn, H., Skogseth, R., Oesterhus, R., Hortobagyl, T., Ballard, C., . . . Aarsland, D. (2016). Cognitive decline in dementia with Lewy bodies: a 5-year prospective cohort study. *BMJ Open, 6*(2), e010357.

79. Rongve, A., Vossius, C., Nore, S., Testad, I., & Aarsland, D. (2013). Time until nursing home admission in people with mild dementia: comparison of dementia with Lewy bodies and Alzheimer's dementia. *International Journal of Geriatric Psychiatry, 29*(4), 392-398.

80. Roy, S., Grum-Tokars, V., Schavocky, J., Saeed, F., Staniszewski, A., Teich, A., . . . et al. (2015). Targeting Human Central Nervous System Protein Kinases: An Isoform Selective p38alphaMAPK Inhibitor That Attenuates Disease Progression in Alzheimer's Disease Mouse Models. *ACS Chem. Neurosci, 6*, 666–680.

81. Sabbagh, M., Taylor, A., Galasko, D., Galvin, J., Goldman, J., Leverenz, J., . . . Quinn, J. (2023). Listening session with the US Food and Drug Administration, Lewy Body Dementia Association, and an expert panel. *. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 9*(1).

82. Salehi, A., Roux, P., Kubu, C., Tannis, L.-L., & Verdi, J. (2000). NRAGE, A Novel MAGE Protein, Interacts with the p75 Neurotrophin Receptor and Facilitates Nerve Growth Factor–Dependent Apoptosis. *Neuron, 27*(2), 279-288.

83. Schmitz, T., Mur, M., Arhourian, M., Bedard, M.-A., Spreng, M.-A., & Spreng, R. (2018). Longitudinal Alzheimer's Degeneration Reflects the Spatial Topography of Cholinergic Basal Forebrain Projections. *Cell Reports, 24*(1), 38-46.

84. Schmitz, T., Spreng, R., & The Alzheimer's Disease Neuroimaging Initiative. (2016). Basal forebrain degeneration precedes and predicts the cortical spread of Alzheimer's pathology. *Nature Communications, 7*, 13249.

85. Schumacher, J., Ray, N., Hamilton, C., Donaghy, P., Firbank, M., Roberts, G., . . . Thomas, A. (2022). Cholinergic white matter pathways in dementia with Lewy bodies and Alzheimer's disease. *Brain, 145*(5), 1773-1784.

86. Schumacher, J., Taylor, J.-P., Hamilton, C., Firbank, M., Cromarty, R., Donaghy, P., . . . Thomas, A. (2021). In vivo nucleus basalis of Meynert degeneration in mild cognitive impairment with Lewy bodies. *NeuroImage: Clinical, 30*, 102604.

87. Sullivan, G., & Feinn, R. (2012). Using Effect Size—or Why the P Value Is Not Enough. *Journal of Graduate Medical Education, 4*(3), 279-282.

88. Surendranathan, A., Kane, J., Bentley, A., Barker, S., Taylor, J.-P., Thomas, A., . . . O'Brien, J. (2020). Clinical diagnosis of Lewy body dementia. *BJPsych Open, 6*(4).

89. Tahami Monfared, A., Desai, M., Hughes, R., Lucherini, S., Yi, Y., & Perry, R. (2020). Treatment Options for Dementia with Lewy Bodies: A Network Meta-Analysis of Randomised Control Trials. *Neurology and Therapy, 9*(2), 521-534.

90. Tang, Y.-L., Han, L., Li, S., Hu, T., Xu, Z., Fan, Y., . . . Wang, J. (2023). Plasma GFAP in Parkinson's disease with cognitive impairment and its potential to predict conversion to dementia. *NPJ Parkinson's Disease, 9*, 23.

91. Tarawneh, R., & Pankratz, V. (2024). The search for clarity regarding "clinically meaningful outcomes" in Alzheimer disease clinical trials: CLARITY-AD and Beyond. *Alzheimer's Research & Therapy, 16*(1), 37.

92. Tolonen, A., Rhodius-Meester, H. F., Bruun, M., Koikkalainen, J., Barkhof, F., Lemstra, A. W., . . . Waldemar, G. (2018). Data-Driven Differential Diagnosis of Dementia Using Multiclass Disease State Index Classifier. *. Frontiers in Aging Neuroscience, 10*.

93. *Treat Before "Aβ Bothers Tau," Scientists Say at CTAD | ALZFORUM* (2023).

94. van de Beek, M., van Steenoven, I., van der Zande, J., Porcelijn, I., Barkhof, F., Stam, C., . . . Lemstra, A. (2021). Characterization of symptoms and determinants of disease burden in dementia with Lewy bodies: DEvELOP design and baseline results. *. Alzheimer's Research & Therapy, 13*(1).

95. Vann Jones, S., & O'Brien, J. (2013). The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. *Psychological Medicine, 44*(4), 673-683.

96. Walker, Z., Possin, K., Boeve, B., & Aarsland, D. (2015). Lewy body dementias. *Lancet, 386*(10004), 1683-1697.

97. Wilkins, K., Parker, J., & Bronte-Stewart, H. (2020). Gait variability is linked to the atrophy of the Nucleus Basalis of Meynert and is resistant to STN DBS in Parkinson's disease. *Neurobiology of Disease, 146*, 105134.

98. Wilson, J., Yarnall, A., Craig, C., Galna, B., Lord, S., Morris, R., . . . Rochester, L. (2021). linergic Basal Forebrain Volumes Predict Gait Decline in Parkinson's Disease. *Movement Disorders, 36*(3), 611-621.

99. Xia, Y., Maruff, P., Dore, P., Bourgeat, P., Laws, S., Fowler, C., . . . Fripp, J. (2023). Longitudinal trajectories of basal forebrain volume in normal aging and Alzheimer's disease. *Neurobiology of Aging, 132*, 120-130.