

Clinical Trial Highlights – Parkinson's Disease Cognition

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Introduction

Non-motor symptoms (NMS) constitute a considerable portion of the Parkinson's Disease (PD) syndrome. The spectrum of NMS is widespread and can range anywhere from olfactory to bladder dysfunction with a significant impact on the quality of life of a person with PD (PwP) [1]. Cognitive impairment (CI) is one of the most common and challenging NMS in PD. The spectrum of PD-CI ranges from subjective symptoms to dementia. Not only are the cognitive symptoms disabling by themselves, but their presence also may limit the management of motor disability as dopaminergic medication can worsen CI. As such, this also affects the motor profile furthering the debility. The reported prevalence rate of mild cognitive impairment (MCI) and PD dementia (PDD) varies depending on multiple factors, including the diagnostic criteria used in the first place. But largely, the prevalence increases with the disease progression. In general, PD-MCI is prevalent among 25-30% PwP, and approximately 10-20% may have it at the time of diagnosis [2]. Within three years of follow up, 25% of PwP with normal cognition may develop PD-MCI. Likewise, PD-MCI to PDD progression is around 20% within three years of follow up and 34% beyond that [3]. PDD is present in 83% of PwP at advanced stages, at 20+ years disease duration [4].

Currently, there are limited therapeutic options for PD-CI. Understanding the flow of progression of PD-CI with underlying mechanisms is essential to developing therapies aimed at reducing the evolution or providing symptomatic benefit. Similar to the underlying mechanism for motor impairment in PD, studies suggest that CI is a consequence of a complex multifactorial process. The various factors playing a role in PD-CI have been reviewed in detail elsewhere [2].

α -synuclein pathology is central to PD and is hypothesized to spread cortically from the brainstem [5]. PD-CI positively correlates with the presence of α -synuclein containing Lewy bodies in the limbic and neocortex. But the underlying mechanisms are considered more intricate and extend beyond α -synuclein to other proteinopathies. There is evidence to suggest an additive role of amyloid and tau pathology in PDD [6]. Synaptic dysfunction and subsequent retrograde somatic degeneration also play a role [7].

The fundamental role of neurotransmitters in PD-CI is more complex and goes beyond the archetypal dopaminergic system. Dopamine posits a more complex and non-linear relationship to PD-CI pathology. While there is some evidence of improvement of early executive dysfunction with dopamine replacement therapy, there is also evidence linking a relative cortical to striatum hyperdopaminergic state to CI [8].

There is convincing evidence highlighting the role of other non-dopaminergic systems in PD-CI, such as cholinergic, noradrenergic, GABAergic, and serotonergic systems. There is evidence indicating a widespread reduction of the subcortical and cortical cholinergic activity in PDD [9]. The acetylcholinesterase inhibitor (ACE-I), rivastigmine, is the only medication approved for the management of the cognitive functioning in PDD [10]. Serotonin and noradrenergic systems have also garnered increasing interest in PD therapeutics with evidence suggesting a positive impact on the frontal network dysfunction [11]. Though evaluated mainly for motor effects, there is a suggestion that modulation of adenosine A2A receptors on GABAergic neurons may also improve cognition [12].

One of the challenges in drug development for PD-CI is that animal models may not reflect the actual nature of PD-CI development. As such, molecules with promising preclinical data often fail in human clinical trials. There is a significant unmet need for developing therapies to improve the CI without impairing motor profile, and to reduce conversion rates to PD-MCI and PDD.

References

- [1] A. Schrag, M. Jahanshahi, N. Quinn, What contributes to quality of life in patients with Parkinson's disease?, *Journal of Neurology Neurosurgery and Psychiatry*. 69 (2000) 308–312. <https://doi.org/10.1136/jnnp.69.3.308>.
- [2] D. Aarsland, B. Creese, M. Politis, K.R. Chaudhuri, D.H. Ffytche, D. Weintraub, C. Ballard, Cognitive decline in Parkinson disease, *Nature Reviews Neurology*. 13 (2017) 217–231. <https://doi.org/10.1038/nrneurol.2017.27>.
- [3] D. Saredakis, L.E. Collins-Praino, D.S. Gutteridge, B.C.M. Stephan, H.A.D. Keage, Conversion to MCI and dementia in Parkinson's disease: a systematic review and meta-analysis, *Parkinsonism and Related Disorders*. 65 (2019) 20–31. <https://doi.org/10.1016/j.parkreldis.2019.04.020>.
- [4] M.A. Hely, W.G.J. Reid, M.A. Adena, G.M. Halliday, J.G.L. Morris, The Sydney Multicenter Study of Parkinson's disease: The inevitability of dementia at 20 years, *Movement Disorders*. 23 (2008) 837–844. <https://doi.org/10.1002/mds.21956>.
- [5] H. Braak, K. del Tredici, U. Rüb, R.A.I. de Vos, E.N.H. Jansen Steur, E. Braak, Staging of brain pathology related to sporadic Parkinson's disease, *Neurobiology of Aging*. 24 (2003) 197–211. [https://doi.org/10.1016/S0197-4580\(02\)00065-9](https://doi.org/10.1016/S0197-4580(02)00065-9).
- [6] D.R. Howlett, D. Whitfield, M. Johnson, J. Attems, J.T. O'Brien, D. Aarsland, M.K.P. Lai, J.H. Lee, C. Chen, C. Ballard, T. Hortobágyi, P.T. Francis, Regional Multiple Pathology Scores Are Associated with Cognitive Decline in Lewy Body Dementias, *Brain Pathology*. 25 (2015) 401–408. <https://doi.org/10.1111/bpa.12182>.
- [7] W.J. Schulz-Schaeffer, The synaptic pathology of α -synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia, *Acta Neuropathologica*. 120 (2010) 131–143. <https://doi.org/10.1007/s00401-010-0711-0>.
- [8] A.H.V. Schapira, K.R. Chaudhuri, P. Jenner, Non-motor features of Parkinson disease, *Nature Reviews Neuroscience*. 18 (2017) 435–450. <https://doi.org/10.1038/nrn.2017.62>.
- [9] H. Shimada, S. Hirano, H. Shinotoh, A. Aotsuka, K. Sato, N. Tanaka, T. Ota, M. Asahina, K. Fukushi, S. Kuwabara, T. Hattori, T. Suhara, T. Irie, Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET, *Neurology*. 73 (2009) 273–278. <https://doi.org/10.1212/WNL.0b013e3181ab2b58>.
- [10] H.F. Wang, J.T. Yu, S.W. Tang, T. Jiang, C.C. Tan, X.F. Meng, C. Wang, M.S. Tan, L. Tan, Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: Systematic review with meta-analysis and trial sequential analysis, *Journal of Neurology, Neurosurgery and Psychiatry*. 86 (2015) 135–143. <https://doi.org/10.1136/jnnp-2014-307659>.
- [11] Z. Ye, C.L. Rae, C. Nombela, T. Ham, T. Rittman, P.S. Jones, P.V. Rodríguez, I. Coyle-Gilchrist, R. Regenthal, E. Altena, C.R. Housden, H. Maxwell, B.J. Sahakian, R.A. Barker, T.W. Robbins, J.B. Rowe, Predicting beneficial effects of atomoxetine and citalopram on response inhibition in Parkinson's

disease with clinical and neuroimaging measures, *Human Brain Mapping*, 37 (2016) 1026–1037. <https://doi.org/10.1002/hbm.23087>.

- [12] R.J. Vorovenci, A. Antonini, The efficacy of oral adenosine A2A antagonist istradefylline for the treatment of moderate to severe Parkinson's disease, *Expert Review of Neurotherapeutics*, 15 (2015) 1383–1390. <https://doi.org/10.1586/14737175.2015.1113131>.

Overview of clinical trials for PD cognition

There are nine programs at the clinical stage of development for the treatment of cognitive symptoms in PD. Eight are in phase 2, and one is in phase 1. A summary of the clinical trials targeting cognition in PD is shown in the table below.

ORGANISATION	DRUG	MECHANISM OF ACTION	PHASE	FOCUS*	PLANNED COMPLETION DATE
Anavex	Anavex 2-73	Sigma-1 receptor activation	2	PDD	July 2020
Aptinyx	NYX-458	NMDA receptor modulator	2	PD-MCI	June 2021
China Medical University Hospital	DAAOI-P	NMDA receptor modulator	2	PDD	July 2022
Integrative Research Laboratories (IRL)	IRL752	"Cortical enhancer"	2	PDD	May 2018
Lawson Health Research Institute	Ambroxol	Increases GCase activity	2	PDD	December 2021
Lilly	LY3154207	Positive allosteric modulator of the D1 receptor	2	PDD and DLB	July 2020
University of Michigan	Citalopram	SSRI	2	Visuospatial cognition	September 2025
Yonsei University, Korea	Donepezil	Cholinesterase inhibitor	2	PD-MCI	August 2019
Enterin	ENT01 (Kenterin)	Inhibits aSN aggregation	1	PDD	February 2020

*PDD - Parkinson's Disease Dementia

PD-MCI - Parkinson's Disease with Mild Cognitive Impairment

DLB – Dementia with Lewy Bodies

aSN – α -synuclein

It is immediately apparent that the nine trials listed are using eight different mechanisms of action. This diversity is unusual when compared to other areas of PD drug development. The targets include multiple neurotransmitter pathways, sigma-1, cholinergic and NMDA, as well as dopamine D1.

IRLAB has been developing a novel "cortical enhancer"- IRL752. It has "a cortically regioselective facilitatory impact on catecholaminergic and cholinergic neurotransmission accompanied by cognitive impairment-reversing features" [1]. The recently published Phase 2a trial of IRL752 in PDD demonstrated a good safety profile. Interestingly, in the analysis, the drug improved the axial symptoms, including postural instability. IRL752 did not have a significant impact on the spatial working memory, and only had mild improvement in the executive function [2]. IRLAB has announced its plans for a phase 2b study but with a focus on postural instability and falls, possibly influenced by the phase 2a results. No announcements have been made regarding future trials to assess the impact on cognition. It is unknown whether the announced phase 2b trial for falls and postural instability will include any cognitive outcome measures [3].

The Yonsei University study was due to finish in August 2019, and the latest update to the clinicaltrials.gov entry was in January 2019. The results of the study are yet to be published. Previous studies of donepezil in MCI in other indications have failed to slow progression to dementia. This open-label study is assessing the potential of a different outcome in PD.

Two projects are targeting a reduction of levels of aggregated α -synuclein, directly in the case of Enterin's ENT-01; and indirectly with Lawson Health's amroxol project, given that levels of glucocerebrosidase (GCase) have an inverse relationship with levels of α -synuclein. Michigan University's trial is using the SSRI, citalopram, to target the loss of serotonergic terminals to address visuospatial loss in PDD.

There is also a wide range in the types of participants being recruited. Two trials are recruiting participants in the earlier stages of cognitive decline (PD-MCI), and five of the nine studies are recruiting participants with confirmed PDD. The Michigan study is recruiting PD participants without any confirmed cognitive deficits, and Lilly's study is recruiting both PDD and DLB participants.

Recruitment criteria also vary in the age range and the stage of PD, as defined by the Hoehn & Yahr (H&Y) scale. Four of the studies have a lower age limit of 50, two start at 40, and while Michigan's lower limit is 65, Enterin's trial inclusion is for PwP age range 30-90. Only three trials include H&Y status in the inclusion criteria with the University of Michigan having a tight range of 2.0 to 2.5, and the Lilly trial a lot wider at 0 to 4.

The duration of the trial treatment period ranges from IRL752 at 28 days, up to the University of Michigan at 26 months. The latter study is investigating the impact of citalopram treatment on the conversion rate of PD with normal cognition to PD-CI. Due to the nature of the question, the study is expected to require more time. The treatment duration for the remaining studies vary from only 10 weeks for ENT-01 to 52 weeks for Lawson Health's amroxol trial.

There is little commonality in the outcome measures of the trials. Only one primary measure is used in more than one trial, the Continuity of Attention composite score of the Cognitive Drug Research Computerised Cognition Battery (CDR-CCB; Lilly and Anavex). There is a wide range of cognitive assessment tools used, some of which were developed for Alzheimer's disease (AD), including the AD assessment scale - cognitive subset (ASAS-cog), Dementia Severity Rating Scale (DSRS), Delis-Kaplan Executive Function Scale (D-KEFS), Clinical Dementia Rating Scale (CDR), and the Trail Making Test.

Five studies use a Neuropsychiatric Inventory (NPI) as a secondary outcome measure. Only four out of the nine studies use the Montreal Cognitive Assessment (MoCA), with a further two using the Mini-Mental State Examination (MMSE), one of which is a Korean adaptation.

Five of the nine trials are using objective instrumental outcome measures. Indeed, the only primary outcome for the University of Michigan study is the change in visuospatial cortex Pittsburgh compound B (PiB) distribution volume. This method can assess the density of β -amyloid plaques. The China Medical University study uses three different MRI techniques whilst Lawson Health are using MRI to assess brain ventricle volume and hippocampal atrophy. Yonsei University plans to use MRI to measure cortical thickness, and subcortical volume and shape. Both Yonsei and IRL use electroencephalography to assess functional connectivity.

The majority of the studies use the Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) examination (seven of the nine trials) though none of the trials specify whether the test is performed on or off medication.

In summary, there is a significant variation in the design of the studies targeting CI, likely reflecting a lack of consensus on the best target population and outcomes. This will make it more difficult to compare potential treatments. A consensus on these parameters will accelerate the availability of effective symptomatic therapies

and disease modifying therapies (DMTs) for PD-CI. On the positive side, there is a good range of mechanisms of action under investigation.

There are very few projects in the preclinical stage to target the mechanisms and symptoms of PD-MCI and PDD. In addition, it is not yet clear whether DMTs for PD will slow or stop the progression of all domains of PD, including cognitive symptoms. In that context, it is essential to continue the research and development of new medicines to deal with the severe impact that PD-MCI and particularly PDD has on the quality of life of PwP and their families.

References

- [1] Hjorth S, Waters S, Waters N, et al. (3S)-3-(2,3-difluorophenyl)-3-methoxypyrrolidine (IRL752) -a Novel Cortical-Preferring Catecholamine Transmission- and Cognition-Promoting Agent. *J Pharmacol Exp Ther.* 2020;374(3):404-419. doi:10.1124/jpet.120.000037
- [2] P. Svenningsson, P. Odin, N. Dizdar, A. Johansson, S. Grigoriou, P. Tsitsi, K. Wictorin, F. Bergquist, D. Nyholm, J. Rinne, F. Hansson, C. Sonesson, J. Tedroff, K. Andersson, M. Sundgren, W. Duzynski, C. Carlström, A Phase 2a Trial Investigating the Safety and Tolerability of the Novel Cortical Enhancer IRL752 in Parkinson's Disease Dementia, Movement Disorders. 35 (2020) 1046–1054. <https://doi.org/10.1002/mds.28020>.
- [3] IRL752 - Irlab, (n.d.). <https://www.irlab.se/project-portfolio/irl-752>.

Anavex®2-73

Background: Anavex®2-73 (blarcamesine) is a well-studied drug candidate with seven studies, completed or in progress, for the treatment of Rett Syndrome and Alzheimer's disease, and one for PD. It is an orally-available sigma-1 receptor (S1R) activator. Activation of S1R leads to a number of effects, resulting in protection from cellular stress [1]. Proof of concept and target engagement have been demonstrated.

Title: ANAVEX®2-73 Study in Parkinson's Disease Dementia

Phase: 2

Objective: To evaluate the safety, efficacy, and tolerability of ANAVEX®2-73 for cognitive impairment in patients with PDD.

Status: Active, not recruiting.

Clinicaltrials.gov ID: NCT03774459

Sponsor: Anavex Life Sciences Corp.

Collaborators: Anavex Germany

Estimated Enrolment: 120

Estimated Completion Date: July 2020

Study Design: The study is double-blind, randomized, placebo-controlled, and multicenter (25 sites). There are three arms, two with active treatment at low and high doses, and placebo, delivered as oral capsules. The trial is recruiting participants over the age of 50, with a MoCA score between 13 and 23.

Outcome Measures: There are two primary and two secondary outcome measures, all measured at 14 weeks. The primary ones are:

1. Change from baseline to end of treatment in cognitive drug research (CDR) computerized assessment system for Continuity of Attention.
2. Number of participants with treatment-related adverse events as assessed by CTCAE (common terminology criteria for adverse events) v4.0.

Secondary outcomes are:

1. Change from baseline to end of treatment as measured by the MDS-UPDRS part III score (motor scores).
2. Incidence of sleep disorders symptom checklist (SDS-CL-25)

Comments: There are three indications under investigation for ANAVEX®2-73 - Rett syndrome, Alzheimer's disease, and PD, bringing more clinical experience with this drug.

The primary cognitive outcome measure is tightly focused on the attention domain. The MoCA score inclusion criterion is a relatively wide range, including both MCI and PDD.

Results: A summary of trial results was published in October 2020, although as yet without peer review [2]. The study demonstrated statistically significant improvements in CDR Cognitive Domain of Attention assessed by Choice Reaction Time; Digital Vigilance; and CDR system Episodic Memory. There was also a statistically significant dose dependent improvement of CDR system Episodic Memory.

Anavex 2-73 did not impair sleep and had a positive effect on REM sleep behavior disorder. It was generally safe and well tolerated, in common with experience in previous trials.

References

[1] <https://www.anavex.com/wp-content/uploads/2020/02/Anavex-Presentation-February-2020.pdf>

[2] <https://www.anavex.com/wp-content/uploads/2020/11/CTAD-Anavex-PDD-001-Topline-data-Presentation-2020.pdf>

Aptinyx – NYX-458

Background: Regulation of the N-methyl-D-aspartate receptor (NMDAR) is directly affected by the loss of dopaminergic input in PD. A resultant downregulation effect leading to NMDAR dysregulation and overactivation has been associated with PD-CI [1]. NMDAR has two heteromeric subunits, NR1 and NR2, which contain glycine and glutamate binding sites, respectively. Co-agonist binding of both glycine and glutamate is needed for NMDAR activation, which can be modulated if either site is blocked. Repurposing of available NMDAR antagonists, memantine and amantadine, was shown to have some therapeutic potential in PD-CI but lacks robust clinical data [2].

NYX-458 is a novel molecule synthesized by Sai Life Sciences (Hyderabad, India) that is being developed by Aptinyx Inc. The molecule modulates the NR2 activity resulting in long-lasting changes in metaplasticity and dendritic spine morphology in the cortical regions. The preclinical studies report a rapid and long-lasting improvement across a number of cognitive domains – attention, working memory, and executive function. There was no effect on the PD motor profile [3]. According to the Aptinyx website, phase 1 human studies have demonstrated a favorable safety and pharmacokinetic profile [4]. The molecule has entered phase 2 clinical trial.

Title: A Study to Evaluate NYX-458 in Subjects With Mild Cognitive Impairment Associated With Parkinson's Disease

Phase: 2

Objective: To assess the safety and tolerability of NYX-458 in participants with PD-MCI.

Status: Active, not recruiting

Clinicaltrials.gov Identifier: NCT04148391

Sponsor: Aptinyx

Collaborator: CogState Ltd.
Worldwide Clinical Trials

Estimated Enrolment: 135

Estimated Completion Date: June 2021

Study Design: This is a phase 2, randomized, parallel-group, triple blinded study evaluating the safety and tolerability of NYX-458 in MCI associated with PD.

Participants between 50-80 years of age with a primary diagnosis of MCI associated with PD will be eligible for inclusion. They should be on a stable antiparkinsonian medication regimen. Participants with MoCA <17 and those meeting criteria for dementia will be excluded. The exclusion criteria also include an ambiguous point of excluding those on medication with primarily central nervous system activities.

The study will be conducted over 16-18 weeks which will include the following, in sequential order:

1. Screening: 2 to 4-weeks
2. Intervention: 12-weeks
3. Follow up: 2-weeks

The trial is studying the safety profile of 3 dosing regimens of the investigation drug. The participants will be randomized to one of the following four arms:

1. Experimental: where participants will receive a 10mg daily dose for 12 weeks
2. Experimental: where participants will receive a 30mg daily dose for 12 weeks
3. Experimental: where participants will receive 100mg daily dose for 12 weeks
4. Placebo

The study is being conducted at multiple sites across the USA.

Outcome Measures: The primary outcome measure focuses on safety by assessing the number of participants with adverse events. Secondary outcomes aim to measure efficacy across multiple cognitive scales though not well outlined in the clinicaltrials.gov.

Comments:

NMDAR is an interesting potential target, and NYX-458 is a promising molecule based on preclinical studies. The current clinical trial, as expected and rightly so, is focusing on the safety and tolerability of 3 doses of

NYX-458. Whether preclinical benefits will translate into clinically meaningful effect is yet to be determined with further studies, contingent upon Phase 2 safety results.

References

- [1] P. Meoni, B.H. Bunnemann, A.E. Kingsbury, D.G. Trist, N.G. Bowery, NMDA NR1 subunit mRNA and glutamate NMDA-sensitive binding are differentially affected in the striatum and pre-frontal cortex of Parkinson's disease patients, *Neuropharmacology*. 38 (1999) 625–633. [https://doi.org/10.1016/S0028-3908\(98\)00219-6](https://doi.org/10.1016/S0028-3908(98)00219-6).
- [2] B. Vanle, W. Olcott, J. Jimenez, L. Bashmi, I. Danovitch, W.W. Ishak, NMDA antagonists for treating the non-motor symptoms in Parkinson's disease, *Translational Psychiatry*. 8 (2018). <https://doi.org/10.1038/s41398-018-0162-2>.
- [3] A.L. Barth, J.S. Schneider, T.H. Johnston, M.P. Hill, J.M. Brotchie, J.R. Moskal, C.N. Cearley, NYX-458 Improves Cognitive Performance in a Primate Parkinson's Disease Model, *Movement Disorders*. 35 (2020) 640–649. <https://doi.org/10.1002/mds.27962>.
- [4] Pipeline - Aptinyx, (n.d.). <https://www.aptinyx.com/pipeline>

China Medical University- DAAOI-P

Background: D-amino acid oxidase (DAAO) is a flavoenzyme that catalyzes the oxidative deamination of most amino acids. It modulates the NMDAR activity by degrading the main agonists of the receptor. Increased activity of the DAAO leads to reduced D-serine levels resulting in hypoactivity of the NMDAR. Impaired NMDAR signaling has been associated with Alzheimer's disease and schizophrenia [1]. Impaired NMDAR activity is associated with PD-CI as well, prompting the use of NMDA antagonists, but inhibition of DAAO has not been explored. DAAO-inhibitor (DAAOI) works on the principle of reducing the breakdown of D-serine with the eventual goal to improve NMDAR functioning. A novel DAAOI molecule has been developed by the China Medical University (CMU) in Taiwan, which modulates the NR1 subunit of NMDAR. CMU also studied sodium benzoate, a DAAOI derived from cinnamon, as adjunctive therapy in schizophrenia with positive results [2]. Interestingly, sodium benzoate has been shown to have a neuroprotective effect in PD preclinical models [3].

Title: Multidisciplinary Study of Novel NMDA Modulation for Neurodegenerative Disorder

Phase: 2

Objective: To study the safety and efficacy of D-amino acid oxidase inhibitor (DAAOI-P) in Parkinson's disease participants with dementia.

Status: Recruiting

Clinicaltrials.gov Identifier: NCT04470037

Sponsor: China Medical University Hospital

Collaborator: Ministry of Science and Technology, Taiwan

Estimated Enrolment: 60

Estimated Completion Date: July 2022

Study Design: This is a phase 2, randomized, parallel assigned, placebo-controlled, and a quadruple blinded interventional study assessing the safety and efficacy of DAAOI-P in PD participants with dementia. The study is being conducted at the CMU Hospital in Taiwan.

The study includes two arms, a placebo arm and an experimental arm where participants will receive the investigational drug DAAOI-P [250-1500mg].

Adult participants with PD between the ages of 50 and 90 years with clinically diagnosed PDD according to the criteria of the Movement Disorders Society will be included. Both probable and possible PDD will be included in this study. Co-existing medical conditions or medications that can independently cause cognitive impairment preventing a reliable diagnosis of PDD, will be excluded. Participants who have been on anticholinergics within 30 days of recruitment will also be excluded.

Outcome Measures: The primary outcome focuses on improvement in gait and neuropsychiatric symptoms as measured by the change in the UPDRS.

Secondary outcome measures except the neuroimaging will be assessed at baseline, 8, 16, and 24 weeks and include.

1. Change in gait function as measured by the cyclogram of gait.
2. Fall assessment test of China Medical University hospital.
3. Change in cognitive function as measured by Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog), Behavioral pathology in Alzheimer's Disease rating scale (Behave-AD), and clinical dementia rating (CDR) scale.
4. Change in Neuropsychiatric inventory scale.
5. Change in the PDQ-39 scale.
6. Change in perceptual discriminability, emotion recognition accuracy, and imitation probability.
7. Neuroimaging, including structural MRI, resting-state functional MRI, and working memory fMRI, assessed at baseline and 24 weeks.
8. Changes in mismatch negativity in an electroencephalogram.
9. Changes in transcranial magnetic stimulation assessments.

Comments:

NMDA modulation has been the target of several medications for CI. No prior studies of DAAOI for PD-CI were found. The outcome of this Phase 2 study centers on efficacy assessments with a focus on the gait and cognition. The efficacy of DAAOI in PDD is yet to be established.

References:

- [1] L. Pollegioni, S. Sacchi, G. Murtas, Human D-amino acid oxidase: Structure, function, and regulation, *Frontiers in Molecular Biosciences*. 5 (2018) 107. <https://doi.org/10.3389/fmolb.2018.00107>.
- [2] C.H. Lin, C.H. Lin, Y.C. Chang, Y.J. Huang, P.W. Chen, H.T. Yang, H.Y. Lane, Sodium Benzoate, a D-Amino Acid Oxidase Inhibitor, Added to Clozapine for the Treatment of Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial, *Biological Psychiatry*. 84 (2018) 422–432. <https://doi.org/10.1016/j.biopsych.2017.12.006>.
- [3] S. Khasnavis, K. Pahan, Sodium benzoate, a metabolite of cinnamon and a food additive, upregulates neuroprotective Parkinson disease protein DJ-1 in astrocytes and neurons, *Journal of Neuroimmune Pharmacology*. 7 (2012) 424–435. <https://doi.org/10.1007/s11481-011-9286-3>.

Lawson Health Research Institute - Ambroxol

Background:

Ambroxol was licensed in 1978 as an expectorant for patients with acute or chronic respiratory disease. Ambroxol has been shown to be centrally penetrant and to increase the levels of glucocerebrosidase (GCCase) in both Gaucher disease and PD models [1]. It is an inhibitory chaperone that mobilizes GCCase from the endoplasmic reticulum by binding to and inhibiting the enzyme active site, thereby facilitating transportation to the lysosome [2].

Mutations in the GBA gene that codes for GCCase are prevalent at around 5% to 15% of Caucasian PD patients, 25% of Ashkenazi Jewish PD patients, and 1% of individuals without PD [3]. There is an inverse relationship between levels of α -synuclein and GCCase activity, opening the possibility of positive benefits on disease progression of PD [1]. As such, ambroxol is being studied by a number of groups as a potential disease-modifying therapy in both GBA+ PD and sporadic PD. The rationale for this study is two-fold. First, the inverse relationship between α -synuclein and GCCase activity predicts that an increase in GCCase activity will reduce levels of α -synuclein. Second, that reducing α -synuclein will lead to improvements in cognition, thereby assuming that α -synuclein levels are responsible for PDD.

A recent open-label 6 months study in 17 PD participants showed that ambroxol crosses the blood-brain barrier and increases the levels of GCCase in the cerebrospinal fluid (CSF) in participants both with and without GBA mutations. The drug administered at high doses compared to the usual doses used for pulmonary indication was shown to be safe and tolerable. Further improvements in MDS-UPDRS Part 3 scores were noted, again in both those with and without GBA mutations [4].

The Lawson Health Research Institute now plans to evaluate the safety and efficacy of ambroxol in participants with PDD.

Title: Ambroxol as a Treatment for Parkinson's Disease Dementia.

Phase: 2

Objective: To test the hypothesis that ambroxol is safe and well tolerated, and will improve the cognitive and motor symptoms of PDD.

Status: Recruiting

Clinicaltrials.gov ID: NCT02914366

Sponsor: Lawson Health Research Institute

Collaborators: Weston Brain Institute; University of Western Ontario; London Health Sciences Centre.

Estimated Enrolment: 75

Estimated Completion Date: December 2021

Study Design: Randomized, double-blind, parallel assignment, with a treatment time of 52 weeks, carried out at a single center. There are three arms in the study:

Arm 1: Ambroxol high dose (1050mg per day)

Arm 2: Ambroxol low dose (525mg per day)

Arm 3: Placebo.

Participants with a MoCA score between 16 and 24 and age >50 are being recruited. The GBA1 gene in each participant will be sequenced, but the mutation status is not an inclusion or exclusion criterion.

Outcome Measures: Primary outcome measures, taken at baseline, 26 weeks and 52 weeks are:

1. Changes in the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog).
2. Changes in the ADCS-Clinician's Global Impression of Change (CGIC).

Secondary outcome measures include a spectrum of scales measuring motor and non-motor disability, specific domains of cognition, CSF and peripheral ambroxol PK profile, and GCAs levels. The study also includes MRI imaging outcomes measuring brain ventricle volume and hippocampal atrophy (baseline and week 52).

1. Changes in the MoCA (baseline, week 26 and week 52).
2. Changes in the Clinical Dementia Rating Scale (CDR) (baseline, week 26 and week 52).
3. Changes in the Trail Making Test (baseline, week 26 and week 52).
4. Change in the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) (baseline, week 26 and week 52).
5. Changes in the Stroop Test (baseline, week 26 and week 52).
6. Changes in the Unified Parkinson's disease Rating Scale motor subsection (UPDRS-III) (baseline, week 26 and week 52).
7. Changes in the Purdue Pegboard (baseline, week 26 and week 52).
8. Changes in the Timed Up and Go (baseline, week 26 and week 52).
9. Change in Quantitative Movement Testing - gait assessment on electronic mat (Zeno Walkway System) (baseline, week 26 and week 52).
10. Changes in Cerebrospinal Fluid (CSF) biomarkers - levels of α -synuclein (pg/ml), Tau (pg/ml), phospho-Tau (pg/ml) and beta amyloid-42 (pg/ml) (baseline, week 12 and week 52).
11. Changes in Magnetic Resonance Imaging (MRI) - brain ventricle volume (cm³) and hippocampal atrophy (cm³) (baseline and week 52).
12. Changes in the Mini-Mental State Examination (screening, baseline, week 4, week 6, week 12, week 18, week 26, week 34, week 42, week 52).
13. Changes in GCAs in lymphocytes (baseline, week 2, week 4, week 6, week 8, week 12, week 18, week 26, week 34, week 42, week 52).
14. Changes in Plasma Ambroxol levels (baseline, week 2, week 4, week 6, week 8, week 12, week 18, week 26, week 34, week 42, week 52).
15. Mayo Fluctuation Questionnaire (baseline, 26 weeks and 52 weeks).

Comments:

A more detailed description of the trial has been published [5].

Targeting the GBA pathway is of great interest, and a number of programs are in development. This study focuses specifically on the impact on cognition. The secondary outcome measures are comprehensive and require a high number of participant visits (11) and procedures, including three lumbar punctures.

The dose of ambroxol under evaluation is 1,050mg per day, approximately 15mg/kg/day. This is much higher than the OTC dose. An even higher dose, 1,260mg, was used in the phase 2 efficacy trial described by Mullins et al. [4]. In the Lawson Health study, the number of 75mg tablets per day is up to 14 per day for the higher dose. The number of tablets to be taken each day by participants with PDD or MCI may thus be a challenge for compliance. However, one inclusion criterion requires the presence of a responsible caregiver for at least 4 days per week.

References:

- [1] Migdalska-Richards A, Ko WKD, Li Q, Bezdard E, Schapira AHV. Oral ambroxol increases brain glucocerebrosidase activity in a nonhuman primate. *Synapse*. 2017;71(7):e21967. doi:10.1002/syn.21967

- [2] Bendikov-Bar I, Maor G, Filocamo M, Horowitz M. Ambroxol as a pharmacological chaperone for mutant glucocerebrosidase. *Blood Cells Mol Dis*. 2013;50(2):141-145. doi:10.1016/j.bcmd.2012.10.007
- [3] Zhang Y, Shu L, Sun Q, et al. Integrated Genetic Analysis of Racial Differences of Common GBA Variants in Parkinson's Disease: A Meta-Analysis. *Front Mol Neurosci*. 2018;11:43. Published 2018 Feb 15. doi:10.3389/fnmol.2018.00043
- [4] Mullin S, Smith L, Lee K, et al. Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucocerebrosidase Gene Mutations: A Nonrandomized, Noncontrolled Trial. *JAMA Neurol*. 2020;77(4):427-434. doi:10.1001/jamaneurol.2019.4611
- [5] Silveira CRA, MacKinley J, Coleman K, et al. Ambroxol as a novel disease-modifying treatment for Parkinson's disease dementia: protocol for a single-centre, randomized, double-blind, placebo-controlled trial. *BMC Neurol*. 2019;19(1):20. Published 2019 Feb 9. doi:10.1186/s12883-019-1252-3

Lilly – LR3154207

Background: D1 receptors (D1R) are a subtype of dopamine receptors present in both subcortical and cortical regions and have been postulated to be involved in PD-CI, making it a potential target. Prior preclinical studies have demonstrated improvement in cognition with D1R modulation, but the development of D1R agonists has faced several limiting challenges such as tachyphylaxis and inverted U-shaped dose-response curves. However, molecules acting as positive allosteric modulators (PAM) of the D1R seem to overcome these challenges [1].

LY3154207 is a novel human D1R subtype-selective PAM that has been developed by Eli Lilly and Company [2]. Backed by preclinical evidence of positive motor and cognitive benefits, the safety profile of the molecule was studied in the phase 1 trial [NCT02562768]. The trial had 2 parts assessing the safety profile and pharmacokinetics in healthy and PD participants, respectively. The study is completed; however, the results are unavailable. The company has moved the molecule forward into the phase 2 trial, the PRESENCE study, which is discussed here. Separately, LY3154207 has been shown to improve wakefulness in sleep-deprived healthy males, highlighting its potential role in excessive daytime sleepiness [3].

Title: Effect of LY3154207 on Cognition in Mild-to-Moderate Dementia Due to Lewy Body Dementia (LBD) Associated With Idiopathic Parkinson's Disease (PD) or Dementia With Lewy Bodies (DLB)

Phase: 2

Objective: To evaluate the safety and efficacy of three doses of LY3154207 in participants with mild to moderate Lewy body dementia.

Status: Completed

Clinicaltrials.gov Identifier: NCT03305809

Sponsor: Eli Lilly and Company

Collaborators: No others specified

Estimated Enrolment: 344

Estimated Completion Date: July 2020

Study Design: This is a phase 2, randomized, parallel assigned, double-blinded, interventional study assessing the safety and efficacy of the study drug, LY3154207, in participants with Lewy body dementia.

Participants between the ages of 40 and 85 years with a clinical diagnosis of PD or dementia with Lewy bodies deemed to have increased functional impairment due to a decline in cognitive functions are eligible for inclusion. The MoCA score must be between 10-23. Certain medication classes are allowed if the participants have been on a stable dose for 3 weeks before the screening and expected to remain on a stable dose throughout the study. The medications allowed include antihypertensives, antiparkinson, antidepressants, medications for cognition and psychosis [clozapine, quetiapine, and pimavanserin]. Participants on antipsychotics other than listed above and anticholinergics will be excluded. Participants are required to have reliable caregivers. Standard exclusionary criteria apply.

Participants will be randomly assigned to one of the four arms:

1. Experimental arm 1: high dose of the investigational drug orally.
2. Experimental arm 2: mid dose of the investigational drug orally
3. Experimental arm 3: low dose of the investigational drug orally
4. Placebo arm

Outcome Measures: The primary outcome measure will assess the change at 12 weeks from baseline in the continuity of attention composite score of the cognitive drug research computerized cognition battery (CDR-CCB).

The secondary outcome measures assess the change in various scales at 12 weeks from baseline. The scales included mostly assess the cognitive and psychiatric domains. Additional measures assess the change in the MDS-UPDRS total score, vital signs, and even the pharmacokinetics.

Comments:

D1R is a potentially interesting target for the management of both PD motor and non-motor disability. While there are other D1R agonists being explored for motor benefits, LY3154207 focuses on cognition. The phase 2 has completed enrolment and is awaiting results.

References

- [1] K.A. Svensson, J. Hao, R.F. Bruns, Positive allosteric modulators of the dopamine D1 receptor: A new mechanism for the treatment of neuropsychiatric disorders, in: *Advances in Pharmacology*, Academic Press Inc., 2019: pp. 273–305. <https://doi.org/10.1016/bs.apha.2019.06.001>.
- [2] J. Hao, J.P. Beck, J.M. Schaus, J.H. Krushinski, Q. Chen, C.D. Beadle, P. Vidal, M.R. Reinhard, B.A. Dressman, S.M. Massey, S.L. Boulet, M.P. Cohen, B.M. Watson, D. Tupper, K.M. Gardinier, J. Myers, A.M. Johansson, J. Richardson, D.S. Richards, E.J. Hembre, D.M. Remick, D.A. Coates, R.M. Bhardwaj, B.A. Diserod, D. Bender, G. Stephenson, C.D. Wolfangel, N. Diaz, B.G. Getman, X.S. Wang, B.A. Heinz, J.W. Cramer, X. Zhou, D.L. Maren, J.F. Falcone, R.A. Wright, S.N. Mitchell, G. Carter, C.R. Yang, R.F. Bruns, K.A. Svensson, Synthesis and Pharmacological Characterization of 2-(2,6-Dichlorophenyl)-1-((1*S*,3*R*)-5-(3-hydroxy-3-methylbutyl)-3-(hydroxymethyl)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (LY3154207), a Potent, Subtype Selective, and Orally Available Positive Allosteric Modulator of the Human Dopamine D1 Receptor, *Journal of Medicinal Chemistry*. 62 (2019) 8711–8732. <https://doi.org/10.1021/acs.jmedchem.9b01234>.
- [3] K. Biglan, P. Ardayfio, W. Kielbasa, K. Svensson, A D1 receptor positive allosteric modulator (LY3154207) enhances wakefulness in sleep deprived healthy volunteers (P3.6-041), *Neurology*. 92 (2019).

University of Michigan - Citalopram

Background: While Selective Serotonin Reuptake Inhibitors (SSRIs) are efficacious in addressing depression, preclinical and clinical data also suggest it may have a positive impact on cognition. In AD animal models and healthy human participants, SSRI lead to lower levels of amyloid- β (A β) in CSF [1]. Clinical data mostly

comes from AD observational studies, wherein long-term SSRI use in MCI participants with depression were associated with a lower risk of conversion to dementia. The beneficial effect is attributed to SSRIs ability to reduce A β plaque formation [1]. In PD, cortical A β plaque levels are associated with the loss of serotonin terminals prompting exploration of serotonergic modulation [2]. Interestingly, post-mortem studies in LBD, including PDD, demonstrate hippocampal neurogenesis with SSRI use [3]. Despite the convincing data, there is a lack of large randomized controlled trials evaluating the efficacy of early and long-term use of SSRIs on cognition.

Citalopram is an SSRI that was first marketed in 1989 and is now widely prescribed, with 24 million prescriptions in the US alone in 2017 [4]. The current study explores the effect of citalopram on the visuospatial domain of cognitive decline, which is an important component of PD-CI.

Title: Citalopram as a Posterior Cortical Protective Therapy in Parkinson Disease

Phase: 2

Objective: This proof-of-concept study aims to test the hypothesis that citalopram use in PD will reduce visuospatial cortex A β plaque accrual, leading to an amelioration of longitudinal visuospatial cognitive decline linked to PDD.

Status: Not yet recruiting.

Clinicaltrials.gov ID: NCT04497168

Sponsor: University of Michigan

Collaborators: National Institute on Aging

Estimated Enrolment: 58

Estimated Completion Date: September 2025

Study Design: Randomized, double-blind, placebo-controlled, single-center study of 20mg per day of citalopram over a treatment period of 26 months.

Outcome Measures: The primary outcome measure is the change in visuospatial cortex Pittsburgh Compound B (PiB) distribution volume ratio (DVR), aimed to assess the density of A β plaques in the brain. Secondary outcome measures include measures of cognition:

1. Change in Benton Judgment of Line Orientation (JOLO) test for visuospatial cognition.
2. Change in MoCA.

All the measures are taken at baseline and 26 months.

Comments:

This study has a clear biomarker driven target and a low number of outcome measures focused clearly on plaque measurement and an improvement in the rate of visuospatial cognitive decline. From a participant perspective, the low number of study visits (2) is also an advantage, particularly for recruitment.

It is interesting that participants should be aged at least 65, a relatively high age for PD trials. The H&Y score is also within a narrow range, 2.0-2.5, unlike that seen in other PD trials. This may lead to reduced variability in results.

References

- [1] B. Mdawar, E. Ghossoub, R. Khoury, Selective serotonin reuptake inhibitors and Alzheimer's disease, *Neural Regeneration Research*. 15 (2020) 41–46. <https://doi.org/10.4103/1673-5374.264445>.
- [2] V. Kotagal, C. Spino, N.I. Bohnen, R. Koeppe, R.L. Albin, Serotonin, β -amyloid, and cognition in Parkinson disease, *Annals of Neurology*. 83 (2018) 994–1002. <https://doi.org/10.1002/ana.25236>.
- [3] A. Gatt, A. Ekonomou, A. Somani, S. Thuret, D. Howlett, A. Corbett, M. Johnson, E. Perry, J. Attems, P. Francis, D. Aarsland, C. Ballard, Importance of Proactive Treatment of Depression in Lewy Body Dementias: The Impact on Hippocampal Neurogenesis and Cognition in a Post-Mortem Study, *Dementia and Geriatric Cognitive Disorders*. 44 (2017) 283–293. <https://doi.org/10.1159/000484437>
- [4] “Citalopram Drug Usage Statistics”. *ClinCalc*. 23 December 2019.

Yonsei University - Donepezil

Background: Donepezil, branded as Aricept, is an ACE-I widely prescribed for the treatment of cognitive impairment with the bulk of evidence coming from AD studies. Despite being broadly used, there is a lack of level A evidence to support the use of ACE-I in MCI [1]. A cholinergic deficit is also a feature of PD, so there is a logical rationale for the use of ACE-I to treat cognitive symptoms in PD [2].

A large (n=550) double-blind, placebo-controlled trial of donepezil in PDD was published in 2012, showing significant improvements in symptoms and suggested that donepezil could improve cognition, executive function, and global status in PDD [3]. Donepezil is licensed for the treatment of PDD in Japan but not the USA. While studied in PDD, there is limited data exploring its effect in PD-MCI [4]. The current study aims to explore the effect of donepezil on the progression of PD-MCI.

Title: Effect of Donepezil on Cognition in Parkinson's Disease with Mild Cognitive Impairment (PD-MCI).

Phase: 2

Objective: To evaluate the efficacy of donepezil in PD-MCI.

Status: Active, not recruiting.

Clinicaltrials.gov ID: NCT02450786

Sponsor: Yonsei University

Collaborators: No others specified

Estimated Enrolment: 80

Estimated Completion Date: August 2019

Study Design: This is an open-label and single center trial. The target dosage is 10mg unless not tolerated, in which case the dosage to be taken will be 5mg. The treatment duration is 48 weeks.

Outcome Measures: The single primary outcome is the rate of cognitive decline using the Korean version of the MMSE measured at baseline and 48 weeks.

The five secondary outcome measures are:

1. Change in cognitive decline (24, 48, and 72 weeks).
2. Change in UPDRS parts I-IV (24, 48, and 72 weeks).
3. Brain structure (cortical thickness, and subcortical volume and shape) and default mode and network with conventional and functional MRI (48 weeks).

4. Brain functional connectivity using digital electroencephalography (48 weeks).
5. Comprehensive neuropsychological test using the Seoul Neuropsychological Screening Battery (SNSB) (48 weeks).

Comments:

The rationale for the Yonsei University trial is that the cholinergic deficits seen in PDD are also present in PD-MCI. The hope is that earlier intervention with donepezil may delay the onset of PDD. The outcome measures are aiming to correlate the results of clinical measurement with structural change via fMRI and EEG. In parallel, the progression of other PD symptoms will be measured using UPDRS.

The treatment duration is 48 weeks, although changes in cognitive decline and UPDRS will be measured again at 72 weeks. The trial is recruiting participants with a confirmed diagnosis of PD-MCI aged over 40. It was due to finish in 2019, although no results appear to have been published yet.

References

- [1] R.C. Petersen, O. Lopez, M.J. Armstrong, T.S.D. Getchius, M. Ganguli, D. Gloss, G.S. Gronseth, D. Marson, T. Pringsheim, G.S. Day, M. Sager, J. Stevens, A. Rae-Grant, Practice guideline update summary: Mild cognitive impairment report of the guideline development, dissemination, and implementation, *Neurology*. 90 (2018) 126–135. <https://doi.org/10.1212/WNL.0000000000004826>.
- [2] W. Poewe, S. Gauthier, D. Aarsland, J.B. Leverenz, P. Barone, D. Weintraub, E. Tolosa, B. Dubois, Diagnosis and management of Parkinson's disease dementia, *International Journal of Clinical Practice*. 62 (2008) 1581–1587. <https://doi.org/10.1111/j.1742-1241.2008.01869.x>.
- [3] Dubois B, Tolosa E, Katzenschlager R, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. *Mov Disord*. 2012;27(10):1230-1238. doi:10.1002/mds.25098.
- [4] J.G. Goldman, D. Weintraub, Advances in the treatment of cognitive impairment in Parkinson's disease, *Movement Disorders*. 30 (2015) 1471–1489. <https://doi.org/10.1002/mds.26352>.

Enterin – ENT-01

Background: ENT-01 is a synthetic form of squalamine, a cationic aminosterol found in the liver of the dogfish shark. Preclinical studies have shown it to compete with α -synuclein for membrane binding sites, to restore normal peristalsis in a PD mouse model, and to prevent α -synuclein aggregation in a *C. elegans* model [1]. ENT-01 is under development by Enterin Inc for the treatment of PD-associated constipation, with a phase 2 open-label study producing very promising results [2].

ENT-01 is not systemically absorbed and exerts its gastrointestinal effects topically via the enteric nervous system (ENS). The trial for PDD will examine the effect of its action on the ENS to influence the gut-brain axis, in theory via inhibition of α -synuclein aggregation.

Title: A Multicenter, Open-Label Study to Evaluate Tolerability and Efficacy of Orally Administered ENT-01 for the Treatment of Parkinson's Disease Dementia.

Phase: 1

Objective: To evaluate the tolerability and efficacy of orally-administered ENT-01 in the treatment of PDD after 10 weeks of treatment.

Status: Active, not recruiting.

Clinicaltrials.gov ID: NCT03938922

Sponsor: Enterin Inc

Collaborators: No others specified.

Estimated Enrolment: 40

Estimated Completion Date: May 2021

Study Design: This is a phase 1, multicenter (3 sites in the USA), open-label study assessing the safety and tolerability of ENT-01 in participants with PDD. The study will recruit participants aged 30-90 years with a clinical diagnosis of PD with dementia. Only MoCA score of < 24 will be included. Standard exclusionary criteria are applied.

All participants will receive the study drug as daily oral dosing for 10 weeks. The study will require 5 visits. Participants will be allowed to adjust the medication dose as specified in the protocol.

Outcome Measures: The primary outcome measure is cognition improvement using the Dementia Severity Rating Scale (DSRS), assessed at baseline and after 10 weeks of treatment.

The secondary outcomes, also assessed at baseline and after 10 weeks of treatment are:

1. Change in the MoCA.
2. Change in symptoms adapted for Parkinson's disease (SAPS-PD). This measures the frequency and/or severity of hallucinations and delusions.
3. Change in Neuropsychiatric Inventory (NPI) and Caregiver Distress (NPI-D).
4. Change in Parkinson's Disease Questionnaire-39 (PDQ-39).

The study will also assess other outcome measures:

1. Change in MDS-UPDRS.
2. Change in skin temperature-determined circadian rhythm.
3. Change in body weight.

Comments:

This study intends to explore the ability of ENT-01 to influence α -synuclein aggregation and the subsequent impact on cognitive symptoms. The timeframe to assess this effect is 10 weeks. Open label design of the study will preclude any meaningful conclusions regarding potential efficacy.

Together with the RASMET (NCT03047629) and KARMET (NCT02781791 and NCT04483479) studies, Enterin are building a solid base of patient experience with ENT-01.

References

- [1] Perni M, Galvagnion C, Maltsev A, Meisl G, Muller MB, Challa PK, Kirkegaard JB, Flagmeier P, Cohen SI, Cascella R, Chen SW, Limbocker R, Sormanni P, Heller GT, Aprile FA, Cremades N, Cecchi C, Chiti F, Nollen EA, Knowles TP, Vendruscolo M, Bax A, Zaslhoff M, Dobson CM. A natural product inhibits the initiation of alpha-synuclein aggregation and suppresses its toxicity. *Proc Natl Acad Sci U S A* 114(2017), E1009–E1017.
- [2] Hauser RA SD, Madrid JA, Rol MA, Frucht S, Isacson S, Pagan F, Maddux BN, Li G, Tse W, Walter BL, Kumar R, Kremens D, Lew MF, Ellenbogen A, Oguh O, Vasquez A, Kinney W, Lowery M, Resnick M, Huff N, Posner J, Ballman KV, Camilleri M, Zaslhoff M, Barbut D. Targeting neurons in the gastrointestinal tract to treat Parkinson's disease. *Clin Parkinsonism Relat Disord* 1(2019), 2–7.

Phase 3 Study in Focus – Tavapadon

While this issue focuses on clinical trials targeting the cognitive domain of PD disability, there are no active or recently completed Phase III studies for this indication. For that reason, we have decided to highlight tavapadon that is being developed for motor indication, but based on the mechanism of action targeting the D1 dopaminergic pathway, it may also be of future interest for cognitive indications.

Background: Tavapadon is a novel D1 selective dopamine agonist being developed by Cerevel Therapeutics. D1 receptors have been of particular interest owing to modulation of the direct pathways. Prior attempts at developing D1 selective agonists were met with tolerability issues and poor pharmacokinetics. Non-catechol-based agents were designed mainly to overcome the challenges noted with previous D1 agonist medications. Tavapadon is one such medication belonging to the novel class of non-catechol-based agents. It is a potent, orally bioavailable, partial dopamine agonist selectively targeting D1/D5 receptors.

Tavapadon has an interesting history of development. Formerly known as PF-06649751, it was initially being developed by Pfizer, who sponsored the initial clinical phase 1 and phase 2 studies. Cerevel Therapeutics, an offshoot of Bain Capital and Pfizer, which was created to continue working on their neuroscience portfolio, eventually took over the drug development.

Even though prior clinical evidence did not support the motor efficacy of partial D1 agonists, based on their unpublished data, the group proceeded with phase 1 studies initially. The phase 1 studies [NCT02373072, NCT02224664] provided a safe passage to phase 2 studies [1].

However, several phase 2 studies [NCT02847650, NCT02687542, NCT03185481] designed to study the safety and efficacy of flexible and fixed dosing were terminated early due to lack of efficacy [2–4]. NCT02687542 was designed to study the efficacy and safety of the multiple fixed dosing up to 15mg in participants with advanced PD. Due to a lack of efficacy in the interim analysis, the study was terminated early. This also led to the termination of the planned continuation study, NCT03185481.

As a result of the lack of efficacy noted in the interim analysis of NCT02687542, NCT02847650 was also terminated early by the sponsor. Despite early termination with only 57 participants enrolled instead of 88, NCT02847650 did meet its primary goal. The results of NCT02847650 were published recently [5]. In this double-blind, placebo-controlled, flexible-dose, 15-week study in early PD participants, a statistically significant improvement in the MDS-UPDRS part III score [4.8 (2.26)] was noted with tavapadon compared to the placebo arm. The drug was well-tolerated, and common side effects included nausea, headache, dry mouth, somnolence, and tremor [6].

Based on this, the molecule has been moved to Phase 3 trials. TEMPO-1 and TEMPO-2 will study the efficacy and safety profile of the drug in a fixed and flexible dosing schedule in participants with early PD. Another Phase 3 study has been announced, TEMPO-3, which will study the flexible dosing of tavapadon but in late-stage PD. The primary outcome measure for TEMPO-3 will be the change in daily “on” time without troublesome dyskinesia. The study has recently been posted on clinicaltrials.gov and plans to start enrolment in late 2020 [7]. It has been registered on the EudraCT as 2019-002951-40 [8].

TEMPO-1

Title: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, 27-Week Trial to Evaluate the Efficacy, Safety, and Tolerability of Two Fixed Doses of Tavapadon in Early Parkinson’s Disease (TEMPO-1 TRIAL)

Objective: To assess the motor efficacy and safety profile of fixed doses of tavapadon in Early PD.

Status: Active, not recruiting

Clinicaltrials.gov Identifier: NCT04201093

Sponsor: Cerevel Therapeutics, LLC

Collaborator: No other specified

Estimated Enrolment: 522

Estimated Completion Date: October 2022

Study Design: This is a phase 3, randomized, parallel assigned, double-blinded, placebo-controlled, **fixed-dose** study evaluating the efficacy, safety and tolerability, and pharmacokinetics of two fixed doses of tavapadon in participants with early PD.

Clinically diagnosed PD participants between age 40-80 years with H&Y stage less than 2 and within 3 years of disease duration from the time of diagnosis are eligible to participate. The MDS-UPDRS part II and III scores should be ≥ 2 and 10, respectively, at the time of screening. Participants should be dopaminergic drug naïve and be willing to refrain from non-permitted PD medications. Participants who have been taking dopaminergic agents but for less than three months and at least two months before signing consent will be eligible for inclusion. The use of MAO-Inhibitors is allowed. Apart from standard exclusionary criteria, participants with impulse control disorders, certain neuropsychiatric symptoms, and MoCA < 26 will be excluded.

The participants will be randomized to one of the three arms, which are:

1. Experimental arms: there will be two experimental arms where participants will be randomized to receive tavapadon titrated to either 5mg or 15mg orally daily for 27 weeks.
2. Comparator arm where participants will receive a matching placebo orally once a day for 27 weeks.

The study is being conducted at 11 sites across the USA.

Outcome Measures: The primary outcome assesses the change in MDS-UPDRS parts II and III combined score up to 27 weeks from baseline.

The secondary measures include the following:

1. Percentage of responders with 'Much improved' or 'Very much improved' rating on the Participant global impression of change (PGIC) up to 27 weeks.
2. The PGIC score up to 27 weeks.
3. Change in MDS-UPDRS I, II, and III combined and individual scores up to 27 weeks from baseline.
4. Change in Clinical global impression (CGI) - severity of illness score and CGI- Improvement score up to 27 weeks from baseline.
5. Change in Epworth sleepiness scale, Impulsive-compulsive disorders in Parkinson's disease rating scale up to 27 weeks.
6. Change in Columbia-suicide severity rating scale up to 27 weeks.
7. Number of participants with treatment-emergent adverse events will be monitored up to 31 weeks.

TEMPO-2

Title: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Flexible-Dose, 27-Week Trial to Evaluate the Efficacy, Safety, and Tolerability of Tavapadon in Early Parkinson's Disease (TEMPO-2 Trial)

Objective: To assess the motor efficacy and safety profile of flexible dosing of tavapadon in Early PD

Status: Active, not recruiting

Clinicaltrials.gov Identifier: NCT04223193

Sponsor: Cerevel Therapeutics, LLC

Collaborator: No other specified

Estimated Enrolment: 296

Estimated Completion Date: November 2022

Study Design: This is a phase 3, double-blind, randomized, placebo-controlled, parallel-group, **flexible-dose**, 27-week trial designed to evaluate the efficacy, safety, and tolerability of tavapadon in participants with early PD.

The inclusion and exclusion criteria for TEMPO-2 are the same as TEMPO-1

This study has two arms:

1. Experimental arm where participants will be randomized to receive tavapadon anywhere from 5 to 15mg daily for 27 weeks.
2. Placebo comparator arm where participants will receive a placebo for 27 weeks.

The study is being conducted at seven sites across the USA, different to the TEMPO-1 study sites.

Outcome Measures: The primary and secondary outcome measures for TEMPO-2 are similar to TEMPO-1 with minor changes in duration.

The primary outcome remains the same as TEMPO-1 and will assess the change in MDS-UPDRS part II and III combined score up to 27 weeks from baseline.

The secondary measures are the same as TEMPO-1 except for the change in MDS-UPDRS I, II, and III individual scores will be assessed up to 29 weeks.

TEMPO-3

Title: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Flexible-Dose, 27-Week Trial to Evaluate the Efficacy, Safety, and Tolerability of Tavapadon as Adjunctive Therapy for Parkinson's Disease in Levodopa-Treated Adults With Motor Fluctuations (**TEMPO-3** Trial)

Objective: To assess the motor efficacy and safety profile of flexible dosing of tavapadon as adjunctive therapy in advanced PD

Status: Not yet recruiting

Clinicaltrials.gov Identifier: NCT04542499

Sponsor: Cerevel Therapeutics, LLC

Collaborator: No other specified

Estimated Enrolment: 368

Estimated Completion Date: August 2022

Study Design: This is a phase 3, double-blind, randomized, placebo-controlled, parallel-group, **flexible-dose**, 27-week trial designed to evaluate the efficacy, safety, and tolerability of tavapadon as adjunctive therapy in advanced PD participants already on levodopa and with motor fluctuations.

The inclusion criteria for TEMPO-3 is different to TEMPO-1 and 2 for obvious reasons. It will include clinically diagnosed PD participants between age 40-80 years with “on” state H&Y stage between 2–3. Participants should be levodopa responsive, taking at least 400mg/day and be on a stable dose for at least four weeks before screening. Other adjunctive therapies are allowed if started >90 days before signing the consent and is expected to be stable throughout the study. Standard exclusionary criteria apply. Participants from prior tavapadon trial will be excluded.

This study has two arms:

1. Experimental arm where participants will be randomized to receive tavapadon anywhere from 5 to 15mg daily for 27 weeks.
2. Placebo comparator arm where participants will receive a placebo for 27 weeks.

The study is being conducted at 21 sites across the USA.

Outcome Measures: All the measures will assess the change from baseline. The primary outcome will assess the change in the total “on” time without troublesome dyskinesia based on the Hauser diary entries at 27 weeks. The secondary outcomes will measure the following:

1. Change in the total ‘Off’ times at 27 weeks.
2. Change in total “on” and “off” times without troublesome dyskinesia at weeks 2, 5, 8, 11, 14, 18, 22, 26, and 27.
3. Change in MDS-UPDRS part I, II, and III individual scores at 27 weeks.

Comments:

Tavapadon is an exciting molecule with the potential for therapeutic benefit by modulating the direct pathways in the basal ganglia circuitry. However, the drug has had a few setbacks in phase 2 studies. The advanced stage of the disease and fixed medication dose may account for the lack of efficacy in the interim analysis of NCT02687542. TEMPO-3, likely learning from phase 2 results, will study the molecule as adjunctive therapy with flexible dosing. Notably, the NCT02847650 trial showed a safe profile with a positive change in motor scoring in early PD, but the results were not clinically meaningful. Given the results were from a Phase 2 study with partial data analysis, we will be on the lookout for TEMPO-1 and 2 study results. While D1R is a potential target for PD-CI, TEMPO studies do not include any secondary cognitive measures and exclude participants with MoCA less <26 for early PD and those with troublesome CI in advanced PD. Their focus remains on the motor profile of PD.

References:

- [1] U.S. Sohur, D.L. Gray, S. Duvvuri, Y. Zhang, K. Thayer, G. Feng, Phase 1 Parkinson's Disease Studies Show the Dopamine D1/D5 Agonist PF-06649751 is Safe and Well Tolerated, *Neurology and Therapy*. 7 (2018) 307–319. <https://doi.org/10.1007/s40120-018-0114-z>.
- [2] Efficacy, Safety and Tolerability of PF-06649751 in Parkinson's Disease Patients With Motor Fluctuations - *ClinicalTrials.gov*, (n.d.). <https://clinicaltrials.gov/ct2/show/NCT02687542>.
- [3] Efficacy, Safety and Tolerability of PF-06649751 in Parkinson's Disease Patients at Early Stage of the Disease - *ClinicalTrials.gov*, (n.d.). <https://clinicaltrials.gov/ct2/show/NCT02847650>.
- [4] Efficacy, Safety and Tolerability of PF-06649751 in Parkinson's Disease Patients With Motor Fluctuations - *ClinicalTrials.gov*, (n.d.). <https://clinicaltrials.gov/ct2/show/NCT02687542?term=PF-06649751&rank=5>.
- [5] Efficacy, Safety and Tolerability of Tavapadon in Subjects With Early Stage Parkinson's Disease - *MDS Abstracts*, (n.d.). <https://www.mdsabstracts.org/abstract/efficacy-safety-and-tolerability-of-tavapadon-in-subjects-with-early-stage-parkinsons-disease>.
- [6] R. Riesenber, J. Werth, Y. Zhang, S. Duvvuri, D. Gray, PF-06649751 efficacy and safety in early Parkinson's disease: a randomized, placebo-controlled trial, *Therapeutic Advances in Neurological Disorders*. 13 (2020). <https://doi.org/10.1177/1756286420911296>.
- [7] Cerevel Therapeutics Initiates Phase 3 Program Testing Tavapadon in PD for Improved Motor Function, (n.d.). <https://parkinsonsnewstoday.com/2020/01/16/cerevel-therapeutics-initiates-phase-3-program-testing-tavapadon-parkinsons-improved-motor-function>.
- [8] *Clinical Trials register* - <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2019-002951-40>.