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Clinical Trial Highlights – an update on previously reviewed trials

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BACKGROUND

The Journal of Parkinson's Disease started the Clinical Trial Highlights (CTH) section in January 2019. The objective was "to raise awareness of the clinical trial landscape in Parkinson's disease (PD), promoting discussion and progress in the conduct and outcome of studies." In addition, it was intended to be "a resource centre for academics, medics, industry and PwP, particularly those wanting to participate in clinical trials." After three years, it is useful to step back and review the progress of the trials we featured. Since the start, we have reviewed studies in seven categories. CTH has hosted two reviews of the clinical trials pipeline. It also provides a resource list covering various aspects of information on, and participating in, clinical trials in PD. The home page for CTH is at https://www.journalofparkinsonsdisease.com/clinical-trial-highlights .

OVERVIEW

Some of the trials we reviewed had already been completed at the time of our publications, but the projects were still active and were included in the review in order to give a full overview of the drug development in each area. When we exclude these previously completed studies from this current update, we have reviewed 58 studies of which 13 have been completed and six of these studies have also published results on www.clinicaltrials.gov .

Since our previously published review of each category, new trials have started and the reviewed trials have progressed. This brief update gives the current status of trials in the respective categories.

CATEGORY UPDATE

Targeting α-synuclein

The formation of oligomers and fibrils of α-synuclein is strongly associated with the pathology of PD. There are potential therapies under development that target the spread of multimeric forms of a α-synuclein from cell to cell, using synthetic antibodies that recognise specific epitopes on aggregated α-synuclein. Other small molecule-based therapies aim to prevent mis-folding or the formation of multimers. A summary of the status of therapies targeting α-synuclein is shown in Table 1.

Antibody-based therapies

Roche's prasinezumab, a synthetic monoclonal antibody, failed to meet its primary outcomes in the phase 2 PASADENA study (NCT03100149), a statistically significant reduction in parts I, II and III of the MDS-UPDRS. However, it did show signals of efficacy on selected prespecified secondary and exploratory clinical

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endpoints and was generally well-tolerated [1]. The PASADENA study has entered a year-long extension and a new phase 2 study, entitled PADOVA (NCT04777331), that is enrolling early but treated PD participants, is now under way.

Biogen's antibody program, BIIB054 (cinpanemab), failed to meet its primary and secondary outcomes in the phase 2 SPARK study (NCT03318523). The program has been terminated. AstraZeneca's MEDI1341 has completed a single ascending dose phase 1 study (NCT03272165), and is now in a phase 1 multiple ascending dose study (NCT04449484).

Lundbeck's antibody-based LuAF82422 has completed phase 1 for PD, with results yet to be announced (NCT03611569). The company recently announced their intention to evaluate the compound in a phase 2 study for multiple system atrophy (MSA) [2].

New programs have entered the clinical stage of development. A phase 1 trial was registered for ABBV0805, a synthetic antibody against aggregated α- synuclein. It started in March 2020 but was withdrawn in July 2020 for "strategic considerations" (NCT04127695).

Affiris' vaccine against α-synuclein, PD01, has been renamed ACI-7104 following the acquisition of Affiris by AC Immune, and a phase 2 study is being planned but as yet does not appear to have been registered. AC Immune have also completed a study to optimise morphomer-based α-synuclein PET tracers (NCT05067192).

Vaxxinity's (formerly named United Neurosciences) program for UB-312 is now in phase 1 (NCT04075318).

UCB's anti-α-synuclein antibody, UCB7853 is in early phase 1 with testing in healthy male volunteers (NCT04651153).

Small molecule approaches

The two studies on nilotinib, a c-Abl inhibitor that increases α-synuclein clearance, at Georgetown University (NCT02954978) and Northwestern University/ MJFF (NCT03205488) both demonstrated acceptable tolerability and safety but failed to show symptomatic benefit in motor or cognitive domains. It appears that low brain penetrance was the major factor in the disappointing results, so the c-Abl kinase remains a strong target for future therapies.

Phenylbutyrate up-regulates DJ-1 and has been shown to protect dopaminergic neurons *in vitro* [3]. The Colorado University phase 1 study on glycerol phenylbutyrate is planned to complete in October 2021.

Squalamine inhibits the formation of aggregated α-synuclein in pre-clinical models, and restores the function of the enteric nervous system [4]. Following a successful phase 2a trial in PD-associated constipation (RASMET; NCT03047629), Enterin has started two further phase 2 trials for ENT-01, a synthetic version of squalamine. The first is a phase 2b in constipation (KARMET; NCT03781791); the other is evaluating the potential for the use of ENT-01 in PD dementia (NCT03938922).

Mannitol has been shown to inhibit α-synuclein aggregation in pre-clinical animal models [5]. It is now in a phase 2 study (NCT03823638) although the entry on clinicaltrials.gov is of "Unknown" status.

Modag's Anle138b also modulates α-synuclein oligomer formation and protects against dopaminergic neuronal loss in preclinical models [6]. It has completed a phase 1 dose-ranging study (NCT04208152), and is now in a phase 1 trial to assess pharmacokinetics and pharmacodynamics in PD patients (NCT04685265).

UCB and their partner Neuropore have successfully completed a phase 1 with UCB0599, an inhibitor of α-synuclein misfolding (NCT04875962). The molecule is now in phase 2 (NCT04658186).

Annovis Bio (formerly QR Pharma) has initiated a phase 2 trial (NCT04524351) with ANVS401 (posiphen). Pre-clinical work showed that the molecule targets neurotoxic proteins (α-synuclein, tau and β-amyloid) to enhance axonal transport [7].

A summary of clinical trials targeting α-synuclein is shown in Table 1.

Table 1 – summary of clinical trials in PD targeting α-synuclein.

SPONSOR	AGENT	REGISTRY NUMBER	PHASE	REGISTRY STATUS	COMPLETION DATE
Biogen	BIIB054	NCT03318523	2	Terminated	29 April 2021
Lundbeck	Lu AF82422	NCT03611569	1	Recruiting	31 August 2021 (estimated)
Roche	Prasinezumab	NCT03100149	2	Active, not recruiting	23 April 2026 (estimated)
AstraZeneca	MEDI1341	NCT03272165	1	Completed	31 March 2021
UCB	UCB7853	NCT04651153	1	Recruiting	June 2023 (estimated)
Colorado University	Glycerol phenyl butyrate	NCT02046434	1	Active, not recruiting	October 2021
Georgetown University	Nilotinib	NCT02954978	2	Unknown	July 2020 (estimated)
Northwestern University/ MJFF	Nilotinib	NCT03205488.	2	Completed	28 September 2019
Abbvie	ABBV0805	NCT04127695	1	Withdrawn	July 2022
Vaxinnity	UB312	NCT04075318	1	Recruiting	30 December 2022
Enterin	ENT-01	NCT03781791	2	Recruiting	September 2021 (estimated)
Enterin	ENT-01	NCT03938922	2	Active, not recruiting	25 May 2021 (estimated)
Hadassah Medical Organisation	Mannitol	NCT03823638	2	Unknown	31 December 2020 (estimated)
Modag	Anle138b	NCT04208152	1	Completed	4 August 2020
Modag	Anle138b	NCT04685265	1	Recruiting	June 20222 (estimated)
UCB	UCB0599	NCT04875962	1	Completed	19 February 2020
UCB	UCB0599	NCT04658186	2	Recruiting	July 2024 (estimated)
Annovis Bio	ANVS401 (posiphen)	NCT04524351	2	Active, not recruiting	1 December 2021 (estimated)

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Gene therapy

Our original review had two programs in phase 2 and two in phase 1. Of these, one phase 1 has been officially terminated (Jichi Medical University; NCT02418598), while the phase 2 for VY-AADC (Amino Acid Decarboxylase) from Voyager Therapeutics has been placed on clinical hold by the FDA, and Voyager's partner, Neurocrine, has terminated the agreement between the companies [1].

The Axo-Lenti-PD program at Axovant continues (NCT03720418), with target completion due in 2022, although the final trial end date is in 2031. The NINDS study for AAV-GDNF (Glial cell-Derived Neurotrophic Factor; NCT16211851) remains active but not recruiting, as it approaches the projected study end date of February 2022.

Since our review, two further studies have been registered. Ask Bio (formerly Brain Neurotherapy Bio) is also pursuing GDNF delivered by an AAV2 vector in phase 1 (NCT04167540). Prevail Therapeutics has PR001 in a phase 1/2 trial in patients with at least one mutation in the GBA1 gene (NCT04127578). MeiraGTx appears to be still preparing for a phase 2 study with AAV-GAD (Glutamic Acid Decarboxylase), but as yet there are no registry entries for this therapy. A summary of trials of gene therapy in PD is shown in Table 2.

Table 2 – summary of clinical trials in PD using gene therapy.

SPONSOR	AGENT	REGISTRY NUMBER	PHASE	REGISTRY STATUS	COMPLETION DATE
Jichi Medical University	AAV-hAADC	NCT02418598	1	Terminated	31 March 2018
Voyager Therapeutics	VY-AADC02	NCT03562494	2	Active, not recruiting	December 2022 (estimated)
Axovant	AXO-Lenti-PD	NCT03720418	2	Active, not recruiting	June 2022/December 2031 (estimated)
NINDS	AAV2-GDNF	NCT01621581	1	Active, not recruiting	1 February 2022 (estimated)
Ask Bio	AAV2-GDNF	NCT04167540	1	Recruiting	June 2026 (estimated)
Prevail Therapeutics	AAV9-GBA1	NCT04127578	1/2	Recruiting	June 2027 (estimated)

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Dyskinesia

In the July 2019 edition, we reviewed 7 trials in detail focusing on symptomatic management of dyskinesia [1]. Three trials are ongoing, two have been discontinued, and two are complete. Since our initial review, three more trials for symptomatic treatment for dyskinesia have been initiated.

Addex therapeutics have been developing dipraglurant, an allosteric modulator of the metabotropic glutamate 5 receptor (mGluR5), targeting dyskinesia. Since their completion of a phase 2a trial with results published in

2016, the company has initiated two clinical trials, NCT04857359 and NCT05116813 [2-4]. NCT04857359 is a Phase 2b/3, double blind, randomized, placebo-controlled study aiming to evaluate the efficacy of dipraglurant for dyskinesia in PwP receiving levodopa. The trial is of 12 weeks' duration measuring changes to UDysRS. After 12 weeks, participants will have the option to join NCT05116813, an open label extension study that will evaluate long term safety and tolerability of the drug over 12 months by monitoring the incidence of adverse events. Both studies have started recruitment and are estimating completion in December, 2022 and August, 2023 for the open label extension and placebo-controlled studies respectively.

No updates are available regarding the eltoprazine trials. The Hôpitaux de Paris trial evaluating buspirone for dyskinesia continues to recruit and is expected to complete by end of 2021 or beginning of 2022. The trial with JM-010, a combination therapy of buspirone and zolmitriptan, continues to recruit participants and has extended the completion date to March 2022 from the original date of June 2021. NCT02589340, studying the effect of buspirone in combination with amantadine on dyskinesia was terminated in March 2021 due to low enrolment (n=6, estimated enrolment was for 15 participants) [5]. Having enrolled 23 patients, the phase 2 study investigating pridopidine was terminated in November 2020 citing COVID-19 as the reason [6]. The molecule continues to be explored for Huntington's disease and amyotrophic lateral sclerosis.

IRL790, a novel dopamine receptor D3 antagonist, completed the phase 2 study in June 2019, as anticipated, enrolling a total of 75 participants. Formal results have not been published yet. Based on the company website and clinicaltrial.gov updates, the study achieved a clinically meaningful effect on dyskinesia as measured by Hauser diaries and UPDRS scale, which were the secondary outcomes for the study. The updates have not mentioned the effect on the primary outcome measure of UDysRS [7, 8]. The molecule has since been advanced to a longer (3 months) and larger (140 participants) phase 2b/3 study evaluating its effect on dyskinesia (NCT04435431). The trial has been recruiting since October 2020 and is estimated to complete by January 2022 [9]. The primary outcome will measure change in the ON-time without troublesome dyskinesia based on 24 hr Hauser diary entries instead of UDysRS, likely due to not meeting the primary end point in the Phase 2a study [7-9]. Since the last review, IRL790 has been granted the International Non-proprietary Name (INN), mesdopetam [8].

Two of the new trials are exploring molecules affecting NMDA receptors. NCT04912115, sponsored by PharmaTher Inc. is a multi-center, phase 2, randomized, double-blind, prospective trial evaluating the effects of intravenous infusion of ketamine on dyskinesia in participants with PD over a period of 8 weeks. The study includes an active control arm with intravenous midazolam infusion. It is estimated to complete by December 2021 [10]. NCT04147949, sponsored by VistaGen Therapeutics, Inc., is a randomized, double-blind, placebo-controlled, crossover, proof of concept, phase 2 study exploring the efficacy and safety of AV-101 (L-4-chlorokynurenine) in PwP with dyskinesia, over a period of 2 weeks. AV-101 is a prodrug for 7-chlorokynurenic acid, which is a potent and specific NMDA receptor glycine site antagonist with poor CSF penetrance [11].

A summary of clinical trials for dyskinesia is shown in Table 3.

Table 3 – summary of clinical trials in PD for dyskinesia.

SPONSOR	AGENT	REGISTRY NUMBER	PHASE	REGISTRY STATUS	COMPLETION DATE
Coeptis/Elto Pharma	Eltoprazine	NCT02439125	2	Unknown	December 2017
Hôpitaux de Paris	Buspirone	NCT02617017	3	Unknown	June 2018
Contera/ Bukwang	JM-010 (buspirone and zolmitriptan)	NCT03956979	2	Recruiting	March 2022
Oregon University	Buspirone and amantadine	NCT02589340	1	Terminated	23 February 2021
Integrative Research Laboratories	IRL-790	NCT03368170	2	Completed	12 June 2019

Table 3 – (Continue)

SPONSOR	AGENT	REGISTRY NUMBER	PHASE	REGISTRY STATUS	COMPLETION DATE
Prilenia	Pridopidine	NCT03922711	2	Terminated	22 July 2020
Pharmather	Ketamine	NCT04912115	2	Enrolling by invitation	31 December 2021 (estimated)
VistaGen Theapeutics	AV-101	NCT04147949	2	Not yet recruiting	April 2024 (estimated)
Addex Pharma	ADX48621 (dipraglurant)	NCT04857359	2/3	Recruiting	August 2023 (estimated)
Addex Pharma	ADX48621 (dipraglurant)	NCT05116813	2/3	Recruiting	December 2022 (estimated)

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Levodopa and dopamine agonist infusion therapies

Despite the two currently available infusion therapies, there is scope for the development of more sophisticated and user-friendly alternatives for drug delivery. In our previous issue on infusion therapies, we had reviewed 6 trials [1]. Five trials are ongoing and one has been completed. In the interim, two new trials have been initiated and one of them has already been concluded.

Abbvie has been working on subcutaneous (sc) infusion of ABBV-951, now known as foslevodopa/foscarbidopa. ABBV-951 is a solution of these prodrugs for levodopa/carbidopa (LD/CD) which has been proven to have a stable LD exposure via the sc route [2]. NCT03781167 is the phase 3 efficacy trial of ABBV-951 in PwP. The recruitment status of the trial has been updated to active, not recruiting. Results and further information are not yet available.

Since the last review, Abbvie also initiated and recently concluded a 12-week, phase 3, randomized, double-blind, double-dummy, active-controlled study of continuous sc infusion of ABBV-951 in patients with advanced Parkinson's disease. The study was first posted on clinicaltrials.gov in May 2020 (NCT04380142). In October 2021, Abbvie announced statistically significant positive results from the study [3]. At week 12, continuous 24 hr/day sc infusion of ABBV-951 improved ON time by 2.72 hr as compared to oral LD/CD (0.92hr). Similarly, the OFF time reduced by 2.75 hr with ABBV-951 and by 0.96 hr among those on oral LD/CD. The benefits were noted as early as 1 week after starting infusion. While most of the adverse events (AE) are reported to be mild to moderate, 21.6% discontinued treatment with ABBV-951 as compared to 1.5% in the active control arm. Common AE included infusion site AE, dyskinesia, motor fluctuation, hallucination, balance disorder, falls, constipation, and peripheral swelling. The results are expected to be published soon.

Neuroderm's ND0612 sc infusion (NCT04006210) continues to recruit and has extended its study completion date to October 2023. It has also increased anticipated enrolment to 380 from 300. Rennes University's EARLY-PUMP study continues to recruit and has extended its study completion date to June 2025. US WorldMed's INFUS-ON trial of continuous apomorphine infusion pump continues to recruit patients. Supernus Pharmaceuticals, Inc has acquired US WorldMed's CNS portfolio including the apomorphine infusion pump now labelled as SPN-830. Supernus filed an NDA for SPN-830 based on previous trials but is working on pump optimisation.

IPO-001, a phase 1 pharmacokinetic study of Infudopa SubC™ and Infudopa IntraV™ compared to LD/CD intestinal gel, completed in April 2020. According to Dizlin Pharmaceutical's press release the study demonstrated similar plasma levodopa levels with Infudopa SubC™ compared to LCIG and non-inferiority with respect to plasma level fluctuations. Both formulations are reported to provide similar motor control compared to LCIG. Mild to moderate infusion site reactions were noted with the sc route which was expected [4]. Results and publication are awaited. Dizlin intends to file for marketing authorization of Infudopa IntraV™ in Europe and USA in 2023 [5]. The company has declared a future clinical tolerability study but no further details are available.

Lillie University Hospital in France is conducting a proof-of-concept clinical phase 1/2b study (NCT04332276) which is currently recruiting participants. The study will evaluate the feasibility, safety first, and then the effectiveness of continuous dopaminergic stimulation by cerebroventricular administration of A-dopamine for advanced PD. This comes after a successful pre-clinical study where intracerebroventricular administration of the drug demonstrated improved motor symptoms without tachyphylaxis and dyskinesia with high dose [6]. A-dopamine, which is dopamine prepared in anaerobic conditions to avoid oxidation, will be stored in an intra-abdominal pump expected to be refilled once in 2 weeks. The study is estimated to complete by March 2023.

A summary of clinical trials for infusion therapies is shown in Table 4.

Table 4 – summary of clinical trials in PD for infusion therapies.

SPONSOR	AGENT	REGISTRY NUMBER	PHASE	REGISTRY STATUS	COMPLETION DATE
Abbvie	ABBV-951	NCT3781167	3	Active, not recruiting	27 September 2022 (estimated)
Mitsubishi Tanabe/ Neuroderm	ND0612	NCT04006210	3	Recruiting	30 October 2023 (estimated)
Rennes University	EARLY PUMP	NCT02864004	3	Recruiting	3 September 2024 (estimated)
US World Meds	INFUS-ON	NCT02339064	3	Active, not recruiting	September 2021
Dizlin	Infudopa	NCT03419806	1	Completed	20 April 2020
Lille University Hospital	DIVE	NCT04332276	1/2	Recruiting	March 2023 (estimated)

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GLP-1 agonists

The repurposing of GLP-1 agonists from diabetes to PD, which we reviewed in April 2020, has a rich pipeline of trials, with one each in phase 1 and phase 3, and six in phase 2. Three of the phase 2 trials are due to complete at the end of 2021, so we expect results to be announced in the first half of 2022. No further trials for GLP-1 agonists have been added to the registries. A summary of clinical trials for GLP-1 agonists in PD is shown in Table 5.

Table 5 – summary of clinical trials in PD targeting for GLP-1 agonists.

SPONSOR	AGENT	REGISTRY NUMBER	PHASE	REGISTRY STATUS	COMPLETION DATE
University College, London	Exenatide	NCT04232969	3	Recruiting	30 April 2024 (estimated)
Stockholm Healthcare Services/Karolinska Institute	Exenatide	EUDRA CT 2019-000732-26	2	Not stated	Not stated
Peptron	PT320	NCT04269642	2	Active, not recruiting	31 December 2021 (estimated)
Florida University	Exenatide	NCT03456687	1	Active, not recruiting	May 2022 (estimated)
Neuraly	NLY-01	NCT04154072	2	Recruiting	December 2022 (estimated)
Cedars Sinai	Liraglutide	NCT02953665	2	Active, not recruiting	December 2021 (estimated)
Oslo University	Semaglutide	NCT03659682	2	Not yet recruiting	31 December 2024 (estimated)
Toulouse University Hospital	Lixisenatide	NCT03439943	2	Active, not recruiting	December 2021 (estimated)

PD Cognition

There is a significant unmet need for developing therapies for symptomatic and disease modification for PD cognitive impairment (CI) and PD dementia (PDD). We have reviewed 8 clinical studies in different stages and targets aimed to improve cognition in PwP with CI [1]. Three studies have been completed while the remaining five are ongoing. There are four new studies under this category since our last review.

Anavex®2-73 (blarcamesine) is an orally-available sigma-1 receptor (S1R) activator which is being evaluated for PD dementia in a phase 2, multi-center, double-blind, randomized, placebo-controlled trial. The study is now complete and enrolled 132 participants in a 1:1:1 ratio into either treatment arm of 30mg, 50mg ANAVEX®2-73, or placebo. The results have not been published but according to the Anavex life sciences press release, the study showed positive results in both cognitive and motor domains. It met its primary cognitive endpoints, which were CDR system Continuity of Attention (CoA) ($p = 0.029$) and CDR system Power of Attention (PoA) ($p = 0.015$). The study also met its secondary motor endpoints which included MDS-UPDRS Part III ($p = 0.024$) and MDS-UPDRS total ($p = 0.038$). At the end of 14 weeks, the adjusted mean difference in MDS-UPDRS Total score was -14.51 ($p = 0.034$) with the high dose treatment arm compared to placebo [2]. The data will be submitted to FDA to seek regulatory guidance.

NMDA modulation has been the target of several medications for CI. NYX-458 by Aptinyx, and DAAOI-P by China Medical University are two drugs modulating the NMDA system and continue to recruit. NCT02914366 evaluating ambroxol for PDD continues with recruitment as well. It was estimated to complete by December 2021 but no further updates are available.

The study completion date for NYX-458 has been extended to December 2022. The trial has made a few changes since our last update. The inclusion criteria have been extended to include dementia with Lewy bodies (DLB). The study initially intended to have three experimental arms evaluating 10mg, 30mg, or 100mg daily dose of NYX-458. The modifications indicate that it will only be comparing 30mg of the drug against placebo. The inclusion criteria have been updated to include PD with CI or DLB, both with MoCA between 15-25.

LY3154207 (Mevidalen) is a novel human D1R subtype-selective positive allosteric modulator that has been developed by Eli Lilly and Company. PRESENCE (NCT03305809) was a phase 2, placebo-controlled, study evaluating the effectiveness of different doses of mevidalen over a period of 12 weeks. The study has completed and results were anticipated at the American Academy of Neurology 2021 annual meeting [3]. The data have been released to the clinicaltrials.gov registry and are yet to be peer-reviewed. The study failed to achieve its

primary outcome, which was Continuity of Attention (CoA) Composite Score of the Cognitive Drug Research Computerized Cognition Battery (CDR-CCB). Among the long list of secondary outcomes evaluating the cognitive and psychiatric domains, statistically significant mild improvement was noted with high dose (75mg) in the Alzheimer's Disease Cooperative Study-Clinician Global Impression of Change (ADCS-CGIC) Score, Epworth sleepiness scale, and MDS-UPDRS (I-III) mostly. AE were more in the higher dose arm. Falls were the most common AE followed by fatigue, dizziness, and nausea [4].

University of Michigan's proof of concept trial (NCT04497168) exploring if citalopram therapy could delay visuospatial cognitive decline in PD continues with recruitment. No updates have been posted for Enterin-ENT-01 which is still active, not recruiting (NCT03938922).

While studied extensively for PDD, there is limited evidence of the efficacy of donepezil in PD-MCI. Yonsei University explored this in their two-arm, open-label, non-randomized trial investigating the effect of donepezil on PD-MCI over 48 weeks. Results were published in February 2021 and failed to reach the primary outcome [5]. Of the 80 enrolled participants, the study result included 21 from the treatment arm and 29 as controls. There was no statistically significant change to any of the cognitive scales utilized after 48 weeks of treatment with donepezil. Short evaluation duration, high dropout rates and non-randomized design could be a few of the reasons that contributed to negative results. The conversion rate from PD-MCI to PDD was notably lower at 4%, though this seems to be largely influenced by follow up duration and small sample size. Even though no clinical change was noted, the correlation with EEG demonstrated that donepezil may modulate and enhance cholinergic function in PD-MCI, mainly localized to the medial temporal region. Perhaps, further studies of longer duration and larger dataset may help understand if modulating the cholinergic system has any meaningful clinical benefit for PD-MCI.

Four new studies targeting PD cognition have been posted since our last review. CuraSen Therapeutics, Inc. is targeting the adrenergic system for PD cognition. It is evaluating the cognitive benefits and pharmacodynamic effects of co-administration of CST-103/CST-107 in a phase 2, randomized, placebo-controlled, double-blind, crossover trial (NCT04739423). The study will include approximately 40 participants with PD-MCI with REM-sleep behavior disorder, MCI, and DLB or PD-dementia. The study is currently recruiting and anticipated to finish by 2022. CST-103 is a beta-2 adrenoceptor agonist, which was shown to increase cerebral blood flow in PD-MCI in a recent phase 1b trial [7]. CST-107 is a beta blocker with minimal brain penetration and is being co-administered with CST-103 to counter the peripheral AE of increased heart rate, tremor, and palpitations. In the phase 1b trial of CST-103, co-administration with CST-107 did not have any effect on the CST-103 induced changes to cerebral blood flow.

Eisai Inc. has been developing E2027, a selective phosphodiesterase (PDE) 9 inhibitor. It is currently in a phase 2, open-label study (NCT04764669) to evaluate the pharmacodynamic effects, efficacy, safety, and tolerability of E2027 in participants with DLB or PD Dementia, with or without amyloid co-pathology. The study anticipates enrolling 32 participants and is estimated to complete in January 2022.

PD-MIND (NCT04810104) is an international, multi-center, randomized, double-blind, placebo-controlled, parallel-group, phase 2a study of AZD0328, a selective $\alpha 7$ nicotinic receptor agonist, in PD-MCI. The study will enrol 160 participants with PD-MCI assigned to either placebo or active treatment for 12 weeks. It is anticipated to complete in June 2022. NCT04643327 is a proof of concept double-blind, randomised-controlled within-subject crossover trial evaluating the efficacy of levetiracetam for PD-MCI. The study is estimated to complete by December 2023.

Athira Pharma's ATH-1017 is based on Hepatocyte Growth Factor (HGF) and will be administered subcutaneously in a phase 2 study (NCT04831821). The study is planning to enrol 75 participants with PDD or DLB and is double blind, randomized and placebo-controlled. The treatment duration is six months.

The Central South University in China is assessing the potential for sulphoraphane, extracted from broccoli sprouts, in a phase 2 study with two primary outcome measures, the MATRICS Cognitive Consensus Battery and MDS-UPDRS (NCT05084365). Treatment time is 6 months and the design is randomized, double-blind and placebo-controlled, with enrolment of 100 patients.

A summary of clinical trials in PD cognition is shown in Table 6.

Table 6 – summary of clinical trials for PD cognition.

SPONSOR	AGENT	REGISTRY NUMBER	PHASE	REGISTRY STATUS	COMPLETION DATE
Anavex	Anavex 2-73	NCT03774459	2	Completed	30 September 2020
Aptinyx	NYX-458	NCT04148391	2	Recruiting	30 December 2022 (estimated)
China Medical University Hospital	DAAOI-P	NCT04470037	2	Recruiting	July 2022 (estimated)
Lawson Health Research Institute	Ambroxol	NCT02914366	2	Recruiting	December 2021 (estimated)
Lilly	LR3154207	NCT03305809	2	Completed	10 July 2020
University of Michigan	Citalopram	NCT04497168	2	Recruiting	September 2025 (estimated)
Yonsei University	Donepezil	NCT02450786	2	Completed	August 2019
Enterin	ENT-01	NCT03938922	1	Active, not recruiting	25 May 2021 (estimated)
Curasen	CST-103/CST-107	NCT04739423	2	Recruiting	March 2022 (estimated)
Eisai	E2027	NCT04764669	2	Active, not recruiting	22 January 2022
King‘s College London	AZD0328	NCT04810104	2	Not yet recruiting	June 2022 (estimated)
Queensland University	Levetiracetam	NCT04643327	2	Recruiting	December 2023 (estimated)
Athira Pharma	ATH-1017	NCT04831281	2	Not yet recruiting	March 2023 (estimated)
Central South University	Sulphoraphane	NCT05084365	2	Not yet recruiting	31 December 2022 (estimated)

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Kinase inhibitors

Our review of kinase inhibitors was published in April 2021 so we would not expect to see major change in the composition of the trials targeting protein kinases. A summary of clinical trials for kinase inhibitors in PD is shown in Table 7.

Table 7 – summary of clinical trials in PD for kinase inhibitors.

SPONSOR	AGENT	REGISTRY NUMBER	PHASE	REGISTRY STATUS	COMPLETION DATE
Biogen	BIIB094	NCT03976349	1	Recruiting	29 September 2023 (estimated)
Denali	DNL151	NCT04557800	1	Completed	19 February 2021
Il Yang Pharm	Radotinib	NCT04691661	2	Not yet recruiting	13 April 2022 (estimated)
Sun Pharma Advanced Research Company Limited	K0706	NCT03655236	2	Recruiting	March 2023 (estimated)
1st Biotherapeutics	FB-101	NCT04165837	1	Recruiting	30 June 2020 (estimated)
Inibikase Therapeutics	IkT-148009	NCT04350177	1	Enrolling by invitation	31 December 2021 (estimated)

Phase 3 in focus

Since the start of the CTH section, we have covered twelve phase 3 studies in focus, ten symptomatic and two potentially disease modifying therapies. Six of the covered studies have been completed, and six continue with recruitment.

STEADY-PD III was a Phase 3, parallel group, placebo-controlled 36 months study evaluating the efficacy of isradipine 10mg daily as a disease modifying agent in early PD. The primary outcome looked at change in ON state UPDRS I-III from baseline to 36 months. The study enrolled 336 participants with 95% completion rate but failed to demonstrate slowing of disease progression [1].

Intec Pharma's gastric retentive Accordion Pill™ Carbidopa/Levodopa (AP-CD/LD) was being evaluated in a phase 3 study for its safety and efficacy in advanced PD. Though the results have not been published, a news press release in 2019 announced that the study did not demonstrate superiority over C/L in reducing motor fluctuations in advanced PD patients [2]. Results of Gocovri EASE LID and EASE LID 3 trials have already been covered in our previous CTH issue [3]. The results were statistically significant and showed a clinically significant improvement in ON time without troublesome dyskinesia and a concomitant reduction in time with troublesome dyskinesia.

Amneal has been developing another long-acting LD/CD, IPX203 for advanced PD to reduce motor fluctuations. The results from two initial phase 2 studies of IPX203 were promising. The Phase 3, multi-center, randomized, double-blind, double-dummy, active-controlled, parallel-group study (RISE-PD) has completed with 631 participants enrolled. Results have been announced in a press release by the company but have not been published yet. According to Amneal's website, the study successfully met its primary end point. Compared to immediate release LD/CD, IPX203 demonstrated statistically significant higher 'Good ON' time [0.53hr, p=0.0194) at 7 weeks. Post-hoc analysis showed increased 'good ON' time by 1.55 hr (p=<0.0001) per dose compared to active control by week 20. The OFF time was reduced comparatively by 0.48 hr (p=0.0252). Amneal plans to file a new drug application in mid 2022 [4].

The Tavapadon studies, TEMPO-1,TEMPO-2, and TEMPO-3 are ongoing and recruiting participants. Exenatide is currently in recruiting phase as well.

Theravance Biopharma is evaluating ampreloxetine, a long-acting, once-daily norepinephrine reuptake inhibitor, as a potential treatment for symptomatic neurogenic orthostatic hypotension. There are three phase 3 trials designed around this molecule. SEQUOIA is a 4-week, multicentre, randomized, double-blind, placebo-controlled, parallel-group study of ampreloxetine (TD-9855) in treating symptomatic neurogenic orthostatic hypotension in subjects with dysautonomia in Multiple System Atrophy, PD, or Primary Autonomic Failure. REDWOOD is the next extension study followed by OAK, which is the open label safety and tolerability study [5]. SEQUOIA completed in June 2021 with 631 participants enrolled. Theravance biopharma announced negative results in a press release in September 2021 [6]. The study failed to meet its primary end point. Further data analysis is underway. The two sequential phase 3 trials continue to recruit but continuation is being re-evaluated.

A summary of the status of trials reviewed as part of Phase 3 in Focus is shown in Table 8.

Table 8 – summary of status of trials reviewed as part of Phase 3 in Focus

SPONSOR	AGENT	REGISTRY NUMBER	PHASE	REGISTRY STATUS	COMPLETION DATE
NINDS	Isradipine	NCT02168842	3	Completed	November 2018
Intec Pharma	Accordion Pill	NCT02605434	3	Unknown	December 2019
Adamas Pharma	Gocovri EASE LID	NCT02136914	3	Completed	December 2015
Adamas Pharma	Gocovri EASE LID 3	NCT02274766	3	Completed	10 March 2016
Amneal	IPX203	NCT03670953	3	Completed	15 June 2021
University College, London	Exenatide	NCT04232969	3	Recruiting	30 April 2024 (estimated)
Cerevel Therapeutics	Tavapadon TEMPO 1	NCT04201093	3	Recruiting	October 2023 (estimated)
Cerevel Therapeutics	Tavapadon TEMPO 2	NCT04223193	3	Recruiting	August 2023 (estimated)
Cerevel Therapeutics	Tavapadon TEMPO 3	NCT04542499	3	Recruiting	March 2023 (estimated)
Theravance Biopharma	Ampreloxetine SEQUOIA	NCT03750552	3	Completed	21 July 2021
Theravance Biopharma	Ampreloxetine REDWOOD	NCT03829657	3	Recruiting	August 2022 (estimated)
Theravance Biopharma	Ampreloxetine OAK	NCT04095793	3	Recruiting	December 2025

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