

CLINICAL TRIAL HIGHLIGHTS – DYSKINESIA

Kevin McFarthing§,

Parkinson's advocate, Innovation Fixer Ltd, Oxford, UK

§ *To whom correspondence should be addressed at kevin.mcfarthing@innovationfixer.com*

Neha Prakash

Parkinson's Disease and Movement Disorders Center

Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Tanya Simuni

Parkinson's Disease and Movement Disorders Center,

Northwestern University Feinberg School of Medicine, Chicago, IL, USA

INTRODUCTION

To paraphrase the old saying, every silver lining has a cloud. Levodopa remains the gold standard of symptomatic relief because it works, but as Parkinson's Disease (PD) progresses and the therapeutic window of levodopa narrows, many people with Parkinson's (PwP) develop involuntary movements. This phenomenon is termed levodopa-induced dyskinesia (LID), despite the fact that the mechanism of LID is much more complex.

At this point we would like to comment on the nomenclature from the perspective of PwPs. The term “levodopa-induced dyskinesia” suggests that dyskinesia appears purely as a result of taking levodopa. In reality, it is now widely accepted that the emergence of dyskinesia in the course of the disease reflects progressive neurodegeneration, not the duration of levodopa therapy. Unfortunately, the mistaken view that levodopa can only be taken for a certain length of time persists, leading to widespread “levodopa-phobia”. Perhaps a small step towards dispelling this myth is to simply describe the symptoms as “dyskinesia”.

The review below provides a summary of the prevalence and current understanding of the pathogenesis of dyskinesia followed by a Phase 3 study in spotlight of amantadine ER, the only molecule currently approved for management of dyskinesia in PD and then a review of the novel therapeutic options in development.

PATHOGENESIS OF DYSKINESIA

Dyskinesia are involuntary hyperkinetic movements presenting mostly as chorea or choreoathetoid form, but rare ballistic, dystonic or stereotypical variants have been described as well. Various subtypes of dyskinesia and body distribution have been recently summarized in a review by Espay et al. [1]. Briefly, dyskinesia can be classified as peak dose and diphasic. The body distribution, timing and even treatment strategies for the two subtypes differ [1].

The risk of developing dyskinesia is approximately 25- 40% after 4-6 years of levodopa therapy and increases thereafter. Dyskinesia impacts both the social and functional aspects of one's life. Even though surveys validate a significant negative impact of dyskinesia on social life, patients continue to prefer to be ON with dyskinesia instead of being OFF [2]. Understanding the pathophysiology of dyskinesia aids in developing newer and redirecting established drugs for adequate management.

For a long time, it was believed that levodopa therapy was a major cause of dyskinesia. However, preclinical data have demonstrated that levodopa therapy may sensitize the nigrostriatal system but does not induce dyskinesia in the setting of preserved dopaminergic circuit [3]. Data from numerous clinical studies have established that delaying levodopa initiation does not prolong the latency to dyskinesia onset. Accordingly, dyskinesia is not a result of duration of levodopa therapy but rather a combination of various intrinsic and extrinsic factors.

Advanced stage of disease responds differently to levodopa owing to various molecular and network alterations [4]. Primary molecular factors linked to dyskinesia include a lack of presynaptic dopamine storage capacity, increased extracellular levodopa and pulsatile stimulation of dopamine receptors [4,5,6]. Other factors associated with higher risk of developing dyskinesia include young age of onset, female gender, low body weight, certain subtype of PD, certain genetic mutations and polymorphisms within various receptor genes [1].

Though the dopaminergic system plays a key role in the pathogenesis, various non-dopaminergic neuromodulation has been linked to dyskinesia. Detailed coverage of all the systems is beyond the scope of this paper but these non-dopaminergic pathways are currently targeted by a number of drugs in development discussed later. Altered glutaminergic signalling, by either disease-led redistribution of NMDA subunits or NMDA receptor gene polymorphism, has been linked to dyskinesia [7,8]. Amantadine is an effective and the only anti-dyskinetic medication available in the market acting largely by inhibition of glutaminergic hyperactivity, though it also affects other systems.

With the loss of striatal dopaminergic innervation, the aromatic amino acid decarboxylase within serotonin neurons is used to convert exogenous levodopa to dopamine. Consequently, the dysregulated dopamine delivery and maladaptive serotonergic transmission is linked to expression of dyskinesia [9]. Preclinical data on modulating 5-HT receptors to control dyskinesia has been promising and serve as the rationale for targeting the serotonergic system.

Other major systems within the basal ganglia linked to dyskinesia include cholinergic, opioid, adrenergic and the cannabinoid system [1]. The current clinical trials and available therapies focus on symptomatic management but there is a need to ultimately direct our attention towards preventing the development of dyskinesia in the first place.

References

- [1] Espay AJ, Morgante F, Merola A, Fasano A, Marsili L, Fox SH, Bezard E, Picconi B, Calabresi P, Lang AE (2018) Levodopa-induced dyskinesia in Parkinson disease: Current and evolving concepts. *Ann. Neurol.* 84, 797–811.
- [2] Hung SW, Adeli GM, Arenovich T, Fox SH, Lang AE (2010) Patient perception of dyskinesia in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 81, 1112–5.
- [3] Nadjar A, Gerfen CR, Bezard E (2009) Priming for l-dopa-induced dyskinesia in Parkinson's disease: A feature inherent to the treatment or the disease? *Prog. Neurobiol.* 87, 1–9.
- [4] de la Fuente-Fernandez R, Sossi V, Huang Z, Furtado S, Lu J-Q, Calne DB, Ruth TJ, Stoessl AJ (2004) Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. *Brain* 127, 2747–2754.
- [5] Porras G, De Deurwaerdere P, Li Q, Marti M, Morgenstern R, Sohr R, Bezard E, Morari M, Meissner WG (2014) L-dopa-induced dyskinesia: beyond an excessive dopamine tone in the striatum. *Sci. Rep.* 4, 3730.
- [6] Antonini A, Fung VSC, Boyd JT, Slevin JT, Hall C, Chatamra K, Eaton S, Benesh JA (2016) Effect of levodopa-carbidopa intestinal gel on dyskinesia in advanced Parkinson's disease patients. *Mov. Disord.* 31, 530–537.
- [7] Mellone M, Stanic J, Hernandez LF, Iglesias E, Zianni E, Longhi A, Prigent A, Picconi B, Calabresi P, Hirsch EC, Obeso JA, Di Luca M, Gardoni F (2015) NMDA receptor GluN2A/GluN2B subunit ratio as synaptic trait of levodopa-induced dyskinesias: from experimental models to patients. *Front. Cell. Neurosci.* 9, 245.
- [8] Ivanova SA, Loonen AJM, Pechlivanoglou P, Freidin MB, Al Hadithy AFY, Rudikov E V, Zhukova IA, Govorin N V, Sorokina VA, Fedorenko OY, Alifirova VM, Semke A V, Brouwers JRBJ, Wilffert B (2012) NMDA receptor genotypes associated with the vulnerability to develop dyskinesia. *Transl. Psychiatry* 2, e67–e67.
- [9] Tanaka H, Kannari K, Maeda T, Tomiyama M, Suda T, Matsunaga M (1999) Role of serotonergic neurons in L-DOPA-derived extracellular dopamine in the striatum of 6-OHDA-lesioned rats. *Neuroreport* 10, 631–4.

PHASE 3 IN FOCUS – ADAMAS PHARMA’S GOCOVRI

Background: The Phase 3 in focus for this edition of Clinical Trial Highlights continues the theme of symptomatic relief of dyskinesia in PD. We will review two Phase 3 trials already completed on amantadine ER (Gocovri), previously known as ADS-5102 during development, EASE LID [1] and EASE LID 3 [2].

Gocovri is a capsule containing 137mg extended-release amantadine, an uncompetitive antagonist at the N-methyl-D-aspartate receptor known to have benefit to relieve the symptoms of dyskinesia and currently the only available molecule for management of dyskinesia. The rationale of extended release is to provide a therapeutic level of amantadine in the blood for a longer period of time, in this case enabling once a day dosing. Two capsules are administered at bedtime to give a slow increase during sleep, peak levels in the morning and a sustained concentration during the day.

Comments: The primary outcome measure was the change in the Unified Dyskinesia Rating Scale (UDysRS) which has a range from 0 to 104. This is in common with most of the clinical trials for dyskinesia in PD.

The two trial plans are summarised in Table 1 below. The designs were very similar, with differences only in the additional extended timepoint of 24 weeks and some secondary outcomes, for example, the use of Clinician’s Global Impression of Change (CGIC) in EASE LID.

Among the inclusion criteria for EASE LID were a score of at least 2 on question 4.2 of the Unified Parkinson’s Disease Rating Scale (UPDRS); at least two episodes of half an hour of troublesome dyskinesia when ON; and at least 3 administrations of levodopa per day. Exclusion criteria included a history of dyskinesia that was exclusively diphasic, OFF state, myoclonic, dystonic, or akathetic without peak-dose dyskinesia. The inclusion and exclusion criteria for EASE LID 3 did not specify these restrictions, although the baseline data would indicate that these criteria would be met comfortably.

TABLE 1 – Summary of EASE LID and EASE LID 3 trial plans

	EASE LID	EASE LID 3
Title	ADS-5102 for the Treatment of Levodopa-Induced Dyskinesia (EASE LID Study)	Efficacy and Safety Study of ADS-5102 in PD Participants with Levodopa-Induced Dyskinesia (EASE LID 3)
Status	Complete	Complete
clinicaltrials.gov ID	NCT02136914	NCT02274766
Enrolment	121	75
Study design	Randomized, double blind, placebo-controlled, multi-centre (44 sites).	Randomized, double blind, placebo-controlled, multi-centre (32 sites).
Primary outcome measures	Change in UDysRS to week 12, measured at weeks 0, 2, 4, 8 and 12.	Change in UDysRS to week 12, measured at weeks 0, 2, 4, 8 and 12.
Key Secondary outcome measures	Change from baseline in the UDysRS total score at 24 Weeks. ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia) at 12 and 24 weeks. OFF time (amount of time the PD medication is not controlling motor symptoms) at 12 and 24 weeks. Change from baseline at 12 and 24 weeks in the UPDRS score. ON time with troublesome dyskinesia.	Change in the standardized PD home diary (ON time without dyskinesia, ON time with troublesome dyskinesia, OFF time) at 12 weeks.

The results from both trials are summarized in Table 2 below:

TABLE 2 – Summary of EASE-LID and EASE-LID 3 results

	EASE LID; Gocovri vs placebo*	EASE LID 3; Gocovri vs placebo*
Change in UDysRS at week 12	-7.90 (2.30)	-14.40 (3.0)
Change in UDysRS at week 24	-9.30 (2.70)	ND
Change in ON time without troublesome dyskinesia at week 12 (hours)	2.74 (0.61)	1.90 (0.78)
Change in ON time without troublesome dyskinesia at week 24 (hours)	2.22 (0.63)	ND
Change in ON time with troublesome dyskinesia at week 12 (hours)	-1.54 (0.51)	-1.13 (0.65)
Change in ON time with troublesome dyskinesia at week 24 (hours)	-1.45 (0.53)	ND
Change in OFF time at week 12 (hours)	-0.9 (0.37)	-1.10 (0.46)
Change in OFF time at week 24 (hours)	-0.81 (0.39)	ND
CGIC score (reported improvement) at week 12	51/63 vs 21/58	ND
CGIC score (reported improvement) at week 24	43/63 vs 27/58	ND

ND = not determined

* Standard error values in parentheses

There were no significant differences in the UPDRS score (total or parts I, II or III) between Gocovri and placebo at either 12 or 24 weeks, suggesting Gocovri does not make other PD symptoms worse.

In the EASE LID study, adverse events (AEs) were recorded for 88.9% of Gocovri participants, compared to 60.0% in the placebo group. Most were mild to moderate, at 68.3% (Gocovri) and 53.8% (placebo). The most common AEs, at $\geq 5\%$ in the active arm, included visual hallucinations, peripheral edema, dizziness, dry mouth, and constipation. Other AEs occurring in less than 5% of participants in the Gocovri group included nausea (4.8%), confusion (3.2%), and orthostatic hypotension (1.6%) [1].

Visual hallucinations were reported by 15 participants (23.8%) in the Gocovri group and 1 participant in the placebo group. One report in the active group was classed as severe but did not meet the criteria for a serious AE. Thirteen participants (20.6%) in the Gocovri group discontinued the study drug because of AEs as did 4 participants (6.7%) in the placebo group [1].

In the EASE LID 3 trial, AEs were reported for 84% of Gocovri participants and 50% on placebo. Most reported AEs were classed as mild to moderate (70% with Gocovri and 45% with placebo). The most common AEs with an incidence of $\geq 5\%$ in the Gocovri group were dry mouth, nausea, decreased appetite, insomnia, orthostatic hypotension, constipation, falls, and visual hallucinations. One participant reported 2 Gocovri-related serious AEs (constipation and urinary retention) [2].

A further participant on Gocovri experienced suicidal ideation (assessed by the investigator as related to the study drug), and a second participant attempted suicide (assessed by the investigator as not related to the study drug). Nineteen percent of the Gocovri group and 8% of placebo participants discontinued the study because of AEs [2].

Although Gocovri has not been compared to immediate release (IR) amantadine in a directly comparative efficacy study, there is a pharmacokinetic comparison showing Gocovri, administered once a day at bedtime, has a delayed time to maximum plasma concentration (12-16 hours), with a sustained level of amantadine throughout the day [3]. The steady state profile of Gocovri was significantly different to that of IR amantadine administered twice daily, such that the two formulations are not bioequivalent.

The results clearly show a statistically and clinically significant improvement in ON time without troublesome dyskinesia and a concomitant reduction in time with troublesome dyskinesia. Further analyses of the participant diaries have been published using pooled data from both trials [4].

Osmotica Pharmaceuticals has recently launched an extended release amantadine preparation (Osmolex ER) in the US. The new drug is approved for the treatment of PD and for drug induced extrapyramidal reactions in adults. Two Phase 3 trials were conducted for dyskinesia, ALLAY-LID-I (NCT02153645) and ALLAY-LID-II (NCT02153632). Despite this, the New Drug Application (NDA) was based on bioequivalence to amantadine and Osmolex ER does not have the LID indication. It is not interchangeable with either amantadine or Gocovri.

Many PwP find dyskinesia one of the most distressing and embarrassing symptoms of PD, restricting social interaction and causing other knock-on effects such as weight loss. Therapies that prevent dyskinesia or replace the troublesome kind will be valuable tools to use in PD. While Gocovri is a valuable addition to the treatment armamentarium, it does have a fairly high incidence of drug induced adverse effects and as such the development of novel therapeutics remains of value. These are reviewed further in this issue.

References

- [1] Pahwa R, Tanner CM, Hauser RA, Isaacson SH, Nausieda PA, Truong DD, Agarwal P, Hull KL, Lyons KE, Johnson R, Stempien MJ (2017) ADS-5102 (Amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson disease (EASE LID study): A randomized clinical trial. *JAMA Neurol*, 74, 941-949.
- [2] Oertel W, Eggert K, Pahwa R, Tanner CM, Hauser RA, Trenkwalder C, Ehret R, Azulay JP, Isaacson S, Felt L, Stempien MJ (2017) Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). *Mov Disord*, 32, 1701-1709.
- [3] Hauser RA, Pahwa R, Wargin WA, Souza-Prien CJ, McClure N, Johnson R, Nguyen JT, Patni R, Went GT (2019) Pharmacokinetics of ADS-5102 (Amantadine) Extended Release Capsules Administered Once Daily at Bedtime for the Treatment of Dyskinesia. *Clin Pharmacokinet* 58, 77-88
- [4] Hauser RA, Kremens DE, Elmer LW, Kreitzman DL, Walsh RR, Johnson R, Howard R, Nguyen JT, Patni R (2019) Prevalence of Dyskinesia and OFF by 30-Minute Intervals Through the Day and Assessment of Daily Episodes of Dyskinesia and OFF: Novel Analyses of Diary Data from Gocovri Pivotal Trials. *J Parkinson's Disease* Pre-press. 1-10.

EXPERIMENTAL THERAPIES FOR DYSKINESIA IN THE CLINIC

There are eight therapies in clinical phase, summarised in Table 1 below. Seven of the programs are listed on www.clinicaltrials.gov, these will be described in more detail later in this article. There are around a million people in the US with PD of whom an estimated 150,000 to 200,000 suffer from associated dyskinesia [2]. This is one reason why LID has been classified by the US FDA as an orphan disease.

When compared to clinical trials measuring the influence of a therapy on the progression of PD, studies measuring symptom relief require a much shorter assessment time. The duration of intervention for the dyskinesia therapies under review varies from seven days to twelve weeks, although the former (Oregon University) includes a two-week titration period and an assessment at six weeks post-treatment initiation.

All the projects have the Unified Dyskinesia Rating Scale (UDysRS) as the primary outcome, with only one study having additional primary outcomes. This focus on efficacy is complemented by secondary outcome measures that include the Unified Parkinson's Disease Rating Scale (UPDRS). Some studies have started to include digital technology as exploratory outcomes hoping to collect more real life data.

Table 1 - Dyskinesia therapies in the clinic

ORGANISATION	THERAPY	MODE OF ACTION	CLINICAL STAGE
Addex Therapeutics	Dipraglurant	mGluR5 negative allosteric modulator	Phase 2 (complete)
Coeptis/Elto Pharma	Eltoprazine	5HT 1A/1B partial agonist	Phase 2
Hôpitaux de Paris	Buspirone	5-HT1A agonist	Phase 3
Contera/Bukwang	JM-010 (buspirone and zolmitriptan)	5-HT1A agonist and 5-HT1B/5-HT1D agonist combination	Phase 2
Oregon University	Buspirone and amantadine	5-HT1A agonist and NMDA inhibitor combination	Phase 2
Integrative Research Laboratories	IRL-790	Dopamine D3 receptor antagonist	Phase 2
Prilenia	Pridopidine	Sigma-1 receptor inhibitor	Phase 2
Trevi Therapeutics	Nalbuphine	Opioid μ antagonist/ κ agonist	Phase 1

All of the targets are alternative, non-dopaminergic neurotransmitter systems, aiming to reduce dyskinesia while ideally retaining the positive benefits of levodopa. One program is focused on the glutamate pathway, using negative allosteric modulation of metabotropic glutamate receptors.

Clevexel Pharma were developing CVXL-0107 (naftazone), a glutamate release inhibitor. This mode of action is thought to help relieve the symptoms of dyskinesia by reducing cortical input to the striatum; decreasing globus pallidus-mediated movement inhibition; and slowing down neurodegeneration through inhibition of excitotoxicity. Pre-clinical data then a multiple n=1 study [5] suggested that naftazone may have antiparkinsonian and antidyskinetic properties. A Phase 2a study (NCT02641054) was initiated to test the hypothesis but showed no difference between naftazone and placebo [6].

In addition, there are a number of molecules in earlier stages of development. Trevi Therapeutics are developing nalbuphine for dyskinesia. The program is in Phase 1 but has not yet been registered on www.clinicaltrials.gov. Four other projects are in preclinical stage. Vistagen Therapeutics are developing AV-101, a NMDA receptor antagonist which has preclinical data for dyskinesia in PD. While Vistagen's priority appears to be the current Phase 2 study for Major Depressive Disorder, they plan to move AV-101 into Phase 2 in 2020 [4]. Air Liquide Santé are developing inhaled xenon gas and Curemark have CM-PK, although very few details are available. Neurolix are planning to move NLX-112, a 5HT1A inhibitor, into Phase 1 in 2019. IRL have IRL-488 and IRL-555 in discovery phase.

References

- [1] <http://www.irlab.se/wp-content/uploads/2019/06/IRLAB-Redeye-Growth-Day-2019.pdf>
- [2] <http://ir.adamaspharma.com/static-files/562da194-4ec1-4bdd-b5d7-941d8b4b8d21>
- [3] https://www.addextherapeutics.com/files/4915/5955/1249/Addex_Corporate_Deck_June_2019.pdf
- [4] <https://www.vistagen.com/pipeline>
- [5] Rascol O¹, Ferreira J, Nègre-Pages L, Perez-Lloret S, Lacomblez L, Galitzky M, Lemarié JC, Corvol JC, Brotchie JM, Bossi L. A proof-of-concept, randomized, placebo-controlled, multiple cross-overs (n-of-1) study of naftazone in Parkinson's disease. *Fundam Clin Pharmacol*. 2012 (4):557-64. doi: 10.1111/j.1472-8206.2011.0095
- [6] Naftazone in advanced Parkinson's disease: An acute L-DOPA challenge randomized controlled trial. Corvol J-C *et al* *Parkinsonism Relat Disord*. 2019 Mar;60:51-56. doi: 10.1016/j.parkreldis.2018.10.005

ADDEX THERAPEUTICS AND DIPRAGLURANT

Background: Addex Therapeutics have a technology platform aimed at discovering allosteric modulators of key drug targets. ADX48621, or dipraglurant, is a product of this platform and negatively modulates the metabotropic glutamate 5 receptor (mGluR5). It normalizes abnormal glutamate stimulation and mirrors the pharmacokinetic profile of levodopa, an advantage in the treatment of dyskinesia [1]. A Phase 2a study was carried out in 2012, with results published in 2016 [2].

Title: ADX48621 for the Treatment of Levodopa Induced Dyskinesia in Patients With Parkinson's Disease.

Status: Complete.

Clinicaltrials.gov ID: NCT01336088

Sponsor: Addex Pharma.

Enrolment: 83

Completion: February 2012

Study Design: Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of ADX48621 (dipraglurant). The trial design contained a dose escalation from 50mg once daily up to 100mg three times a day.

Outcome Measures: The primary outcome measure was the number of participants with abnormal safety and tolerability assessment parameters after 4 weeks.

Secondary outcome measures were the severity of dyskinesia as measured by the modified Abnormal Involuntary Movement Scale (mAIMS) after 4 weeks; change in PD severity as measured by participant diary at weeks 1, 2, 3 and 4, UPDRS part III at weeks 2 and 4, UPDRS total score at week 4; and participant and clinician-rated global impression of change in dyskinesia and PD at 4 weeks.

Comments: The dipraglurant treatment group of 52 participants had a higher incidence of adverse events (AEs) – 88.5% - than the placebo group of 24 (75%). While most participants completed the dose escalation, 2 participants in the active group discontinued due to AEs. No treatment effects were seen in safety monitoring variables.

Dipraglurant had a statistically significant effect against placebo as measured by mAIMS on day 1 (19.9% vs 4.1%). By day 28 a strong placebo response (21.5%) compared to the dipraglurant measure (31.4%) meant that statistical significance was not achieved at the end of the study.

The clinician-rated global impression of change showed a statistically significant improvement with dipraglurant (71.2%) versus placebo (49.9%). According to participant diaries, daily on time with dyskinesia reduced and on time without dyskinesia increased.

Two pivotal Phase 3 studies are scheduled to start by the end of 2019. Both studies plan the same enrolment (200 participants) split equally between dipraglurant and placebo, with the same primary and secondary outcomes. The first study (#301) will start an open label extension (OLE) after 3 months; the second study (#302) starts the OLE after 6 months. The Phase 3 studies are expected to report results in the third quarter of 2021.

As with other experimental therapies for dyskinesia, dipraglurant has been granted orphan drug status by the US FDA, allowing seven years of market exclusivity.

References

- [1] https://www.addextherapeutics.com/files/4915/5955/1249/Addex_Corporate_Deck_June_2019.pdf
- [2] Tison F, Keywood C, Wakefield M, Durif F, Corvol JC, Eggert K, Lew M, Isaacson S, Bezard E, Poll SM, Goetz CG, Trenkwalder C, Rascol O. A Phase 2A Trial of the Novel mGluR5-Negative Allosteric Modulator Dipraglurant for Levodopa-Induced Dyskinesia in Parkinson's Disease. *Mov Disord* 2016; 31(9) 1373-1380 doi.org/10.1002/mds.26659

ELTOPRAZINE

Background: Eltoprazine is a small oral molecule demonstrated to affect the serotonergic pathway. Though it also interacts with other receptors in the 5-HT system, it has strong affinity towards 5-HT1A/B receptors thought to be primarily responsible for its action. Initially introduced in studies for pathological aggression in intellectually disabled patients, it has since been repurposed to study its effect in ADHD, dementia, and PD patients. Though clinical benefit for aggression is still inconclusive, its safety and tolerability have been demonstrated in human trials in both oral and intravenous forms [1].

In preclinical animal models, eltoprazine was shown to significantly reduce dyskinesia in levodopa primed models in a dose dependent fashion. When used in combination with levodopa in drug naïve models, it demonstrated protective effect. At lower dose, it was also shown to potentiate the anti-dyskinetic effect of amantadine. However, the benefit in dyskinesia came with mild loss of anti-parkinsonian benefit of levodopa [2].

Based on positive results from the preclinical data, PsychoGenics along with the Michael J Fox Foundation funded a double blind, placebo-controlled Phase 1/2a study exploring the safety profile and efficacy of eltoprazine for dyskinesia in PD participants. A total of 24 participants were recruited across two sites in Sweden. As a dose finding study, this trial looked at the ability of eltoprazine to suppress dyskinesia in PD participants after single dosing administered along with levodopa, while maintaining the benefits of levodopa. The three tested doses of Eltoprazine, i.e. 2.5mg, 5mg or 7.5mg, were pre-selected on the basis of safety profile from previous trials in non-PD participants. Compared to randomized placebo dosing, 5mg single dose was shown to have statistically significant reduction in dyskinesia up to 3 hr post dosing. The 2.5mg and 7.5mg doses showed clinical improvement but failed to reach statistical significance. The dosing was safely tolerated without altering levodopa benefits [3]. Though the benefits were modest, the trial successfully paved the way for the Phase 2 studies.

The molecule has survived multiple mergers and acquisitions. eltoprazine was initially developed in the 1980's as DU-28853 by Duphar and subsequently acquired by Solvay pharmaceuticals. It was out-licensed to PsychoGenics Inc. once Solvay merged with Abbott Pharmaceuticals [4]. Post the Phase 1/2a trial, PsychoGenics licensed eltoprazine to Amarantus Bioscience Holdings Inc. in 2014 which has since launched the Phase 2 study in 2015 detailed below.

Title: Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, 4-way Crossover, Dose-finding Study of Eltoprazine Safety, Tolerability, and Efficacy in the Treatment of Levodopa-induced Dyskinesia in Patients With Parkinson's Disease

Objective: The objective of the study is to assess the safety, tolerability, and efficacy of eltoprazine in treating LID in PD participants.

Status: Active, not recruiting

Clinicaltrials.gov Identifier: NCT02439125

Sponsor: Amarantus BioScience Holdings, Inc.

Estimated Enrolment: 60 participants

Estimated Primary Completion Date: June 2017

Study Design: This is a double blind, placebo-controlled, crossover, dose range finding interventional study designed to assess the safety, tolerability, and efficacy of eltoprazine on dyskinesia in PD participants. They are exploring 3 treatment doses and will assess their efficacy as compared to the placebo on the severity of dyskinesia, parkinsonian symptoms and participant function along with safety and tolerability. The study uses standard scales as noted below along with motion sensors and electronic diaries.

The inclusion criteria require individuals between 30 to 85 years of age with a diagnosis of PD of at least 3 years duration and should be on stable dose of levodopa for 4 weeks prior to screening visit. The dyskinesia is required to be

1. moderate to severely disabling
2. present during 25% of the waking day on an average, and
3. present for at least 3 months prior to study entry.

Standard exclusionary criteria are applied. Participants with surgical treatment for PD namely DBS are not blindly excluded but will be, if the procedure was done within the last 6 months of study inclusion or is planned during the study.

There are 4 study arms as noted here, all with dosing for 3 weeks:

1. Eltoprazine HCl 2.5mg BID (5mg/day)
2. Eltoprazine HCl 5mg BID (10mg/day)
3. Eltoprazine 7.5mg BID (15mg/day)
4. Placebo capsules BID

Participants will be randomly assigned to each of the 4 arms. They will complete the 3-week treatment cycle before crossing over to the next study arm.

The study is being conducted in USA at the Parkinson's Disease and Movement Disorders Center at Boca Raton, FL.

Outcome:

The primary outcome measure is the change in the total UDysRS score. This will be assessed at the end of each treatment period on days 21, 42, 63 and 84.

Secondary outcome measures will include

1. Effect on PD motor symptoms as assessed by MDS-UPDRS, participant diaries and physiological measurement using the motion sensor system after 84 days.
2. Change in dyskinesia severity using the physiological motion sensor system after 84 days.
3. Participant function using the questionnaires in MDS-UPDRS and UDyRS to quantify dyskinesia and parkinsonian motor symptoms. This will also be assessed after 84 days.
4. Lastly, safety and tolerability as assessed by adverse events, physical and neurological exams, safe laboratory values, vital signs and ECG. This will be assessed after 94 days.

Current status

Though listed as active and not recruiting, it is unknown if they have met the target already. The Clinicaltrials.gov website has not been updated and no results have been posted yet.

Comments: The molecule carries potential for meaningful benefit in dyskinesia. The design of the Phase 1/2a study limits any effective assessment of efficacy. In 2016, the US FDA granted the molecule orphan drug designation status for PD. Since 2017, Eltoprazine's development has been handled by Elto Pharma, Inc., a joint venture between Amanrantus and PsychoGenics. Elto Pharma recently entered into agreement with Coeptis Pharmaceuticals, Inc. regarding further development.

Though the results from the phase 2b study were expected by now, given the delay, we will have to wait to find out whether the molecule is truly efficacious for dyskinesia without compromising the levodopa benefits.

References:

- [1] Wigal SB, Duong S (2011) Pharmacokinetic evaluation of eltoprazine. *Expert Opin. Drug Metab. Toxicol.* **7**, 775–781.
- [2] Bezard E, Tronci E, Pioli EY, Li Q, Porras G, Björklund A, Carta M (2013) Study of the antidyskinetic effect of eltoprazine in animal models of levodopa-induced dyskinesia. *Mov. Disord.* **28**, 1088–1096.
- [3] Svenningsson P, Rosenblad C, Af Edholm Arvidsson K, Wictorin K, Keywood C, Shankar B, Lowe DA, Björklund A, Widner H (2015) Eltoprazine counteracts l-DOPA-induced dyskinesias in Parkinson's disease: a dose-finding study. *Brain* **138**, 963–73.
- [4] <https://www.amarantus.com/therapeutics-pipeline/therapeutics/eltoprazine>.

BUSPIRONE PROGRAMS

Background: Buspirone is an established anxiolytic that acts primarily on the serotonergic system. Though it also affects the 5-HT₂ receptors and is an antagonist for the D₂ receptor, its efficacy is thought to be primarily mediated through the 5-HT_{1A} receptors. Given the evidence of serotonergic involvement in Parkinson's-associated dyskinesia, a number of studies are testing buspirone in PD. Previous human trials have established a safe profile of the drug and it has a comparatively lower risk of serotonin syndrome [1].

Preclinical data suggests that buspirone is effective in reducing dyskinesia and physiologically reduces the firing rate of subthalamic neurons but requires an intact nigrostriatal pathway to do so [2]. Buspirone has been studied in open label trials previously exploring its effect on parkinsonism and dyskinesia. Studies that looked specifically into buspirone's role for parkinsonism demonstrated no benefit at lower doses (30mg/kg) but had worsening of parkinsonism with anti-dyskinetic benefit at higher doses (~100mg/day) [3,4]. However, when explored specifically for dyskinesia in open label studies, benefit was noted in low to moderate dose (15-60mg/day) with variable worsening of parkinsonism [5,6]. The anti-dyskinetic benefit was noted only in moderate to severe cases [6].

Recent clinical data from three PD patients with off state dyskinesia post fetal neural graft are of interest. Imaging studies showed increased serotonergic innervation of the striatum and all three had significant suppression of dyskinesia after using buspirone [7,8]. This supports the serotonergic hypothesis and lays the groundwork for further studies to determine efficacy in dyskinesia.

ASSISTANCE PUBLIQUE – HOPITAUX DE PARIS

Title: Buspirone Treatment of Iatrogenic Dyskinesias in Advanced Parkinson's Disease. Multicenter, International, Placebo-controlled, Randomised, Double-Blind Trial.

Objective:

1. To validate the serotonergic hypothesis of hyperkinetic dyskinesia.
2. To evaluate the efficacy of buspirone to improve dyskinesia compared to placebo.

3. To evaluate for a dose-dependent response.
4. To determine if the combination of buspirone and amantadine is superior to single drug administration for dyskinesia.

Status: Recruiting, although the clinical trials website has not been updated since February 2018

Clinicaltrials.gov Identifier: NCT02617017

Sponsor: Assistance Publique – Hopitaux de Paris

Estimated Enrolment: 100 participants

Estimated Primary Completion Date: June 2018

Study Design: The study is a phase 3 multicenter, randomized, placebo-controlled, double-blind trial looking at the efficacy of buspirone in reducing dyskinesia in PD participants. They aim to enrol 100 clinically diagnosed PD participants between 35 to 80 years of age. The dyskinesia is required to be moderately disabling and to be present more than 25% of the waking time. The participant should be able to identify dyskinesia, ON and OFF periods. They should be on stable antiparkinsonian medications and be considered optimally treated at the time of inclusion. Standard exclusionary criteria are applied. Participants with DBS can be included if the procedure was done 12 months before inclusion and they are on stable stimulation parameters for at least 4 weeks prior to the first visit.

The study will randomly assign participants to two study arms. Arm 1 will receive buspirone orally in escalating doses. For the first two weeks, they will be on 10mg daily morning dose followed by 10mg twice a day for the next two weeks to finally build up to 10mg three times a day from week 5 to 12. Arm 2 will receive capsules of placebo and administered in escalating doses to match the arm 1. Assessments will be done every 2 weeks and at the end of the study.

Outcome: The primary outcome evaluates change in the UdysRS between the placebo and treatment arm from baseline to week 12.

Secondary outcomes include:

1. Comparison of efficacy between the two arms as measured by MDS-UPDRS parts 3 and 4 at different time points within the period of 13 weeks treatment duration.
2. Comparison of quality of life between the two arms as measured by MDS-UPDRS parts 1 and 2 at different time points within the 13 weeks treatment duration.
3. Comparison between the two arms as measured by side effects profile at different time points within the 13 weeks treatment duration.
4. The maximum dose tolerated by the participants at different time points within the 13 weeks treatment duration.

OREGON HEALTH AND SCIENCE UNIVERSITY

Title: Buspirone, in Combination With Amantadine, for the Treatment of Levodopa-induced Dyskinesia

Objective: The study aims to evaluate the efficacy of combination therapy, buspirone and amantadine, in reducing LID in PD participants.

Status: Recruiting

Clinicaltrials.gov Identifier: NCT02589340

Sponsor: Oregon Health and Science University

Collaborator: Portland VA Medical Center

Estimated Enrolment: 15 participants

Estimated Primary Completion Date: December 2019

Study Design: This is a phase 1, single-center, double-blinded, randomized, placebo-controlled, two-period cross-over study designed to assess the safety, tolerability, and efficacy of combination therapy of buspirone and amantadine on dyskinesia.

They are enrolling PD participants between 18 to 99 years of age on a stable medication regimen. Participants should have mild to severe dyskinesia and should be on amantadine (200-500mg/day) with insufficient control. Standard exclusionary criteria are applied. This study will not include participants with DBS.

Included participants will be randomized to one of the two study arms.

Arm 1: Buspirone titrated up over the course of 2 weeks to reach 30mg/day for a week.

Arm 2: Placebo titrated up to match arm 1.

Participants will be crossed over the treatment sequence. Monitoring is done every 2 weeks for safety, tolerance, compliance and dyskinesia assessment.

Outcome:

The primary outcome measure will assess the

1. Area under the curve – measurements for dyskinesia for a 6-hr levodopa dose cycle.
2. Change in UdysRS up to 6 weeks
3. Safety and tolerability assessment by monitoring adverse events for up to 6 weeks.

No secondary outcomes have been specified.

JM-010 – CONTERA PHARMA AND BUKWANG

JM-010 is a combination of buspirone, a 5-HT_{1A} agonist, and zolmitriptan, a 5-HT_{1B/5-HT_{1D}} agonist. A US patent for this potential treatment was granted in 2015. A previous Phase 2a/proof of concept study (NCT02439203) used a crossover study design in 30 participants and met the criteria for efficacy and safety. The current study is a dose-ranging Phase 2 study focused primarily on efficacy.

Title: A Study in Parkinson's Disease in paTients with mOderate to seveRe dyskInesiA (ASTORIA)

Status: Not yet recruiting.

Clinicaltrials.gov ID: NCT03956979

Sponsor: Contera Pharma

Enrolment: 81 participants

Completion: June 2021

Study Design: Randomized, double-blind, double dummy, placebo-controlled, parallel group study.

This Phase 2 study is comparing two dose levels of JM-010 with placebo - 4mg buspirone/0.8mg zolmitriptan and 8mg buspirone/0.8mg zolmitriptan. The time period will be 12 weeks with a further 2 weeks follow up for safety purposes. There will also be a pharmacokinetic (PK) sub-study.

There are three sub-groups in the study with participants randomised in a 1:1:1 ratio. Group 1 will receive the first active dose plus a placebo; group 2 the second active dose plus a placebo; and group 3 two placebos.

The study is seeking PwP between the ages of 18 and 80 on a stable regimen of levodopa. Inclusion criteria also include stable peak effect dyskinesia and at least one hour of ON state dyskinesia during waking hours, with no more than six administrations of levodopa per day. Exclusively diphasic, OFF state, myoclonic, dystonic, or akathetic dyskinesia without peak-dose dyskinesia are all excluded.

Outcome Measures:

Primary - the efficacy of JM-010 compared to placebo using the UDysRS over 12 weeks.

Secondary outcomes are also focused on efficacy:

1. UDysRS total score changes from baseline to weeks 2, 4 and 8.
2. MDS-UPDRS Parts I to IV from baseline to week 2, 4, 8, 12.
3. Clinician's Global Impression of Change (CGIC) score at week 12.
4. Change in ON time with troublesome dyskinesia, ON time with non-troublesome dyskinesia, ON time without dyskinesia, and OFF time as measured by Hauser patient diaries at weeks 2, 4, 8 and 12.

Comments:

The first trial specifically explores the anti-dyskinetic benefit of buspirone and is monitoring its effect on parkinsonism as well. The 2nd study explores if buspirone potentiates the anti-dyskinetic effect of amantadine and the last study tests the synergistic effect of buspirone with zolmitriptan. All studies are studying a lower dose of buspirone, unlikely to worsen parkinsonism. Whether buspirone will deliver on the results as an anti-dyskinetic is yet to be seen.

References:

- [1] Loane C, Politis M (2012) Buspirone: What is it all about? *Brain Res.* **1461**, 111–118.
- [2] Sagarduy A, Llorente J, Miguez C, Morera-Herreras T, Ruiz-Ortega JA, Ugedo L (2016) Buspirone requires the intact nigrostriatal pathway to reduce the activity of the subthalamic nucleus via 5-HT 1A receptors. *Exp. Neurol.* **277**, 35–45.
- [3] Ludwig CL, Weinberger DR, Bruno G, Gillespie M, Bakker K, LeWitt PA, Chase TN (1986) Buspirone, Parkinson's disease, and the locus ceruleus. *Clin. Neuropharmacol.* **9**, 373–8.
- [4] Hammerstad JP, Carter J, Nutt JG, Casten GC, Shrotriya RC, Alms DR, Temple D (1986) Buspirone in Parkinson's disease. *Clin. Neuropharmacol.* **9**, 556–60.
- [5] Kleedorfer B, Lees AJ, Stern GM (1991) Buspirone in the treatment of levodopa induced dyskinesias. *J. Neurol. Neurosurg. Psychiatry* **54**, 376–7.
- [6] Bonifati V, Fabrizio E, Cipriani R, Vanacore N, Meco G (1994) Buspirone in levodopa-induced dyskinesias. *Clin. Neuropharmacol.* **17**, 73–82.
- [7] Politis M, Wu K, Loane C, Quinn NP, Brooks DJ, Rehncrona S, Bjorklund A, Lindvall O, Piccini P (2010) Serotonergic neurons mediate dyskinesia side effects in Parkinson's patients with neural transplants. *Sci. Transl. Med.* **2**, 38ra46.
- [8] Politis M, Oertel WH, Wu K, Quinn NP, Pogarell O, Brooks DJ, Bjorklund A, Lindvall O, Piccini P (2011) Graft-induced dyskinesias in Parkinson's disease: High striatal serotonin/dopamine transporter ratio. *Mov. Disord.* **26**, 1997–2003.

IRL-790 – INTEGRATIVE RESEARCH LABORATORIES

Background: IRL-790 is a dopamine D3 receptor antagonist with psychomotor stabilising properties. A previous Phase 1b study with IRL-790 in 15 participants (NCT03531060) using the UDysRS to assess symptoms showed a median reduction of 11.5 points vs placebo and a mean reduction of 8.2 points vs placebo over four weeks. There was no effect on standard anti-Parkinsonian medication.

Title: Efficacy and Tolerability of IRL790 in Parkinson's Disease Dyskinesia.

Status: Recruiting.

Clinicaltrials.gov ID: NCT03368170

Sponsor: Integrative Research Laboratories

Enrolment: 74 participants

Completion: June 2019

Study Design: Randomized, double blind, placebo controlled, multi-centre (20 locations) assessing a 2.5mg capsule of IRL-790.

Inclusion criteria require PwP between the ages of 18 and 79 on a stable regimen of anti-parkinsonian medication. They must display waking day dyskinesia of $\geq 25\%$ determined as a score of ≥ 2 on question 4.1 of the UPDRS part IV. One intriguing inclusion criterion is that participants must be willing and able to avoid direct exposure to sunlight from day 1 to day 28.

Outcome Measure: Primary outcome: the UDysRS score at 4 weeks. Secondary outcomes are also focused on efficacy, all measured at 4 weeks:

1. UDysRS parts III and IV.
2. Participant diaries assessing change in daily off time, measured every half hour during 24 hours at visit 1.
3. UPDRS part III.
4. UPDRS part IV questions 4.1 and 4.2 related to dyskinesia.

Comments: This study is a Phase 2a study to further assess efficacy of IRL-790 in the reduction of dyskinesia. The trial is still in the early stages but it will be interesting to see if D3 antagonism can deliver anti dyskinesic benefits without compromising motor control.

PRIDOPIDINE

Background: Pridopidine, developed by Arvid Carlsson Research Laboratories, is a potential neuroprotective and neurorestorative molecule shown to exert its effect via the sigma-1 receptors. It has mostly been explored for Huntington's Disease (HD) and was given orphan drug status by FDA for HD. Teva pharmaceuticals took over the development of the drug from NeuroSearch in 2012, but given the lack of positive data from the HD trials Teva is letting go of the molecule and Prilenia Therapeutics Development Ltd. has taken over its development.

In experimental PD animal studies, pridopidine has been shown to protect the nigral dopaminergic cell bodies and upregulate growth factors leading to axonal sprouting and restoration of striatal dopaminergic fibre density.

The nigral neuroprotective effect has been associated with reduced microglial activation [1]. Preclinical data in PD models demonstrate dose dependent reduction in dyskinesia up to 71% without jeopardizing the antiparkinsonian benefits of levodopa. There was also a notable reduction in ON time with disabling dyskinesia [2,3].

Most of the data for pridopidine comes from HD trials. Though the trials fail to demonstrate consistent significant benefit in motor impairment in HD participants, all the studies established a safe and tolerable profile for the drug [4–6]. Since the safety profile is established, the molecule is being explored for dyskinesia in a Phase 2 trial as detailed below.

Title: A 14-week, Double-blind, Randomized, Three-arm, Parallel-Group Study to Assess the Efficacy and Safety of Two Doses of Pridopidine Versus Placebo for the Treatment of Levodopa-induced Dyskinesia in Patients With Parkinson's Disease (gLIDe)

Objective: A multicentre, randomized, double-blind, placebo-controlled, Phase 2 study evaluating the efficacy, safety, and pharmacokinetics of investigational drug pridopidine as compared to placebo for the treatment of LID in PD participants.

Status: Recruiting

Clinicaltrials.gov Identifier: NCT03922711

Sponsor: Prilenia Therapeutics

Estimated Enrolment: 135 participants

Estimated Primary Completion Date: April 2020

Study Design: This is a multicentre, double-blind, randomized, three-arm, parallel-group Phase 2 study evaluating the efficacy and safety of two doses of pridopidine vs placebo for dyskinesia in PD participants. The study will include participants with a clinical diagnosis of PD between the ages of 30 and 85 years. Mild to moderate dyskinesia is a prerequisite. Participants are required to be on a stable medication regimen (PD and non-PD) for at least 28 days prior to the study start date and be able to maintain that through the study duration. Standard exclusionary criteria apply. Participants with surgical intervention such as DBS are excluded.

The participants will be randomized to one of 3 parallel arms:

Arm 1- dose 1 in the form of oral capsules for 12 weeks following a 2 week titration period.

Arm 2- dose 2 in the form of oral capsules for 12 weeks following a 2-week titration period.

Arm 3- placebo in the form of oral capsules for 14 weeks.

The study is currently recruiting participants at two sites in the USA.

Outcome: The primary outcome measure explores the change in dyskinesia from baseline to week 14. The score is calculated as a sum of parts 1, 3, and 4 of the UdysRS. No secondary outcomes have been posted.

Comments: The pharmacology of the molecule and data from animal studies are promising. Given an established safety profile, it is one step ahead in the development for dyskinesia. Physiologically its effect is similar to GDNF growth factors in terms of neuronal dopamine protection and sprouting in the nigrostriatal axons. Though it failed to show efficacy for the HD population, its effect on dyskinesia is yet to be determined.

References:

- [1] Francardo V, Geva M, Bez F, Denis Q, Steiner L, Hayden MR, Cenci MA (2019) Pridopidine Induces Functional Neurorestoration Via the Sigma-1 Receptor in a Mouse Model of Parkinson's Disease. *Neurotherapeutics* **16**, 465–479.
- [2] Johnston TH, Geva M, Steiner L, Orbach A, Papapetropoulos S, Savola J, Reynolds IJ, Ravenscroft P, Hill M, Fox SH, Brotchie JM, Laufer R, Hayden MR (2019) Pridopidine, a clinic ready compound, reduces 3,4-dihydroxyphenylalanine-induced dyskinesia in Parkinsonian macaques. *Mov. Disord.* **34**, 708–716.
- [3] Ponten H, Kullingsjö J, Sonesson C, Waters S, Waters N, Tedroff J (2013) The dopaminergic stabilizer pridopidine decreases expression of l-DOPA-induced locomotor sensitisation in the rat unilateral 6-OHDA model. *Eur. J. Pharmacol.* **698**, 278–285.
- [4] De Yebenes JG, Landwehrmeyer B, Squitieri F, Reilmann R, Rosser A, Barker RA, Saft C, Magnet MK, Sword A, Rembratt Å, Tedroff J (2011) Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): A phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* **10**, 1049–1057.
- [5] Karl K, McGarry A, McDermott MP, Kayson E, Walker F, Goldstein J, Hyson C, Agarwal P, Deppen P, Fiedorowicz J, Kostyk S, Wright A, Leavitt B, Nance M, LeDoux MS, Shannon KM, Siderowf A, Cudkowicz M, Rabinowitz K, Ross V, Watts A, Tedroff J (2013) A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington's disease. *Mov. Disord.* **28**, 1407–1415.
- [6] Reilmann R, McGarry A, Grachev ID, Savola JM, Borowsky B, Eyal E, Gross N, Langbehn D, Schubert R, Wickenberg AT, Papapetropoulos S, Hayden M, Squitieri F, Kieburtz K, Landwehrmeyer GB, Agarwal P, Anderson KE, Aziz NA, Azulay JP, Bachoud-Levi AC, Barker R, Bebak A, Beuth M, Biglan K, Blin S, Bohlen S, Bonelli R, Caldwell S, Calvas F, Carlos J, Castagliuolo S, Chong T, Chua P, Coleman A, Corey-Bloom J, Cousins R, Craufurd D, Davison J, Decorte E, De Michele G, Dornhege L, Feigin A, Gallehawk S, Gauteul P, Gonzales C, Griffith J, Gustov A, Guttman M, Heim B, Heller H, Hjermind L, Illarioshkin S, Ivanko L, Jaynes J, Jenckes M, Kaminski B, Kampstra A, Konkel A, Kopishinskaya S, Krystkowiak P, Komati SK, Kwako A, Lakoning S, Latipova G, Leavitt B, Loy C, MacFarlane C, Madsen L, Marder K, Mason S, Mendis N, Mendis T, Nemeth A, Nevitt L, Norris V, O'Neill C, Olivier A, Orth M, Owens A, Panegyres P, Perlman S, Preston J, Priller J, Puch A, Quarrell O, Ragosta D, Rialland A, Rickards H, Romoli AM, Ross C, Rosser A, Rudzinska M, Russo C V., Saft C, Segro V, Seppi K, Shannon B, Shprecher D, Simonin C, Skitt Z, Slawek J, Soliveri P, Sorbi S, Suski V, Stepniak I, Sungmee P, Temirbaeva S, Testa C, Torvin-Moller A, Uhl S, Vangsted-Hansen C, Verny C, Wall P, Walker F, Wasserman P, Witkowski G, Wright J, Zalyalova Z, Zielonka D (2019) Safety and efficacy of pridopidine in patients with Huntington's disease (PRIDE-HD): a phase 2, randomised, placebo-controlled, multicentre, dose-ranging study. *Lancet Neurol.* **18**, 165–176.

CLINICAL TRIALS HIGHLIGHTS - RESOURCES

PARKINSON'S THERAPIES IN DEVELOPMENT

The Hope List - <http://bit.ly/ParkinsonsHopeList>

FINDING A CLINICAL TRIAL

ClinicalTrials.gov from the US National Library of Medicine - <https://clinicaltrials.gov>

PD Trial Tracker; analysing ClinicalTrials.gov for Parkinson's specific trials - <http://www.pdtrialtracker.info>

Fox Trial Finder - <https://foxtrialfinder.michaeljfox.org>

European Parkinson's Disease Association - <https://www.epda.eu.com/about-parkinsons/treatments/clinical-trials/>

Parkinson's UK - <https://www.parkinsons.org.uk/research/take-part-research>

UK NHS Clinical Trials Gateway - <https://www.ukctg.nihr.ac.uk>

Cure Parkinson's Trust - <https://www.parkinsonsmovement.com/clinical-trials/>

Parkinson's Study Group - <http://www.parkinson-study-group.org/clinical-trials>

American Parkinson Disease Association - <https://www.apdaparkinson.org/resources-support/living-with-parkinsons-disease/clinical-trials/>

CenterWatch - <https://www.centerwatch.com/clinical-trials/listings/condition/117/parkinsons-disease/>

WHAT DOES IT MEAN TO PARTICIPATE IN A PARKINSON'S CLINICAL TRIAL?

Michael J Fox Foundation, Clinical Trial Companion – <https://www.michaeljfox.org/pdcompanion.html>

Parkinson's Foundation - <https://www.parkinson.org/Understanding-Parkinsons/Treatment/Clinical-Trials>