

## Review

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# Twelve Years of Drug Prioritization to Help Accelerate Disease Modification Trials in Parkinson's Disease: The International Linked Clinical Trials initiative

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**Abstract.** In 2011, the UK medical research charity Cure Parkinson's set up the international Linked Clinical Trials (iLCT) committee to help expedite the clinical testing of potentially disease modifying therapies for Parkinson's disease (PD). The first committee meeting was held at the Van Andel Institute in Grand Rapids, Michigan in 2012. This group of PD experts has subsequently met annually to assess and prioritize agents that may slow the progression of this neurodegenerative condition, using a systematic approach based on preclinical, epidemiological and, where possible, clinical data. Over the last 12 years, 171 unique agents have been evaluated by the iLCT committee, and there have been 21 completed clinical studies and 20 ongoing trials associated with the initiative. In this review, we briefly outline the iLCT process as well as the clinical development and outcomes of some of the top prioritized agents. We also discuss a few of the lessons that have been learnt, and we conclude with a perspective on what the next decade may bring, including the introduction of multi-arm, multi-stage clinical trial platforms and the possibility of combination therapies for PD.

**Keywords:** Clinical trials, Parkinson's disease, disease modification, neuroprotection, drug repurposing

## BACKGROUND

Parkinson's disease (PD) is a neurodegenerative condition that affects approximately 1% of the population over the age of 60. As the motor and non-motor symptoms continue to progress, there is considerable loss in quality of life for those living with the condition and also their families [1]. During the past 50 years, the global burden of PD has doubled [2], and current data suggests that the overall and age-specific incidence of PD is increasing at the fastest rate of all neurological conditions [3–5]. With a globally aging population, PD will represent a significant future impact on society, with more than 12 million people projected to be affected worldwide by 2040 [6]. There are currently no licensed treatments for PD that have been definitively shown to slow or stop the progressive nature of this debilitating condition. Therapeutic agents that can alter the trajectory of PD neurodegeneration are urgently required.

In an effort to address this need, in early 2010, one of the co-founders of Cure Parkinson's, Tom Isaacs, and the director of research at Cure Parkinson's, Dr Richard Wyse invited Professor Patrik Brundin (then of Lund University, Sweden) to chair an international committee of PD experts that would focus on

prioritizing the most promising potentially disease modifying treatment candidates for PD. This was in part inspired by the pioneering efforts of the 2003 'Committee to Identify Neuroprotective Agents for Parkinson's' (CINAPS) program launched by Walter Koroshetz and colleagues [7]. However, this new initiative was conceived from the outset to be an annual meeting that would guarantee a continual list of drug candidates prioritized for moving forward to clinical trials – it is this that is now known as the international Linked Clinical Trials (iLCT) initiative.

One important feature of the annual iLCT meetings was *inclusivity*. Thus, it was decided that representatives from PD research organizations with an interest in disease modifying therapies and representatives from regulatory agencies would be invited to attend the iLCT meetings each year and be an integral part of the discussions. In addition, there was also a strong desire to have the patient voice involved with every meeting, and as such, PD research advocates (people living with the condition with a strong interest in the research being conducted) were invited to not only be present but also contribute to the conversations on the viability and potential of the agents being evaluated by the committee. Another important aspect of the iLCT initiative was the need for *commitment*. Clini-

cal trials for PD require years of effort and resources, and there was clear understanding at the start of the iLCT program that it would have a long term ambition of delivering new trials. The iLCT committee has expanded in the 12 years since its inception, from 8 to now 20 active members and all have kindly provided their time and knowledge since the onset of the iLCT project, and remain committed to the overall aims of the initiative. In addition, there are key funding partners (such as Van Andel Institute in Michigan) who are also pledged to maintaining the iLCT program.

## THE iLCT PROCESS

Descriptions of the iLCT initiative have previously been published [8–11] and only a brief overview is provided here. During the 12 months leading up to each annual iLCT meeting, the research team at Cure Parkinson's generates a set of dossiers, each of which describes one compound and provides an overview of the evidence for considering it for a clinical trial as a disease modifying agent in PD (this includes safety/tolerability data, pre-clinical/epidemiological research, and any available clinical data). The dossiers are written in-house by the Cure Parkinson's research team in order to maintain a uniform style and format. Dossiers describing each of these therapeutic candidates are compiled having been selected from suggestions stemming from the recent literature, discussions with biotech companies, PD advocates, academic researchers, and iLCT committee members themselves. Where stakeholders are involved with a particular agent, dossier preparation can be a collaborative process with the associated parties contributing data to the prepared document. When sensitive information is included in the dossier, the material is always marked as 'confidential' and presented to the iLCT committee under a nondisclosure agreement. Since the first meeting in 2012, 239 dossiers have been presented to the iLCT committee, representing a total of 171 agents with updated dossiers being presented across multiple years for some agents (in Supplemental File 1, we provide a list of the non-confidential dossiers that have been presented to the committee).

The iLCT dossiers are given to the committee members 3–4 weeks before the annual meeting and they are asked to score ahead of the meeting each agent individually in terms of their priority to be taken forward into clinical trial testing based on the compiled dossier evidence. These 'pre-meeting' scores

help to triage out the weakest molecules and provides the iLCT committee chairperson with a framework for the discussion of each candidate agent at the actual iLCT meeting. During the iLCT meeting itself, each of the dossiers that survive the pre-meeting triage process are presented by a primary and a secondary presenter from the iLCT committee, followed by input from committee members who had provided high or low scores for a particular agent. The dedicated panel members provide a summary of the agent and also offer their initial opinions as to trial readiness and disease modifying potential. Where a conflict of interest is declared for a particular agent, the relevant committee member(s) steps out of the room. Approximately 30 minutes' deliberation is then given to each dossier (including input from patient advocates) after which the committee members are asked to provide a revised final score. The average scores are used to rank the agents. At the end of the evaluation process, the five top-scoring dossiers are classified as 'prioritized'.

When a dossier is prioritized by the iLCT committee, Cure Parkinson's is provided with a mandate to help take the agent forward into clinical testing for PD. This might be achieved through funding the clinical trial directly or by providing letters of support and convening specialist stakeholder meetings to help shape clinical trial design and/or patient involvement and communication strategies. Where funding is required, Cure Parkinson's often works in collaboration with other organizations (namely iLCT funding partners like the Van Andel Institute and the John Black Charitable Foundation) to provide the necessary composite financial support for the iLCT trial to go ahead. In addition, other PD charities such as The Michael J Fox Foundation and Parkinson's UK have contributed to iLCT trial costs on an individual project basis. Where external funding is available for clinical trials of iLCT prioritized agents, Cure Parkinson's often invests in "added value" sub-studies. This allows for the testing of new assays, genetic stratification, biomarkers or outcome measures, and encourages buy-in from researchers at additional study sites where they have an interest in the sub-study.

This multimodal support has been a cost-effective strategy for the charity, with Cure Parkinson's (and its funding partners) investing £10.3 million into iLCT projects to date, but the overall iLCT program has leveraged an estimated 10-fold on this amount in external investment for clinical trials of therapeutic agents prioritized by iLCT committee. As a whole,

the iLCT program has directly and indirectly (non-funded endorsement and guidance on trial design) supported the initiation or development of 41 clinical trials testing 32 iLCT agents across 17 different countries (UK, USA, Australia, Canada, Czech Republic, France, Germany, Hungary, India, Korea, Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden). This includes 21 completed trials of 15 evaluated iLCT agents, involving 1,439 people with PD and 20 currently active trials of 17 evaluated iLCT drugs, involving 3,306 people with PD (two of the agents being evaluated are now in Phase 3 trials: exenatide and ambroxol). Below we discuss some examples of iLCT prioritized agents as well as provide a breakdown of the clinical trials of non-confidential agents in Supplemental File 2.

### EXAMPLES OF TRIALS OF iLCT PRIORITIZED AGENTS

At the first iLCT meeting in 2012, the glucagon-like peptide 1 (GLP-1) receptor agonist, exenatide, was the top prioritized agent to test in PD patients. Widely used for type 2 diabetes, with a well characterized safety record, GLP-1 receptor agonists have undergone an extensive process to improve their pharmacokinetics and pharmacodynamics for peripheral tissue target engagement [12]. GLP-1 receptor agonists are associated with a reduced risk of developing PD in diabetics [13, 14], and this class of agents has demonstrated neuroprotective properties in both neurotoxic and alpha-synucleinopathy models of PD [15–20]. In addition, a Cure Parkinson's supported proof of concept single-blind study evaluating the progress of 21 patients with moderate PD while on exenatide for 12 months in comparison to randomized control participants provided encouraging results that required further evaluation [21, 22]. Following iLCT prioritization, a Phase 2b study was initiated (with funding from The Michael J Fox Foundation) and met its primary endpoint of a reduction in the progression of motor features (as assessed by MDS-UPDRS part 3) after 48 weeks of double blind treatment [23]. A Phase 3 clinical trial of exenatide in 200 people with PD is now underway in the UK, with results expected in mid/late 2024 [24].

While not always required, two Phase 3 trials, demonstrating a drug's safety and efficacy, are generally expected in order for regulatory approval. Exenatide is now off patent hence even with positive phase 3 data, there may be less commercial appeal for

the marketing authorization holder to pursue a license for a new indication for exenatide as a treatment for PD. As we discuss below, off label use of exenatide could be an option, but this would depend on whether the manufacturers will continue to produce the drug or generic companies can be tempted to do so. This represents one of the significant challenges of drug repurposing, and if/when a treatment ultimately does reach a level of evidence to justify a major push for access, philanthropic PD research groups will need to come together to address this for the benefit of the PD community. Also prioritized by iLCT were three other GLP-1 receptor agonists, Lixisenatide, Liraglutide and NLY01 [25], and it will soon be interesting to compare the results of all these now-completed Phase 2 trials.

In 2014, the iLCT committee prioritized the expectorant ambroxol hydrochloride (Ambroxol). This respiratory medication had been identified in drug screening studies as a chaperone of the PD-associated lysosomal enzyme  $\beta$ -glucocerebrosidase (GCase) and has shown beneficial effects in preclinical models of PD [26–30]. With iLCT committee prioritization, Cure Parkinson's co-funded a Phase 2a study (AiM-PD) which demonstrated that ambroxol significantly elevated GCase protein levels in cerebrospinal fluid samples from 16 people with PD following 6 months of treatment [31]. A Phase 3 evaluation of ambroxol in PD (ASPro-PD) is now underway and involves 2 years of treatment (ambroxol or placebo) in 330 people with PD, half of whom will be *GBA1* variant carriers.

A third example of an iLCT prioritized agent is the secondary bile acid ursodeoxycholic acid (UDCA). UDCA is naturally synthesized in the liver and widely used as a treatment for gallstone disease and primary biliary cholangitis. In preclinical studies, UDCA has been reported to improve mitochondrial function in models of PD [32, 33]. Following iLCT prioritization in 2015, Cure Parkinson's supported a 48-week, double-blind, placebo-controlled clinical trial (the UP study) that involved 30 participants with PD. The results of the study indicated that the agent was safe and well tolerated, and sensor-based gait analysis alongside magnetic resonance spectroscopy data provided evidence that encourages its further clinical evaluation [34].

While the future potential of these three examples still remains to be determined, there are also examples of prioritized iLCT agents that have been found to have no effect on slowing the progression of PD, and it is important to reflect on what has

been learnt from the experience of these clinical trial program. One example here is the tyrosine kinase inhibitor nilotinib (which was iLCT prioritized in 2013). Previous preclinical work had indicated that c-ABL may be a target of interest in PD and its inhibition (by nilotinib) has been reported to be neuroprotective in models of PD [35–37]. In addition, the results of a small pilot open-label clinical study assessing this agent in 12 individuals with PD dementia generated significant media attention [38], adding to the importance of conducting a properly controlled clinical evaluation. Two large Phase 2 clinical trials were set up for this purpose (NILO-PD and PD-Nilotinib), but neither study demonstrated any change in PD progression as a result of the treatment [39, 40]. Cerebrospinal fluid analysis in both studies indicated limited brain penetrance, and thus the question of c-ABL involvement in PD remains unanswered. This matter is currently being addressed through two brain-penetrant cAbl inhibitors in PD clinical trials (Vodobotinib: NCT03655236 and Risvodetinib: NCT05424276).

A second example of a prioritized iLCT agent that had no impact on PD progression was the HMG-CoA reductase inhibitor simvastatin (iLCT prioritized in 2012). This brain penetrant statin had exhibited neuroprotective properties in preclinical models (reviewed in [41]), and it has been reported that simvastatin treatment is associated with a reduced risk of developing and/or delaying the onset of progressive supranuclear palsy [42]. A 24-month, Phase 2 study (PD-STAT) involving 235 individuals with moderate PD showed that although the treatment was well tolerated, there was no significant impact of simvastatin on the downward trajectory of neurodegeneration of PD [43]. Despite the negative outcome, many learnings can be taken from this large study, including addressing the challenges of incorporating digital technology at scale across clinical trials [44] and how best to support participants in such trials [45].

## LESSONS FROM 12 YEARS OF iLCT

Over the course of the iLCT program, many lessons have been learnt, the sharing of which might help attempts to replicate the project in other disease indications.

### *Drug repurposing*

The early iLCT program was primarily focused on drug repurposing and moving prioritized can-

didates rapidly into Phase 2 clinical trials for PD. Drug repurposing/repositioning represents a method for accelerating the development of new therapies by investigating clinically available agents as therapeutic interventions in new indications [46, 47]. Some of the repurposed iLCT prioritized agents have provided encouraging results and subsequently moved forward into larger later phase clinical trials. For other agents however, clinical translation in PD has proven to be more complicated. In many cases, the dose required for testing disease modifying potential in humans is not clear, and initial testing has involved pragmatic decisions, e.g., using the dose approved for other indications, or instead conducting a dose range-finding study. Adjusting dosage also can be difficult, e.g., increasing dosing to elevate CNS exposure can result in peripheral side effects which may affect tolerability.

There are agents evaluated in the iLCT program that have required reformulation (or production of a novel mode of administration) before they could be considered for large PD clinical trials. One example of this is the repurposing of ambroxol. In the Phase 2 study, participants were required to take 21 pills per day in addition to their normal symptomatic anti-PD treatment regime [31]. Such a heavy pill burden can affect compliance, particularly during long-term, chronic studies. Cure Parkinson's has worked with manufacturers to resolve these issues for the Phase 3 ASPro-PD trial, which will utilize a 3 tablet per day reformulation.

Another important consideration when repurposing agents is intellectual property. While it may be possible to conduct clinical trials using generic (out of patent) therapies and even those still covered by patents and/or market exclusivity, there are still hurdles to overcome to allow for eventual patient access for any iLCT agents that may demonstrate efficacy in clinical testing. Where a specific stakeholder with a clear path to market is absent, the onus will be on philanthropic organizations to commit to taking up the regulatory challenge of innovative licensing access pathways [48] as an alternative means of providing patient access. The use of drugs “off label” has always been a fall-back option, but this has its own limitations, with broad patient access unlikely to be achievable due to rules and regulations in different countries, healthcare systems and healthcare insurance companies. In some instances, alternative more equitable routes can be supported via new or extended license applications, and Cure Parkinson's actively pursues all possible avenues and collabora-

tions for future patient access, in preparation for the moment an iLCT agent has been clinically proven to slow disease progression. Seeking advice early in the clinical trial process from regulators can help in building a powerful data package to attract a pharma partner to enable patient access.

#### *Dossier scoring and feedback*

With the inclusion of more agents involving biotech companies or intellectual property stakeholders in the iLCT process, it has been necessary to consider the nature of the feedback provided by the iLCT committee. While the early iLCT prioritization process involved just a single score for each dossier, the committee members are now asked to provide subscores for each dossier discussed at the annual meeting, to help illustrate what the committee felt were the strengths and weaknesses of each agent. There are five subscores based on ‘Safety’ (tolerability, toxicology, etc.), ‘Mechanism of action’ (is the target known and clearly relevant to PD pathogenesis?), ‘Dosing and target engagement’ (is the optimal dose known, and can target engagement be demonstrated?), ‘Preclinical efficacy data’ (has the agent been tested in pathophysiologically relevant models of PD?), and ‘Clinical data’ (does pre-existing clinical data support further testing in a PD cohort?). In addition to these sub-scores, there is an overall score which is the sole determinant for the prioritization process. Along with summarized notes of the discussions in the iLCT meeting, these overall scores and sub-scores provide a constructive source of feedback to stakeholders or third parties interested in the development of specific iLCT agents.

#### *Accelerating the iLCT process*

Every year during discussions at the meeting, the iLCT committee may decide that additional data on a particular agent is required before prioritization for a clinical trial would be recommended. Rather than simply waiting for the required research to be conducted by chance, Cure Parkinson’s has set up the “iLCT pipeline research acceleration” program to proactively accelerate the preclinical research required for iLCT agents of higher potential interest. The iLCT pipeline research acceleration program provides the iLCT committee with a tool by which to acquire the required information more quickly. Based on the iLCT committee feedback, Cure Parkinson’s generates a commissioned funding call, where posi-

tive results may help to fast-track the most promising agents into clinical trials [49]. Following the initiation of the iLCT pipeline research acceleration program after iLCT 2022, Cure Parkinson’s approved funding for its first iLCT pipeline project in February 2023 to test the effects of three agents— methylcobalamin (a form of vitamin B12 evaluated at iLCT 2022), benfotiamine (a lipid-soluble derivative of thiamine/vitamin B1 assessed at iLCT 2022) and ibuprofen (a non-steroidal anti-inflammatory drug presented at iLCT 2021)—on dopamine neuronal survival, locomotor behavior, inflammatory, antioxidant and other markers in  $\alpha$ -synuclein-based mouse models of PD.

In addition to the iLCT pipeline research acceleration program, Cure Parkinson’s is also considering the potential future opportunities that combination therapies may offer for the iLCT program. As part of an internal ‘planning for success’ project, the charity is exploring how best to approach the *in vitro* and *in vivo* preclinical testing of multiple agents in combination, in order to assess possible synergistic benefits. The development of combination therapies requires a robust understanding of how each agent impacts complex signaling pathways, and assessing the crosstalk between the networks involved to determine how each therapy may potentially influence outcomes. Given the success that has been achieved with combination therapies in oncology, cardiovascular disease and infectious diseases, consideration needs to be given to the future of PD treatment if any of the current late-stage monotherapy clinical trials provide evidence of disease modification.

#### **EXPANDING THE CLINICAL TRIAL PROGRAMME**

There are several iLCT prioritized agents that have yet to enter clinical trials mainly due to the limited availability of funds and the amount of time it takes to get these projects up and running. In its efforts to see more iLCT evaluated agents enter trials, Cure Parkinson’s has made non-confidential dossiers available to third parties seeking to conduct such clinical studies. One example of this has been the multi-arm clinical trial platform project known as the Australian Parkinson’s Mission [50]. This multi-arm Phase 2 study involves the recruitment of 240 participants, who are randomly assigned to one of four arms; it is comparing a placebo arm against an alogliptin arm (iLCT prioritized in 2015), an albuterol arm (iLCT

2017), and a nilvadipine arm (iLCT 2017).

In addition to aiding the Australian Parkinson's Mission, iLCT dossiers have also been made available to the treatment selection committee of the new multi-arm, multi-stage (MAMS) Edmond J Safra Accelerating Clinical Trials in PD (EJS ACT-PD; [51]) initiative, which is aiming to start recruiting patients in late 2024. The EJS ACT-PD initiative will be a nationwide clinical trial platform in the UK that will initially involve up to four arms (a placebo arm compared to 3 treatment arms) with 400 participants being randomly assigned to each arm. The goal is to apply the innovative MAMS approach to clinical trials for PD, in order to speed up the identification and development of disease modifying therapies [52, 53].

With the further development of larger, multi-arm clinical trial platforms, there is a need for agent prioritization efforts like the iLCT initiative. In addition to aiding in the identification of interesting therapeutic candidates for clinical testing, these drug evaluation efforts must also be mindful of the work packages required for preparing and de-risking candidate agents (such as dose finding or target engagement studies) for later clinical development. Such activities are essential for accelerating the advancement of agents into late-stage clinical testing, a goal that has been challenging according to recent analyses of trends in the clinical trial pipeline for PD [25].

## SUMMARY

The iLCT initiative was launched in 2012 in an attempt to increase the number of clinical trials testing disease-modifying therapeutic approaches for people with PD. We have shared this review of the iLCT process and 12-years of experience running this program in the hope of providing a template and advice for replication across other indications. While no drug evaluated by iLCT has yet made it to the clinic, we hope the process we are using to identify and test targets will ultimately reduce overall time for a therapy to make it all the way from the 'bench to the clinic'. In addition, with the further development of novel biomarkers and assays allowing for better identification and stratification of PD patients (such as the  $\alpha$ -synuclein seed amplification [54], there will be opportunities to better target the prioritized iLCT agents. As the results of more iLCT-associated clinical trials become available in coming years, the long-term value of maintaining such an initiative will hopefully become further apparent, ideally through

significant improvements in quality of life for individuals living with PD, which has been an underlying aim of the effort throughout.

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## CONFLICT OF INTEREST

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## SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JPD-230363>.

## REFERENCES

- [1] Bloem BR, Okun MS, Klein C (2021) Parkinson's disease. *Lancet* **397**, 2284-2303.
- [2] GBD 2016 Parkinson's Disease Collaborators (2018) Global, regional, and national burden of Parkinson's disease, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* **17**, 939-953.
- [3] Ray Dorsey E, Elbaz A, Nichols E, Abd-Allah F, Abdalalim A, Adsuar JC, Ansha MG, Brayne C, Choi HK, Collado-Mateo D, Dahodwala N, Do HP, Edessa D, Endres M, Fereshtehnejad SM, Foreman KJ, Gankpe FG, Gupta R, Hankey GJ, Hay SI, Hegazy MI, Hibstu DT, Kassean A, Khader Y, Khalil I, Khang YH, Kim YJ, Kokubo Y, Logroscino G, Massano J, Ibrahim NM, Mohammed MA, Mohammadi A, Moradi-Lakeh M, Naghavi M, Nguyen BT, Nirayo YL, Ogbo FA, Owolabi MO, Perera DM, Postma MJ, Qorbani M, Rahman MA, Roha KI, Safari H, Safiri S, Satpathy M, Sawhney M, Shafiqsabet A, Shiferaw MS, Smith M, Szoek CEI, Tabares-Seisdedos R, Truong NT, Ukwaja KN, Venketasubramanian N, Villafaina S, Weldegewergs KG, Westerman R, Wjateratne T, Winkler AS, Xuan BT, Yonemoto N, Feigin VL, Vos T, Murray CJL (2018) Global, regional, and national burden of Parkinson's disease, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* **17**, 939-953.
- [4] Savica R, Grossardt BR, Bower JH, Eric Ahlskog J, Rocca WA (2016) Time trends in the incidence of Parkinson disease. *JAMA Neurol* **73**, 981-989.
- [5] World Health Organization (2022) *Parkinson disease: A public health approach*. World Health Organization. <https://www.who.int/publications/i/item/9789240050983>
- [6] Dorsey ER, Sherer T, Okun MS, Bloem BR (2018) The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis* **8**, S3-S8.
- [7] Ravina BM, Fagan SC, Hart RG, Hovinga CA, Murphy DD, Dawson TM, Marler JR (2003) Neuroprotective agents for clinical trials in Parkinson's disease: A systematic assessment. *Neurology* **60**, 1234-1240.
- [8] Brundin P, Barker RA, Conn PJ, Dawson TM, Kiebert K, Lees AJ, Schwarzschild MA, Tanner CM, Isaacs T, Duffen J, Matthews H, Wyse RKH (2013) Linked clinical trials—the development of new clinical learning studies in Parkinson's disease using screening of multiple prospective new treatments. *J Parkinsons Dis* **3**, 231-239.
- [9] Brundin P, Wyse RK (2019) The Linked Clinical Trials initiative (LCT) for Parkinson's disease. *Eur J Neurosci* **49**, 307-315.
- [10] Stott SRW, Wyse RK, Brundin P (2021) Drug repurposing for Parkinson's disease: The International Linked Clinical Trials experience. *Front Neurosci* **15**, 653377.
- [11] Wyse RK, Cooper AA, Stott SRW (2022) The role of clinical medicine. In *Drug Repurposing*, Cavalla D, ed. The Royal Society of Chemistry, pp. 24-51.
- [12] Hinnen D (2017) Glucagon-like peptide 1 receptor agonists for type 2 diabetes. *Diabetes Spectr* **30**, 202-210.
- [13] Brauer R, Wei L, Ma T, Athauda D, Girges C, Vijjaratnam N, Auld G, Whittlesea C, Wong I, Foltynie T (2020) Diabetes medications and risk of Parkinson's disease: A cohort study of patients with diabetes. *Brain* **143**, 3067-3076.
- [14] Qin X, Zhang X, Li P, Wang M, Yan L, Bao Z, Liu Q (2021) Association between diabetes medications and the risk of Parkinson's disease: A systematic review and meta-analysis. *Front Neurol* **12**, 678649.
- [15] Yun SP, Kam TI, Panicker N, Kim S, Oh Y, Park JS, Kwon SH, Park YJ, Kauppagounder SS, Park H, Kim S, Oh N, Kim N, Lee S, Brahmachari S, Mao X, Lee JH, Kumar M, An H, Kang SU, Lee Y, Lee KC, Na DH, Kim D, Lee SH, Boshnia V V., Liddelow SA, Mari Z, Barres BA, Dawson VL, Lee S, Dawson TM, Ko HS (2018) Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. *Nat Med* **24**, 931-938.
- [16] Zhang L, Zhang L, Li L, Hölscher C (2019) Semaglutide is neuroprotective and reduces  $\alpha$ -synuclein levels in the chronic MPTP mouse model of Parkinson's disease. *J Parkinsons Dis* **9**, 157-171.
- [17] Chen S, Yu SJ, Li Y, Lecca D, Glotfelty E, Kim HK, Choi H II, Hoffer BJ, Greig NH, Kim DS, Wang Y (2018) Post-treatment with PT302, a long-acting Exendin-4 sustained release formulation, reduces dopaminergic neurodegeneration in a 6-Hydroxydopamine rat model of Parkinson's disease. *Sci Rep* **8**, 10722.
- [18] Liu W, Jalewa J, Sharma M, Li G, Li L, Hölscher C (2015) Neuroprotective effects of lixisenatide and liraglutide in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. *Neuroscience* **303**, 42-50.
- [19] Li Y, Perry TA, Kindy MS, Harvey BK, Tweedie D, Holloway HW, Powers K, Shen H, Egan JM, Sambamurti K, Brossi A, Lahiri DK, Mattson MP, Hoffer BJ, Wang Y, Greig NH (2009) GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. *Proc Natl Acad Sci U S A* **106**, 1285-1290.
- [20] Harkavyi A, Abuirmeleh A, Lever R, Kingsbury AE, Biggs CS, Whitton PS (2008) Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. *J Neuroinflammation* **5**, 19.
- [21] Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Ell P, Soderlund T, Whitton P, Wyse R, Isaacs T, Lees A, Limousin P, Foltynie T (2013) Exenatide and the treatment of patients with Parkinson's disease. *J Clin Invest* **123**, 2730-2736.
- [22] Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Kahan J, Ell P, Whitton P, Wyse R, Isaacs T, Lees A, Limousin P, Foltynie T (2014) Motor and cognitive advantages persist 12 months after exenatide exposure in Parkinson's disease. *J Parkinsons Dis* **4**, 337-344.



- [23] Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, Hibbert S, Budnik N, Zampedri L, Dickson J, Li Y, Aviles-Olmos I, Warner TT, Limousin P, Lees AJ, Greig NH, Tebbs S, Foltynie T (2017) Exenatide once weekly versus placebo in Parkinson's disease: A randomised, double-blind, placebo-controlled trial. *Lancet* **390**, 1664-1675.
- [24] Vijiaratnam N, Girges C, Auld G, Chau M, Maclagan K, King A, Skene S, Chowdhury K, Hibbert S, Morris H, Limousin P, Athauda D, Carroll CB, Hu MT, Silverdale M, Duncan GW, Chaudhuri R, Lo C, Del Din S, Yarnall AJ, Rochester L, Gibson R, Dickson J, Hunter R, Libri V, Foltynie T (2021) Exenatide once weekly over 2 years as a potential disease-modifying treatment for Parkinson's disease: Protocol for a multicentre, randomised, double blind, parallel group, placebo controlled, phase 3 trial: The "Exenatide-PD3" study. *BMJ Open* **11**, e047993.
- [25] McFarthing K, Buff S, Rafaloff G, Fiske B, Mursaleen L, Fuest R, Wyse RK, Stott SRW (2023) Parkinson's disease drug therapies in the clinical trial pipeline: 2023 update. *J Parkinsons Dis* **13**, 427-439.
- [26] Yang SY, Taanman JW, Gegg M, Schapira AHV (2022) Ambroxol reverses tau and  $\alpha$ -synuclein accumulation in a cholinergic N370S GBA1 mutation model. *Hum Mol Genet* **31**, 2396-2405.
- [27] McNeill A, Magalhaes J, Shen C, Chau KY, Hughes D, Mehta A, Foltynie T, Cooper JM, Abramov AY, Gegg M, Schapira AHV (2014) Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. *Brain* **137**, 1481-1495.
- [28] Sanchez-Martinez A, Beavan M, Gegg ME, Chau KY, Whitworth AJ, Schapira AHV (2016) Parkinson disease-linked GBA mutation effects reversed by molecular chaperones in human cell and fly models. *Sci Rep* **6**, 31380.
- [29] Migdalska-Richards A, Daly L, Bezdadek E, Schapira AHV (2016) Ambroxol effects in glucocerebrosidase and  $\alpha$ -synuclein transgenic mice. *Ann Neurol* **80**, 766-775.
- [30] Maegawa GHB, Tropak MB, Buttner JD, Rigat BA, Fuller M, Pandit D, Tang L, Kornhaber G, Hamano Y, Clarke JTR, Mahuran DJ (2009) Identification and characterization of ambroxol as an enzyme enhancement agent for Gaucher disease. *J Biol Chem* **284**, 23502-23516.
- [31] Mullin S, Smith L, Lee K, D'Souza G, Woodgate P, Elflein J, Hällqvist J, Toffoli M, Streeter A, Hosking J, Heywood WE, Khengar R, Campbell P, Hehir J, Cable S, Mills K, Zetterberg H, Limousin P, Libri V, Foltynie T, Schapira AHV (2020) Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: A nonrandomized, noncontrolled trial. *JAMA Neurol* **77**, 427-434.
- [32] Mortiboys H, Furnston R, Bronstad G, Aasly J, Elliott C, Bandmann O (2015) UDCA exerts beneficial effect on mitochondrial dysfunction in LRRK2(G2019S) carriers and *in vivo*. *Neurology* **85**, 846-852.
- [33] Mortiboys H, Aasly J, Bandmann O (2013) Ursocholic acid rescues mitochondrial function in common forms of familial Parkinson's disease. *Brain* **136**, 3038-3050.
- [34] Payne T, Appleby M, Buckley E, van Gelder LMA, Mullish BH, Sassani M, Dunning MJ, Hernandez D, Scholz SW, McNeill A, Libri V, Moll S, Marchesi JR, Taylor R, Su L, Mazzà C, Jenkins TM, Foltynie T, Bandmann O (2023) A double-blind, randomized, placebo-controlled trial of ursodeoxycholic acid (UDCA) in Parkinson's disease. *Mov Disord* **38**, 1493-1502.
- [35] Mahul-Mellier AL, Fauvet B, Gysbers A, Dikiy I, Oueslati A, Georgeon S, Lamontanara AJ, Bisquertt A, Eliezer D, Masliah E, Halliday G, Hantschel O, Lashuel HA (2014) c-Abl phosphorylates  $\alpha$ -synuclein and regulates its degradation: Implication for  $\alpha$ -synuclein clearance and contribution to the pathogenesis of Parkinson's disease. *Hum Mol Genet* **23**, 2858-2879.
- [36] Karuppagounder SS, Brahmachari S, Lee Y, Dawson VL, Dawson TM, Ko HS (2014) The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. *Sci Rep* **4**, 4874.
- [37] Hebron ML, Lonskaya I, Moussa CEH (2013) Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of  $\alpha$ -synuclein in Parkinson's disease models. *Hum Mol Genet* **22**, 3315-3328.
- [38] Pagan F, Hebron M, Valadez EH, Torres-Yaghi Y, Huang X, Mills RR, Wilmarth BM, Howard H, Dunn C, Carlson A, Lawler A, Rogers SL, Falconer RA, Ahn J, Li Z, Moussa C (2016) Nilotinib effects in Parkinson's disease and dementia with Lewy bodies. *J Parkinsons Dis* **6**, 503-517.
- [39] Simuni T, Fiske B, Merchant K, Coffey CS, Klingner E, Caspell-Garcia C, Lafontant DE, Matthews H, Wyse RK, Brundin R, Simon DK, Schwarzschild M, Weiner D, Adams J, Venuto C, Dawson TM, Baker L, Kostrzebski M, Ward T, Barlow G (2021) Efficacy of nilotinib in patients with moderately advanced Parkinson disease: A randomized clinical trial. *JAMA Neurol* **78**, 312-320.
- [40] Pagan FL, Hebron ML, Wilmarth B, Torres-Yaghi Y, Lawler A, Mundel EE, Yusuf N, Starr NJ, Anjum M, Arellano J, Howard HH, Shi W, Mulki S, Kurd-Misto T, Matar S, Liu X, Ahn J, Moussa C (2020) Nilotinib effects on safety, tolerability, and potential biomarkers in Parkinson disease: A phase 2 randomized clinical trial. *JAMA Neurol* **77**, 309-317.
- [41] Carroll CB, Wyse RKH (2017) Simvastatin as a potential disease-modifying therapy for patients with Parkinson's disease: Rationale for clinical trial, and current progress. *J Parkinsons Dis* **7**, 545-568.
- [42] Bayram E, Marras C, Standaert DG, Kluger BM, Bordelon YM, Shprecher DR, Litvan I (2020) Progressive supranuclear palsy and statin use. *Mov Disord* **35**, 1253-1257.
- [43] Stevens KN, Creanor S, Jeffery A, Whone A, Zajicek J, Foggo A, Jones B, Chapman R, Cocking L, Wilks J, Webb D, Carroll C (2022) Evaluation of simvastatin as a disease-modifying treatment for patients with Parkinson disease: A randomized clinical trial. *JAMA Neurol* **79**, 1232-1241.
- [44] Day JO, Smith S, Noyce AJ, Alty J, Jeffery A, Chapman R, Carroll C (2022) Challenges of incorporating digital health technology outcomes in a clinical trial: Experiences from PD STAT. *J Parkinsons Dis* **12**, 1605-1609.
- [45] Kehagia AA, North TK, Grose J, Jeffery AN, Cocking L, Chapman R, Carroll C (2022) Enhancing trial delivery in Parkinson's disease: Qualitative insights from PD STAT. *J Parkinsons Dis* **12**, 1591-1604.
- [46] Fletcher EJR, Kaminski T, Williams G, Duty S (2021) Drug repurposing strategies of relevance for Parkinson's disease. *Pharmacol Res Perspect* **9**, e00841.
- [47] Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C, Norris A, Sanseau P, Cavalla D, Pirmohamed M (2019) Drug repurposing: Progress, challenges and recommendations. *Nat Rev Drug Discov* **18**, 41-58.
- [48] Innovative Licensing and Access Pathway: GOV.UK - <https://www.gov.uk/guidance/innovative-licensing-and-access-pathway> (accessed October 23, 2023).

- [49] iLCT Pipeline Research Acceleration Programme: Cure Parkinson's - <https://cureparkinsons.org.uk/for-researchers/apply-for-funding/ilct-pipeline-research-acceleration-programme/> (accessed October 23, 2023).
- [50] ANZCTR Registration - <https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375958> (accessed October 23, 2023).
- [51] EJS ACT-PD, Accelerating Clinical Trials in Parkinson's - <https://ejsactpd.com/> (accessed October 23, 2023).
- [52] Foltynie T, Gandhi S, Gonzalez-Robles C, Zeissler ML, Mills G, Barker R, Carpenter J, Schrag A, Schapira A, Bandmann O, Mullin S, Duffen J, McFarthing K, Chataway J, Parmar M, Carroll C, Shlomo Y Ben, Edwards M, Whone A, Counsell C, Clarke C, Burnell M, Salathiel D, Whips S, Jewell A, Barber T, Weil R, Gray CW, Hu M, Rochester L, Piccini P, Zetterberg H, Noyce A, Chaudhuri R, Lawton M, Jha A, Siu C, Bartlett M, van Wamelen D, Stott S, Tofaris G, Sammler E, Mortiboys H, Wei L, Wong A, Duty S, Dexter D, Scurfield P, Jabbari E, Morris H, Breen D, Lambert C, Korlipara P, Silverdale M, Bhatia K, Yarnall A, Khengar R, Collins H, Hudson F, Baxendale G, Croucher R, Bartolomeu-Pires S, Allison J, Morgan A, Wonnacott S, Athauda D, Henderson E, Clegg S, Matthews K, Deeson E, Miller L, Handley J, Matthews H, Batla A, Bakshi N, Port B, Ellis-Doyle R, Collins SL, Rudiger J, Chapman R, Cedarbaum J, Lang A, Fiske B, Wyse R, Boxer A, Wilson D, Corvol JC, Harris J (2023) Towards a multi-arm multi-stage platform trial of disease modifying approaches in Parkinson's disease. *Brain* **146**, 2717-2722.
- [53] Zeissler ML, Li V, Parmar MKB, Carroll CB (2020) Is it possible to conduct a multi-arm multi-stage platform trial in Parkinson's disease: Lessons learned from other neurodegenerative disorders and cancer. *J Parkinsons Dis* **10**, 413-428.
- [54] Siderowf A, Concha-Marambio L, Lafontant DE, Farris CM, Ma Y, Urenia PA, Nguyen H, Alcalay RN, Chahine LM, Foroud T, Galasko D, Kiebertz K, Merchant K, Mollenhauer B, Poston KL, Seibyl J, Simuni T, Tanner CM, Weintraub D, Videnovic A, Choi SH, Kurth R, Caspell-Garcia C, Coffey CS, Frasier M, Oliveira LMA, Hutten SJ, Sherer T, Marek K, Soto C (2023) Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using  $\alpha$ -synuclein seed amplification: A cross-sectional study. *Lancet Neurol* **22**, 407-417.

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