GAP & CONTROVERSY

Advantages and Challenges of Platform Trials for Disease Modifying Therapies in Parkinson's Disease

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ABSTRACT: Traditional drug development in Parkinson's disease (PD) faces significant challenges because of its protracted timeline and high costs. In response, innovative master protocols are emerging and designed to address multiple research questions within a single overarching protocol. These trials may offer advantages such as increased efficiency, agility in adding new treatment arms, and potential cost savings. However, they also present organizational, methodological, funding, regulatory, and sponsorship challenges. We review the potential of master protocols, focusing on platform trials, for disease modifying therapies in PD. These trials share a common control group and allow for the termination or addition of treatment arms during a trial with non-predetermined end. Specific issues exist for a platform trial in the PD field considering the heterogeneity of patients in terms of phenotype, genotype and staging, the confounding effects of symptomatic treatments, and the choice of outcome measures with no consensus on a non-clinical biomarker to serve as a surrogate and the slowness of PD progression. We illustrate these aspects using the examples of the main PD platform trials currently in development with each one targeting distinct goals, populations, and outcomes. Overall, platform trials hold promise in expediting the evaluation of potential therapies for PD. However, it remains to be proven whether these theoretical benefits will translate into increased production of high-quality trial data. Success also depends on the willingness of pharmaceutical companies to engage in such trials and whether this approach will ultimately hasten the identification and licensing of effective disease-modifying drugs.

Key Words: clinical trials; disease-modifying; master protocols; outcomes; Parkinson's disease; platform trials

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Although no efficacious disease-modifying therapies for Parkinson's disease (PD) have yet been identified,[1-3] clinical research and drug development in PD are entering a new era with major advances in biomarkers (like synuclein seed assays), neuroimaging outcomes (like neuromelanin), and new therapeutic avenues for personalized (LRRK2 kinase inhibitors, GCase enhancers) or more general mechanisms (eg, ferroptosis, insulin signaling modulators) therapies.[3] The optimal disease modification strategy may ultimately involve the combination of multiple drugs to counteract several mechanisms simultaneously.

Developing a new drug is a protracted and costly endeavor, typically focusing on a single intervention[4] and relying on the implementation of a sequential series of phase 2 and phase 3 randomized controlled trials (RCTs). There is a major attrition at the phase 2 trial stage, leading to a poorly efficient process.[5] This traditional "serial" approach is, therefore, being challenged, considering that a clinical trial can be thought of a "machine," and repetitively building and dismantling this "machine" compromises the efficiency of clinical trial conduct.

In various medical fields, researchers have addressed such methodological trial inefficiencies by using innovative platform trials, which coordinate efforts to evaluate multiple treatments simultaneously, with the capability of adding new treatments and eliminating investigational treatments lacking efficacy, therefore, offering enhanced efficiency and a more ethical approach.[6] They can also increase power by sharing the placebo group. Further efficiencies can be gained by enabling phase 2 data to contribute to the phase 3 outcome. This is facilitated by considering each evaluation as a phase 3 definitive trial with early-stage analyses for signals of efficacy, following which active trial arms are terminated or continued. This "multistage" approach has, therefore, the potential to mitigate several inefficiencies of serial evaluations.

In this context, the goal of the present viewpoint is to explore the advantages, challenges, and potential solutions of platform trials applied for disease-modifying approaches in PD.

Definitions and General Concepts

Master protocols are defined as a single overarching protocol that is designed to answer multiple questions.[7] Two innovations are hallmarks of master protocols: (1) the use of a trial network with shared infrastructure to streamline trial logistics, improve data quality, and facilitate data collection and sharing; and (2) a common protocol that uses statistical approaches that enables a broader set of objectives to be met more efficiently than in independent trials.

There are three main types of master protocols: (1) "basket trials" assessing in a single stage design a targeted treatment in multiple diseases or disease subtypes (as in B2225, a basket trial, in which a common biomarker–treatment combination was investigated in 40 different solid tumors or hematologic malignancies)[8]; (2) "umbrella trials" assessing in a single stage design, multiple targeted treatments in the same disease (as in the plasma MATCH study, an umbrella trial that evaluated five different therapies for advanced breast cancer, stratified into multiple subgroups, with eligibility for each intervention arm defined by the intervention's mechanism of action); (3) "platform trials," which are randomized adaptive trials, usually assessing in a multistage design multiple interventions in a potentially perpetual manner (as in the STAMPEDE trial, that in 2009 included men with poor prognosis prostate cancer, starting to test five new treatments alongside long-term hormone therapy, compared to long-term hormone therapy alone "standard care." Of note, in the last 14 years, the control arm has been improved four times). The term multiarm, multistage (MAMS) platform is often used interchangeably with platform trials,[9,10] although MAMS was originally coined for a particular method of seamless phase 2/3 trials simultaneously comparing several investigational treatments, with interim futility analyses followed by a final analysis on the primary endpoint to confirm efficacy.[11-13]

Here, we will focus on platform trials. The key feature of platform trials is that a treatment arm can be terminated at interim time points based on a predefined criteria for lack of activity and that the treatment of an arm meeting its primary efficacy endpoint may become incorporated into the new standard of care, applicable to all arms, to serve as the new reference group. Moreover, new treatments can enter the platform, during the trial as additional arms. Platform trials offer several advantages, such as increased efficiency because of the shared control arm; increased agility in adding new treatment arms; building a stable network of investigators, sharing standard operating and pharmacovigilance procedures, leading to economies of scale and cost efficiency after the initial infrastructure investment; and potential shortening of delays to obtain regulatory and ethical approvals. Their implementation may be particularly favorable for diseases for which there are many drug candidates or when the standard of care is rapidly changing. Despite such advantages, platform trials also raise many challenges,[9,14-17] which are summarized below:

(1) Organizational issues. The management of a platform trial requires a clearly defined and efficient governance and coordination process to deal with scientific, ethical, practical, and financial aspects that arise during the trial. Alongside standard committees overseeing protocol design, implementation, data, and safety

monitoring, an independent platform access committee is often helpful to prioritize new intervention arms. These may include public/patients' involvement and engagement methodologists as well as investigators. The perpetual nature of platform trials requires regular interim analyses. This involves a demanding continuous data monitoring and data management system closely linked with statistical analyses, to efficiently decide on futility or efficacy. A model for such a complex infrastructure has been proposed by the Edmond J Safra Accelerating Clinical Trials in Parkinson's Disease (EJS ACT-PD) team.[18-20]

(2) Methodological issues. Some methodological issues are directly related to the platform design, including, for example, the control group and the use of placebo and blinding. To ensure comparability, analyses of patient responses to a new intervention should be made in relation to patients belonging to a "control group," which must be randomized contemporaneously.[21] Standard of care can change over time; consequently, patients enrolled earlier in the control group may not be representative anymore of the best medical standard of care to compare with when new arms are integrated. Additionally, different interventions may require distinct routes of administration and may be associated with different placebo effects. This can impact on blinding, requiring "multiple-dummy" implementation with implications for feasibility. This explains why most platform trials are conducted with an open-label design with hard endpoints such as mortality. Other methodological issues are also crucial to consider, although generic to any multisite clinical trials. These include, for example, the eligibility criteria, depending on the objectives and the outcomes used for interim and final analyses, ensuring or not representativeness of the whole population, and considering recruitment and retention capacities for such large trials with long-term follow-up.

(3) Statistical issues. The comparison of different treatment arms to a single control arm may theoretically induce multiplicity, for instance, the inflation of type I error rate when performing multiple comparison and thereby increasing the probability of false positive conclusions. However, such multiple comparisons may not require statistical adjustment, except when different forms (eg, doses) of the same drug are tested across multiple groups. Nonetheless, it may be pertinent to account for correlations between statistical tests when comparing each treatment to the shared control. Other methodological issues relate to sample size calculation, and it may be necessary to increase the size of the shared control arm compared to that of the investigational treatment arms, to decrease the correlation among test statistics. Interim analyses are also a source of multiplicity and must be pre-planned and clearly described in the protocol, along with methods to control the type I error rate. The use of Bayesian analyses may be also considered, as they are well-suited to the adaptive nature of platform trials. Adaptive randomization has also been suggested.[22]

(4) Funding issues and sustainability. A platform trial requires significant initial investment to establish the shared infrastructure. Subsequent support is necessary to sustain both the infrastructure and the participating investigation centers, even without a predetermined end to the trial. Usually, initial funding can only be provided through large academic non-profit and public initiatives. Complementary funding may subsequently be required to support individual treatment arms, which include infrastructure maintenance. Therefore, although platform trials are cost-effective over the long-term, their initial cost is larger than for a single traditional RCT.

(5) Sponsorship and relationship between public and private partners. Usually, a trial is sponsored by a single entity, guaranteeing the quality of the study, and owning the data and intellectual property that have been generated. This model may need to be adjusted in platform trials, as they may involve different partners providing sponsorship for a given comparison, therefore, potentially raising complex legal issues. Overall, it is recommended to have only one sponsor, usually an academic entity, with a detailed distribution and delegation of duties. In fact, although co-sponsorship is theoretically possible, the multiplicity of partners makes this aspect of platform trials organization difficult. For that reason, many platform trials focus only on already marketed interventions, in a repurposing or combination strategy. If multiple stakeholders co-exist (academic sponsor and manufactures) early exchanges must define, in advance, the ownership and future use of data.

(6) Regulatory issues. Effective communication with regulators or competent authorities is also crucial. Beginning at an early stage and preferably before applying for authorization, as such methods have not yet been broadly used in many fields. Moreover, new arms need to be added as amendments to the existing protocol to speed up the approval processes and not create complex interactions with regulators.

Gaps and Controversies

There are many potential candidate therapies deserving to be tested for disease-modification in PD.[2,3,23] This poses the question of the best way to select, which candidates to test first. Moreover, PD-patient specific issues also need to be defined[24] considering the heterogeneity of patients in terms of phenotype, genotype and staging, the confounding effects of symptomatic treatments, and the choice of outcome measures in the

absence of consensus on a non-clinical surrogate biomarker of progression.

Population

As for any clinical trial, the population should be tailored according to the project's main objective. For instance, if the primary goal is a proof-of-concept (POC) or a go/no-go assessment (phase-2 type approach), one might choose a homogeneous, well-defined population. Conversely, a trial designed to inform real-world practice and applicability (phase 3-type approach) would recruit a broader and more inclusive population. In addition, the population should fit with the putative mechanism of the treatment(s), which may not be easy in a multiarm design testing different drug. Randomization is essential and additional stratification may be considered for factors known to impact disease progression, such as age at disease onset,[25] staging, genetic background,[26-28] comorbidities,[29] and phenotypic markers (ie, malignant/intermediate/benign phenotypes)[30-32] to ensure comparability between active and placebo arms. It is likely that some interventions may only be efficacious in subtypes of PD and not necessarily in the entire population and consideration should be given whether such candidates should be excluded from the platform or whether an inclusive recruitment strategy could be adopted with later analysis based on subgroup stratification.[18] In addition to clinical and genetic stratification, it has been highlighted as disease-modifying trials should match the mechanism of action of the selected drug with biologically selected population,[33] focusing on the role of specific biological processes for patients and drug selection. For example, following demonstration of a differential subgroup effect in a pre-planned analysis, future treatment arms could be enriched for a mechanistic subgroup identified as most likely to benefit (eg, targeting patients with low serum urate concentrations)[34] patients stratified according to the severity of neuronal respiratory complex I deficiency (if screening feasible methods will be available), which has been associated to non-tremor dominant motor phenotypes,[35] anti-inflammatory agents for patients with positive neuroinflammation neuroimaging markers,[36] or those with polygenic risk scores that have shown to be able to predict PD status.[37] However, this will introduce substantial complexity, especially regarding the population of the control arm, that may be more easily addressable once the platform infrastructure is established and recruitment rates according to defined subgroups can be more precisely estimated.

Outcome Measurements

As for any trial, the choice of outcome measures is crucial. Outcomes must be uniform across the different arms of the master protocol, but could evolve during the life of the protocol, provided that accumulating data provides adequate support to shift outcome for a newly adopted treatment arm, and that such a decision meets regulatory approval. For diseases such as cancer or coronavirus disease for example, death and survival can provide a robust clinically important endpoint that occurs within a reasonable time frame. This is not the case for PD, which progresses more slowly. The goal is then to identify a robust and sensitive way to detect PD progression regardless of the effect of symptomatic therapies, using an outcome that applies to the different subtypes and stages of the disease, which is properly validated, reliable, easy to collect among many centers, clinically meaningful, and affordable. Such an "ideal" outcome is not currently available. Pragmatic compromises, although imperfect, are then necessary for the moment. Very recently, the EJS ACT-PD consortium published an important consensus article[19] presenting an inventory of outcome measures based on current evidence. It made initial recommendations for their potential inclusion as core, supplementary (depending on study arm) or exploratory outcome measures for platform trials in PD. Outcomes measures have been stratified including the potential need for their remote capture, which should be considered for large multicenter trials.[19] Overall, the Movement Disorder Society-Unified Parkinson's Disease Rating scale (MDS-UPDRS), despite numerous limitations,[38] seems the most pragmatic compromise as a primary endpoint for a platform trial on neuroprotection in PD, although new approaches (such as milestone-based) hold promise.[39] The specific subsections of the scale (ie, I–IV) and whether it should be assessed *on* or *off* symptomatic medications will be informed by the phase and trial objectives.[40] Of note, regulatory agencies do not accept MDS-UPDRS part III as the primary outcome of a phase 3 trial, whereas patient-reported outcomes (PROs) such as MDS-UPDRS part I–II are preferred. Moreover, the rapid evolution of outcomes—biofluid, imaging, and digital—may enable alternative approaches to early-stage analyses with greater efficiency and potentially necessitating smaller sample sizes or shorter follow-up durations. Of note, to date, wearable sensors are adopted as exploratory outcomes in clinical trials, because of the lack of formal validation and of agreement on which "tools" should be adapted for which symptoms, disease stage, and outcome. Nevertheless, they present a promising complementary tool for currently available outcomes, and they have a potentially greater sensitivity[41] and the ability to continuously monitor patients in real-life conditions. Platform trials could also be useful to validate these markers, particularly if they are shared across different international initiatives. We should also consider that, in practice, platform trials may allow for addressing different questions for different populations of interest (eg, the FOCUS4 or REMAP-CAP trials), with possibly different controls or different experimental treatments depending on the subpopulation or clinical question. For instance, it

could be possible that a unique platform trial would aim to concomitantly test (1) the efficacy of compound A, B, and C versus a common placebo in an early PD population, adopting motor symptoms progression as primary outcome; and (2) the efficacy of compound A, B, and D versus a common placebo in an advanced PD population, adopting the occurrence of disease severity milestones as primary outcome. Such a trial would keep the benefits of a shared control arm for different interventional arms, but also enable to propose a clinical trial to any patient within a common trial infrastructure with uniform procedures.

Interventions to be Tested

It is crucial to implement an efficient process of drug selection to identify the most promising candidates to be tested in a platform trial. The International Linked Clinical Trials program (iLCT) is an example of a drug repurposing program aimed at identifying drugs that might slow PD progression based on their safety as treatments for other conditions alongside neuroprotective effects in preclinical experiments.[42-44] In brief, the committee has a comprehensive and systematic approach evaluating safety evidence, ability to cross the blood–brain barrier, efficacy in PD in vitro and animal models, epidemiological data, the feasibility of measuring target engagement, and their commercial or patent status. Final decisions on prioritizing drugs for clinical testing in PD occur annually at a meeting of global international and independent experts.[42-44] To date, more than 100 compounds have been considered, some of them being already evaluated in RCTs. Extensive patient input with respect to dose, delivery mode, pill frequency, size, and overall burden is also essential in any platform trial treatment selection process.

Another significant issue is the selection of the optimal dose to be studied. Ideally dose finding studies should have been completed before inclusion in the trial, but there is often a compromise between increasing the number of agents tested and testing multiple doses of a single agent. It is also possible that in the near future, combining interventions that target different or complementary mechanisms will lead to greater efficacy, similar to the treatment of certain cancers or infectious diseases. The implementation of platform trials may also be beneficial in this regard, because different combinations of repurposed drugs can be adopted in each treatment arm, which accelerates the process of testing various drug associations.

Finally, in the near future, not only are drug repurposing strategies likely to be evaluated using platform disease-modifying data, but also new compounds targeting innovative biological pathways. Because these initiatives are sponsored by academic institutions, we anticipate that pharmaceutical companies will initially be hesitant to use these platforms. However, all these initiatives are open to industry, and we hope that once POC is established industry will entrust part of their drug candidate development to them. This will make the prioritization process more challenging. These compounds should probably undergo a comprehensive evaluation process similar to the one adopted by iLCT.

Ongoing Neuroprotection Platform Trials

To the best of our knowledge, there are currently five platform trials at various stages of setup assessing neuroprotective interventions in PD. These projects have made different design decisions especially regarding primary objectives (phase 2- vs. 3-type) and target populations, which make them complementary rather than competitive (Fig. 1, Table 1):

Path to Prevention Platform Trial

The North American Path to Prevention (P2P) platform trial that is sponsored by The Michael J. Fox foundation and is designed to identify agents to reduce conversion from prodromal PD to clinically established PD, dementia with Lewy bodies (DLB), or multiple system atrophy (MSA).[45] It capitalizes on Parkinson's Progression Markers Initiative study infrastructure and population. P2P is a phase 2A, double-blind, placebo-controlled, randomized platform trial. Participants with prodromal α-synucleinopathies (αSN) who are at a high risk of developing clinically defined PD, DLB, or MSA (having idiopathic/isolated rapid eye movement sleep behavior disorder [RBD], hyposmia, or other prodromal features[46] plus a dopamine active transporter [DAT] scan deficit), will be selected. The follow-up is 24 months, with sample size ranging from 50 to 250 participants per regimen. The primary endpoints are the change of the mean striatum specific binding ratio (SBR)-DAT and the time to observe a clinically meaningful motor or cognitive worsening.

P2P addresses a crucial innovative objective, identifying disease-modifying therapies in prodromal PD.[46] Targeting a prodromal PD stage is a quite recent "practice" in PD and the odds of success in a prodromal stage for any agents not having previously proven effective in the disease stage are unknown with no clear precedent in medicine. Note, however, that in the Alzheimer's disease field, recent studies have suggested that a compound may selectively be effective only when provided in an earlier disease stage (eg, subjects with low tau burden had better efficacy of donanemab).[47] Therefore, is seems more likely that a compound effective in intermediate and advanced disease stages may have even more pronounced effect in earlier stages. Moreover, one should continue to consider more

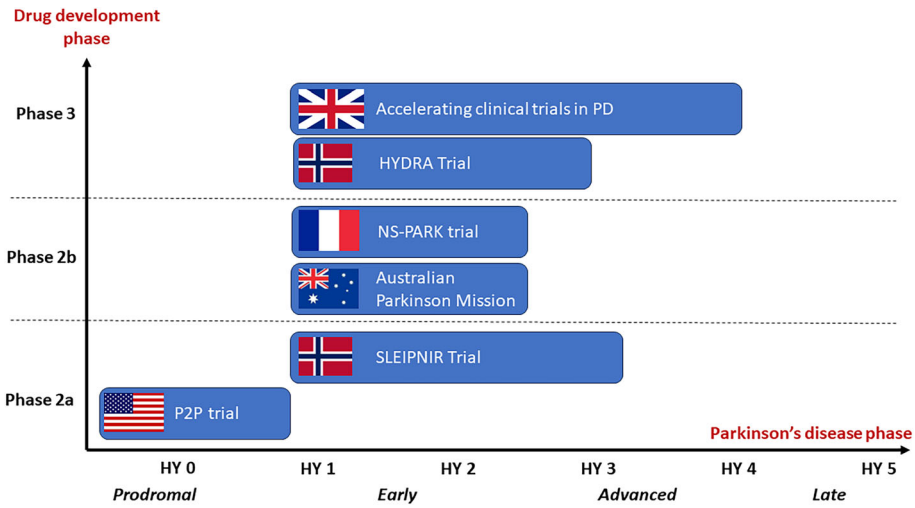

FIG. 1. Upcoming platform trials for Parkinson's disease across its different stages. HY, Hoehn and Yahr stage. [Color figure can be viewed at wileyonlinelibrary.com]

advanced stages for disease-modification PD trials if the mechanism is considered relevant at this stage. This requires adapting the trial's primary outcome to disease stage (ie, for advanced PD patients targeting late disease milestones such as falls, hallucinations, cognitive impairment, etc.). Like any prodromal trial, it faces a number of challenges including ethical issues related to recruitment of participants who do not yet have clinically established PD, their willingness to participate, and the potential adverse reactions in a population with no or minor disability. It targets a heterogeneous population, given that prodromal αSN may evolve into PD, DLB, or MSA. New composite clinical endpoints will be used; whereas their clinimetric properties are not yet fully known, the acceptance of such endpoints by regulatory authorities remains to be explored. Finally, the willingness of pharmaceutical companies to participate in an open data-sharing study, while contributing to the platform is still uncertain.

EJS ACT-PD Platform Trial

This United Kingdom (UK) MAMS is a phase 3-type platform trial (https://ejsactpd.com) conceived by Cure Parkinson's (UK) in 2016 to 2017. It benefits from the academic expertise of the London and Newcastle groups, combining clinical and methodological experience in PD and clinical trials, with the financial support of the UK government, PD charities, philanthropic agencies, and the Edmond J Safra Foundation. It plans to recruit patients with established motor PD, on dopaminergic therapies, with sufficient cognitive reserve to facilitate participation. The objective is to identify treatments that will prevent or delay subsequent progression of motor and non-motor symptoms.[18] It plans to assess various therapeutic strategies among 400 participants per arm, for 36 months duration using double-blind randomized placebo-controlled methodology. The EJS ACT-PD platform trial will adopt the MDS-UPDRS part I + II as the primary outcome.[20] The choice has been made considering feasibility, clinimetric properties, and patient and stakeholder representatives' input who have rated the most important PD symptoms for patients. The project has incorporated the work of the iLCT to assist in the selection of candidates to be tested.

A strength of this program is that it is enrolling patients at all stages of PD, carefully considering inclusivity and diversity as a major priority and is supported by collaborative work between PD, statisticians, and health economics experts and an exceptional public and patient involvement. It is structured as a core management team coordinating contributions from a consortium of >90 stakeholders from across the United Kingdom with an international advisory group. It intends to initially test repurposed medications, and then expand to include agents with commercial partners. The choice of a primary outcome based on MDS-UPDRS subscores driven by patients' perception (part I and II) has the advantage of being more acceptable by regulators than part III (which reflects investigators' scoring), but has the disadvantage of being less sensitive to change and potentially confounding by non-PD related factors,[48] which explain the large sample needed to achieve sufficient power.

French NS-Park Master Trial

This project is an investigator-driven phase 2-type platform trial, set-up by the French NS-Park network and bringing together 27 PD expert centers with long experience in disease modification trials in PD, in collaboration with an epidemiological team with experience in innovative methodologies for clinical trials. It is

TABLE 1 *Overview on on-going or shortly expected platform trials on PD*

Trials features	US P2P platform trial	French NS-Park master trial	UK EJS ACT-PD platform trial	Australian Parkinson's mission	Norway MAMS trials
Target population, main inclusion criteria	Prodromal αSN, with at least one of the following: RBD (probable or definite) Hyposmia (defined as <10% for age and sex) Other prodromal features AND: Presence of DAT deficit at baseline as defined by lowest putamen SBR <65 percentile for age and sex (including relevant genetic variants if they have RBD or hyposmia)	Early PD patients (<5 years of disease duration) treated or untreated with dopaminergic medication and without L-dopa-induced motor complications.	Clinically defined PD patients at any stage	PD, HY = 2.5 in the *on* state, absence of dementia	SLEIPNIR: clinically established PD (MDS criteria), presence of dopaminergic nigrostriatal denervation on DAT-scan or [^{18}F]DOPA-PET, time since diagnosis ≤3 years, HY ≤3, absence of dementia HYDRA: clinically established or probable PD (MDS criteria), presence of dopaminergic nigrostriatal denervation on DAT-scan or [^{18}F]DOPA-PET, time since diagnosis ≤4 years, HY ≤3, absence of dementia.
Study design/ phase	Proof of concept phase 2A randomized double blind	Phase 2-type open-label proof-of concept design	Double-blind, placebo-controlled	Phase 2, double-blind, placebo-controlled	SLEIPNIR: multiarm, randomized, double blinded, phase II trial HYDRA: MAMS, phase-III, randomized, double blinded
Primary endpoint/s	Both: Change from baseline to 24 months on: Dat-Scan SBR in the active treatment arm versus placebo AND Time to observe a clinically meaningful change in motor status (change in MDS-UPDRS part III >5 points) and cognition (developing a new diagnosis of MCI or dementia)	Change from baseline to 12 months on MDS-UPDRS III motor score in *on* state between baseline and 12 months	Change from baseline to 36 months: MDS-UPDRS I + II	MDS-UPDRS III in the *off* state	SLEIPNIR: depending on the compound, target penetration and engagement, including functional neuroimaging and biomarkers in the CSF. HYDRA: MDS-UPDRS III
Secondary endpoints	Feasibility (ability to recruit, retain participants) Safety/tolerability (AEs and ability to complete the study on the assigned dose)	Change between baseline and 12 months for: –MDS-UPDRS II + III –MDS-UPDRS I, II, IV –MDS-NMS –MDS-UPDRS I + II	To be defined	Change between baseline and 60 weeks for PGIC MDS-UPDRS part I, II, III, and IV scores MoCA	To be defined

(Continues)

TABLE 1 *Continued*

Trials features	US P2P platform trial	French NS-Park master trial	UK EJS ACT-PD platform trial	Australian Parkinson's mission	Norway MAMS trials
Sample size	50–250 participants on active treatment	100 patients per arm; for and initial trial with 3 arms (2 interventions +1 control) = 300 patients	400 patients per arm	60 par arm (3 treatment arms +1 placebo arm)	SLEIPNIR: 20–40 patients per arm HYDRA: 300–400 patients per arm
Duration of treatment per arm	24 months	12 months	36 months	48 weeks of treatment, with an additional study visit 12 weeks later	SLEIPNIR: 12 weeks HYDRA: 78 weeks

Note: Biomarkers of αSN pathology (plasma, CSF, skin, potentially other tissue) and AD biomarkers (plasma, CSF, potentially AB and Tau imaging depending on the profile of intervention).
Abbreviations: PD, Parkinson's disease; US, United States; P2P, Path to Prevention; United Kingdom Edmond J Safra Accelerating Clinical Trials in Parkinson's Disease, UK EJS ACT PD; MAMS, multiarm, multistage; αSN, α-synucleinopathies; RBD, rapid eye movement sleep behavior disorder; DAT, a dopamine active transporter; SBR, striatum specific binding ratio; L-dopa, levodopa; HY, Hoehn and Yahr stage; MDS, Movement Disorder Society; [^{18}F]DOPA-PET, fluor-fluorodeoxyglucose-positron emission tomography; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; CSF, cerebrospinal fluid; AEs, adverse events; MDS-NMS, MDS Non-Motor Rating Scale; PGIC, Patients' Global Impression of Change; MoCA, Montreal Cognitive Assessment.

expected to be funded by public and non-profit stakeholders (the French National Infrastructure for Clinical Research [F-CRIN], the French patients' organization France Parkinson, and the Paris Brain Institute). Its goal is to evaluate repurposed compounds on motor progression using an open-label POC design in patients with early PD (<5 years of disease duration).[49] The primary objective is to demonstrate efficacy on the progression of motor disability based on the change in MDS-UPDRS part III motor score in *on* state over 12 months, following the model of the LIXIPARK RCT previously successfully run by NS-Park network.[50] Sample size is estimated at 100 patients/arm. Like the EJS ACT-PD trial, drug selection will take advantage of the works of the iLCT.

The choices made by the French NS-Park Master trial (targeting early PD patients, open-label design, and using MDS-UPDRS III as a primary outcome) are, therefore, different than those of the UK EJS ACT-PD trial. NS-Park Master trial will require less patients, but results will not allow regulatory approval, although facilitating further phase 3 studies in case of positive results. Moreover, it will not explore all stages of PD. Both initiatives should, therefore, be seen as complementary and positive signals from the phase 2-type platform de-risking drug selection and feeding strong candidates to the phase 3-type platform. The adaptive design of platform trials may also allow prolonged follow-up in the French trial, provided that PRO (MDS-UPDRS parts I and II) are included as key secondary outcomes from the beginning.

Australian Parkinson's Mission

The Australian Parkinson's Mission (APM) was conceived as an Australian-led international collaboration between the Garvan Institute of Medical Research, Shake It Up Australia Foundation, the University of Sydney, the Cure Parkinson's (UK), The Michael J. Fox Foundation (United States), and Parkinson's Australia. One component of this international collaboration is a phase 2-type evaluation of three candidate compounds against a shared placebo arm. Treatment selection is closely linked with iLCT processes.

Norway MAMS Trials

Two initiatives at an earlier development stage are scheduled to start shortly, both targeting Hoehn and Yahr stage ≤3 without dementia in Norway. These are (1) SLEIPNIR study, a multiarm RCT-accelerator platform, designed to conduct smaller-scale phase 2/POC, with multiple state-of-the-art biomarkers to test target penetration and engagement; (2) HYDRA study, a phase 3-type MAMS trial, evaluating several agents in an efficacy design and adopting MDS-UPDRS part III as primary outcome.

Conclusions and Perspectives

Platform trials, enabling simultaneous testing of multiple drugs, represent an attractive strategy to address the urgent need of identifying treatments capable of slowing PD. Leveraging insights into PD-specific challenges and methodological advances from previous

experience in other diseases; it seems realistic to envision such trials in PD in a near future. Several initiatives are underway worldwide, preparing a range of complementary trial platforms from POC to regulatory approval, and across various disease stages, from prodromal to more advanced phases. This international effort should be coordinated to maximize the synergy among these studies, ultimately aiming to accelerate the development of neuroprotective strategies for individuals with PD. Several platform trials are scheduled in the next few years, targeting different PD patients and aiming for various outcomes. With the development of multiple platform trials worldwide, the same compounds are likely to be investigated in different PD populations. Therefore, there is a need to coordinate these international efforts to ensure that the results of one trial could inform other ongoing studies. This approach could allow a compound that has demonstrated efficacy in an early PD population to be tested at other disease stages for instance. Success will also depend on the willingness of pharmaceutical companies to engage in such trials and whether this approach will ultimately hasten the identification and licensing of effective disease-modifying drugs. In this sense, international collaborations will be needed not only to coordinate efforts, avoid overlap, and share methodological challenges and solutions, but also to seek large-scale funding investments from organizations such as The Michael J. Fox Foundation, European Union funding agencies, national patients' organizations, and the National Institutes of Health, to sustain these platforms in the long term. This could help preserve the primary role of academic sponsors while allowing industry participation, particularly smaller companies that cannot sustain large clinical trials on their own. ■

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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