Roadmap for treatments that make a difference in Parkinson's disease:
Challenges and guidance towards improving the efficiency and efficacy of clinical trials

Abstract

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease. Currently there is no proven therapy to prevent or delay development of disability associated with the disease. Despite advances in understanding PD biology and discovery of solid targets for therapeutic intervention, an efficient clinical path for developing and testing new therapies remains uncertain. The proposal below aims to assist in clarifying the clinical development of drugs that could impact the progression of PD. Our recommendations fall in to four main topic areas – (1) vocabulary, (2) outcome measures, (3) study populations and (4) trial designs. Key trial design recommendations include:

- Parallel group design in early, untreated PD using motor, disability AND imaging assessments
- Parallel group design in treated PD without motor or non-motor complications measuring delay of clinical milestones/complications (e.g. classic motor complications, onset of postural instability, falls with injury, urinary incontinence, dementia)

This roadmap is intended to serve as a focus for continued discussions among stakeholders within the holistic Parkinson's community toward increasing the efficiency and meaningfulness of clinical trials for new Parkinson's treatments.

The Problem

Parkinson's disease (PD) is a neurodegenerative disorder that, despite the large number of effective medical and surgical treatments for the illness, continues to be inexorably progressive and ultimately leads to intolerable disability. A therapy that prevents or delays the development of disability is the most important unmet medical need in PD therapeutics. Despite multiple attempts, no therapy has been conclusively demonstrated to have such an effect, and no therapy has been approved for such an indication. In recent years, major advances in genetics and neuroscience have led to an increase in our understanding of the etio-pathogenesis of the PD process. This has led to the identification of novel and promising targets for therapy, increasing the likelihood of finding an effective treatment. These targets include alpha synuclein, LRRK2, GBA, the lysosome/autophagy system, c-abl, and inflammation with activated microglia. Many interventions directed at these targets have been identified and are actively being studied in the laboratory. However, despite the promise they hold for a meaningful therapy for PD patients, only a very few are so far actively being tested in the clinic.

Many large pharmaceutical companies are disinclined to enter the PD field or hesitant to bring Parkinson's programs forward into clinical testing because they are primarily interested in seeking a 'disease modifying' indication. Such an indication requires a long and very expensive development plan that is made riskier without a well-defined regulatory pathway for approval being clearly established by regulatory authorities. According to the most recent report from the Tufts Center for the Study of Drug Development (CSDD) the cost for developing a central nervous system (CNS) drug is a staggering 2.6 billion dollars[1], an alarming 85% dollar-adjusted increase

from a mere 10 years ago. Further, the CSDD reports[2] that in comparison to non-CNS drugs, for CNS drugs the time to develop is 18% longer, the chances of success less than half, the time for regulatory approval is 40% longer (14 vs 19 months) and priority review is offered only 1/3 as often (16% vs 50%)[3]. Given that huge commitment in time and resources many companies feel that a 'disease modifying' indication is essential in order to justify this expense, even if there is no clear road map for such an indication As a consequence, despite the plethora of relevant targets and the exciting prospects of a therapy that potentially can meaningfully change the progression of PD disability, many pharma and biotech companies have abandoned this field and many promising interventions are not being studied in the clinic. It would be a tragedy if a viable therapy that can prevent or slow the development of disability in PD is not brought forward simply because we cannot come to agreement on study designs and product labelling that are acceptable to both regulatory authorities and industry[4]. This paper provides suggestions for how we might be able to create a regulatory framework agreeable to all parties that would encourage and facilitate the development of the many promising agents that might prevent or delay disability in PD.

Regulatory Summary

Current treatments for PD can provide improvement in signs and symptoms, predominantly for the motor features of the disease, but also for some non-motor features. Despite those benefits, none of the available treatments have been definitively established to have beneficial effects on the longitudinal evolution of illness. In this regard, the research and pharmaceutical communities are uncertain about the nature of evidence needed to demonstrate such effects in PD. That said, there is a substantial body of guidance from the US Food and Drug Administration (FDA) on analogous topics regarding the longitudinal evolution of illness, especially in cancer and in chronic infections. That guidance, along with FDA guidance on Alzheimer's disease (AD) and European Medicines Agency (EMA) guidance on PD, helps to codify a set of definitions and parameters which may clarify the regulatory landscape for defining treatments that slow PD progression.

A dominant theme in all FDA guidance is the principle of 'clinical meaningfulness'. We understand this term to mean the observed effects of a drug are evident to patients, families and clinicians and favorably improve their function and experience of life. Such effects are usually captured by measures of daily functioning or of overall (global) assessment of benefit. In PD this could be the experiences of daily living scales of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Schwab and England Activities of Daily Living (ADL) scale, or patient-determined global scales such as the Patient Global Impression of Change (PGIC). Whatever outcome measure is used, we think some standard of 'meaningfulness' will need to be met.

A second dominant theme is temporal profile. In contrast to usual approvals, where the time course of benefit is not central to approval (although the endurance of benefits is usually assessed), approvals for 'delay' or prevention of illness progression always have a temporal dimension. For example, clinical or disease features are required to be stable (or absent) for a defined period, or at least differ between compared treatments over that time period. There are further temporal implications from the proposed 2-period designs in AD and PD (delayed washout or delayed start). A delayed washout design indicates a drug effect persists even when

withdrawn (i.e., a persisting 'structural' effect), and a delayed start design indicates there is a benefit to starting a drug earlier that cannot be achieved when starting the same drug at a later time point. In our view, both of these types of effects are more difficult to demonstrate than temporal stability.

The third major theme is the distinction between the disease state (often called the 'characteristic pathophysiology'), and the clinical state (often called 'core symptoms'). Many trials aimed at 'disease modification' have focused on measures of the underlying disease state (such as biomarkers or clinical surrogates), but from prior FDA guidance, there appears to be significant uncertainty about the validity, and 'clinical significance' or 'meaningfulness' of such measures. In contrast, there is a strong emphasis on seeing an impact on 'core symptoms', with some verification that such impacts are 'clinically meaningful', that have the temporal patterns described above, and that result in a reduction in cumulative disability. Such findings are likely to be described as delaying or preventing clinical decline or delaying emergence of disability, as opposed to representing an impact on the biological disease process explicitly. The addition of finding an impact on a biomarker of the 'characteristic pathophysiology' could lend strength to an argument that the intervention is directly improving the biological disease process. Further background on this topic is available in Appendix 3.

Recommendations

The community is confronted by many obstacles in developing treatments to impact the progression of PD. Some of them may have immediate solutions, but others may be more difficult to overcome. We make specific recommendations in areas where we think immediate progress is possible. For example, we think the vocabulary that has been used to date may have inadvertently, and unnecessarily, created confusion and conflict. On the other hand, we are not likely to imminently solve the problem of being unable to measure the integrity of neurons, other brain cell elements, and vital neuronal circuitry. There is no doubt this inability to directly measure cellular integrity complicates the treatment development process, but we can still make advances without solving, for the moment, that problem. Our recommendations will fall in to four main topic areas: vocabulary, outcome measures, study populations and trial designs (further background on these suggestions is found in Appendices 2 and 3). We think these suggestions will clarify the development and approval process, and thereby lessen the obstacles to new product development.

1. **Vocabulary**

There has been considerable controversy in terms of how to define an intervention that slows, stops, or reverses PD progression. The term neuroprotection was introduced in the DATATOP study[5]. While this term remains in common usage, it seems inappropriate, as "protection" of neurons cannot be established during life. Furthermore, preservation of other cellular elements (e.g. glia) may also be relevant. The term "disease-modification" was subsequently employed, but here, too, one cannot currently establish with certainty that a therapy interferes with the disease process itself. As a result, it has been difficult for regulatory agencies to employ these terms in labelling. An alternate approach would be to simply describe the effect of the intervention on clinical progression (i.e., the rate of UPDRS progression, time to development of

a milestone of disease progression, or the time to development of cumulative disability). We openly acknowledge that while such a beneficial effect could occur in the absence of disease modification per se, we assert that slowing the *clinical* progression is a desirable outcome. Language in the label describing these kinds of clinical effects might prove acceptable to both regulatory agencies and pharmaceutical companies. Going forward, it will be critical to utilize clear and accurate language in describing the impacts on clinical progression, and to take a fresh look at what would sensibly be considered necessary and sufficient data to support labelling indicating that an intervention has an effect on progression.

To a greater or lesser degree, the proposed language to describe an intervention's effects has suffered from being more inferential than descriptive and has generally been frowned upon by the regulators. That is, the language infers a mechanism to explain what has been observed, rather than focusing on a clear description of what has been observed. Precise descriptions of findings may be unequivocal, whereas inferences about mechanisms may be assailable or even misleading. We think a new standard should be set, with an accepted set of descriptive terms, for describing the benefits observed. In other words, a description in the label for what was actually found in the clinical trial, with no inferential terms. For example, less worsening of PD features (as measured by UPDRS) over 18 months, less accumulated PD disability (as measured by part 2 of the MDS-UPDRS) over 2 years, and fewer individuals developing new motor complications, falls or cognitive impairment in 3 years are all quantitative descriptions of observations which can be substantiated by clinical data. These descriptions incorporate clinical findings and a temporal profile. Overall, the notion of *delaying something specific* that has *experiential impact for the patient* and is *expected in the typical trajectory of PD* we believe is a justifiable approach.

We also think that this kind of vocabulary needs to be present in product labeling. Many product developers are concerned about the indication statement in FDA labeling. We think this is misguided, since it runs counter to current FDA efforts to simplify and streamline indication statements. That said, we think it is crucial for developers, and prescribers, that the summary description of findings be present in the clinical trials section (section 14) of the label. Those statements are then available to prescribers and can be utilized in educational and promotional activities of drug developers. This language can be supplemented by clear language in the Mechanism of Action (MOA) section of the label (section 12). While the precise mechanism by which drugs exert their clinical effect is often unknown, it is useful for prescribers and patients to know the pharmacological effects of the intervention, since these may well be germane to the observed clinical benefits. This is especially true when the mechanism of action has no known impact on the dopaminergic system per se, since most available interventions function via that MOA. If the intervention does have dopaminergic impacts that should also be in the label.

In summary, we recommend that precise, descriptive (not inferential) language should be used to state the observed effects (including the temporal profile) of interventions, and that such language should be included in the clinical trials section (section 14) of the product label. In addition, information about an intervention's known MOA should be included in the product label (section 12). The specifics of label language should be discussed with regulators as early as possible in drug development.

2. Outcome measures

Outcome measures that are clinical scales should be reliably measurable, meaningful to clinicians, patients, and caregivers, and address the "core symptoms" of PD. The MDS-UPDRS Part III (core motor features) is a reliable, validated approach to measuring the core features of PD, although tilted to motor features. Other scales for core features are also available and include Scales for Outcomes in Parkinson's disease-Cognition (SCOPA-Cog) for cognition, Unified Dyskinesia Rating Scale for dyskinesias and the Non-Motor Symptoms Scale. Scales for other core symptoms of PD exist and may be reasonable to propose.

Assessments of function also exist for PD, historically the most commonly used in PD being the Schwab and England ADL scale. More generic measures of function have been used in PD including the Medical Outcome Survey (MOS) short form (SF) 36 or 12. Most recently the MDS-UPDRS Parts I and II were developed in a rigorous fashion to measure functional abilities of PD patients (largely self-reported), assessing both the motor and non-motor impacts of PD. We suggest that the MDS-UPDRS Parts I and II represent a validated and acceptable way to measure clinical progression of PD features, as experienced by patients and families.

Important clinical milestones are widely recognized in PD and have face validity as relevant to patients and families. These include the diagnosis of PD (in prodromal PD), loss of employment, initiation of treatment, onset of falling, onset of dementia, onset of urinary incontinence, onset of motor complications, onset of hallucinations and institutionalization.

Changes in outcome measures that are scales of core PD features may not necessarily be clinically meaningful, unless of sufficient magnitude, or corroborated by a functional (or global) measure, or by a major clinical milestone.

Biomarkers are also important outcome measures but will play a secondary or supportive role that will depend on the study population (i.e. in early manifest PD they cannot be the primary outcome measure precisely because their clinical meaning is unknown at present). As studies of prodromal PD emerge, the role of these markers may be to identify a drug related change in a biomarker later confirmed by a meaning clinical outcome once symptoms develop. Such biomarkers may be of the disease state, or of the biological action of the intervention. Dopamine transporter (DAT) imaging is a useful measure of dopamine transporter density and has been accepted by regulatory agencies as a tool to improve diagnostic accuracy in clinical trials but lacks status as an outcome measure in trials at present. However, a change in such a marker, along with clinical outcomes may add to the evidence about the effects of the intervention. Alternatives could include ^{18}F-DOPA positron emission tomography (PET) or vesicular monoamine transporter (VMAT) PET, or yet to be developed measure of alpha-synuclein accumulation. Given the central role alpha-synuclein is thought to play in PD, any intervention that could delay accumulation of relevant species would be of interest. Biomarkers of the effects of the intervention, whether to limit inflammation, reduce synuclein accumulation or improve metabolic function, would also be of interest. Although the observed clinical effects may not be directly ascribable to the biomarker effect, such information is important context for the observed clinical effects in our view. Such biomarker (of intervention) effects and may also further support the description of the intervention mechanism of action within product labelling.

Drug development has relied on face to face clinical evaluations to generate data about patient experiences. Increasingly data can be generated, almost continuously, by remote assessments. These assessments can be passive (e.g. counting steps) or interactive scales or questionnaires. The role of such 'digital measures' will certainly increase over time, as their operating characteristics are better understood. For now, we think they should serve as supportive measures of more traditional, validated clinical outcomes.

3. Study populations

- **Pre-motor PD**

Other terms have been used for this state including pre-PD, prodromal PD, and at-risk for PD. The FDA, at least in the setting of AD, has referred to this stage as Early AD. Efforts are being made to more reliably identify such a population, for example using DAT imaging, assessment of sense of smell or genetic testing, among other approaches. While clinical features are insufficient to make a diagnosis, such individuals may have measurable deficits in motor or cognitive performance. A major clinical milestone would be the clinical diagnosis of PD. We think it may be premature to define the population inclusion characteristics at present but think this is a very important population to recognize and plan to study.

- **Early, Untreated PD**

This is the most highly studied population when looking for favorable impacts on PD progression**.** There are several good reasons for studying this population, among them: 1) clinical features are well described; 2) any confounding effect of dopaminergic medication is eliminated; 3) study participation may be more feasible in an early state with less disability; and 4) biomarkers may be more informative during what would be expected to be a more active state for both degeneration and compensation, compared to later disease states. Further, at least with regard to dopamine neurons, recent pathologic studies indicate that after 4 years from diagnosis there is limited staining for dopamine terminals in the dorsal striatum – thus treatments instituted after this time may be less effective, although preserving other cell types may also be important. However, early patients can only be studied off medications for a limited time frame, and initiation of dopaminergic medications may complicate study interpretation, and diagnosis of PD with certainty is more difficult in this early stage and it may be useful to add a biomarker like DAT imaging to improve accuracy. Nonetheless, we think this is a good population to study, despite this limitation, and would prioritize it for study.

- **Treated PD, without Motor or Non-Motor Complications**

Patients without motor complications may be a good population for studying time to develop milestones of disease progression such as falling and dementia, which are not responsive to conventional dopaminergic medication. Indeed, recent studies suggest that potentially serious effects such as falling occur more frequently in this population than was previously appreciated. In addition, fluctuations and dyskinesias are inevitable with dopaminergic treatments over time, and mark the evolution of PD. Changes in neuronal plasticity are thought to underlie these phenomena, driven by the non-physiologic nature of how current treatments (i.e. levodopa) are delivered to the brain, and by loss of dopaminergic nerve terminals. Benefits in delaying complications may represent a "functional" improvement, which may or may not be associated with a corresponding decrease in PD pathology. An intervention with this clinical benefit

(delaying fluctuations) may minimize negative effects on relevant neuronal networks and would be valuable. This population could also be studied for the onset of non-motor complications, including cognitive impairment, autonomic impairment (incontinence and syncope), and hallucinations. This group is complicated to study because of the presence of dopaminergic medications and the uncertain extent of dopaminergic neurodegeneration at this point in the illness. The benefits of studying this group includes the large number of stably treated individuals who fall in this category and represent a large group 'at risk' for subsequent disability. Given our current understanding of mechanisms underlying the development of motor complications and the potential to prevent these problems with available medications, as well as the potential importance of interventions that can forestall disability in the setting of currently available therapies, we would also prioritize this group for study.

- **Treated PD, with Complications present**

Most studies in this population have focused on reducing off time; however, there are other features to study. Gene therapy, deep brain stimulation (DBS), Dudodopa, and other invasive interventions have attempted to modify UPDRS scores in the Off state, which seems like an attractive measure of disease severity. This group is also at risk for more severe clinical milestones including onset of dementia, falls with injury, institutionalization and death. We think this may be an attractive group to study because of the more rapidly emerging, significant disability, but it is a medically complicated population and participant disability may drastically limit retention, in general. A further limitation is the current lack of information on natural history at this stage and the potentially confounding effects of concurrent therapies. For this population a study using a long-term simple study design might be appropriate, but we would not prioritize that approach at present.

4. Clinical Trial Designs

We think that untreated, diagnosed PD offers an appropriate and the least complicated population to study in trying to assess the effect of an intervention on the underlying disease process. The untreated participants eliminate the confounds from dopaminergic treatments, and early PD may have less cumulative neuronal damage than later, potentially irrevocably impaired, populations. We also think that a slightly later population, stably treated on dopaminergic medication as outlined above, can be an effective population to study. Eventually, pre-motor PD would also be an important group to study.

To date there has been considerable focus on two-period designs. This design typically uses UPDRS scores to capture daily function and objective motor performance. The FDA has previously expressed interest in the delayed start design as a means of assessing PD and AD progression, especially with regard to 'disease modifying' claims. We think this design, while scientifically appealing, is pragmatically almost impossible to perform well. In addition, we think the emphasis on 'disease modifying' language is misplaced, as discussed above. While this design, if done well, would no doubt be impactful in regulatory reviews, we suggest the following two study designs, one in early PD and one in later PD, as more feasible and practical, and therefore more desirable alternatives.

- **Parallel Group Design in Early, Untreated PD with Motor (MDS UPDRS Part 3), AND Disability (MDS-UPDRS Parts I + II OR Schwab and England ADL Scale), AND Imaging (DAT) Assessments:** Such a design would use a conventional motor measure (Part III), as well as a validated measure of function (Parts I + II, with an option for a non-UPDRS disability measure Schwab and England, for example, but it could be any suitable measure of disability) in addition to supportive biomarker data via DAT imaging. This approach combines motor improvement (core symptoms) and delay in disability, with a biomarker. An important theme is disability as an outcome may change independently of motor measures. This would be a relatively high bar of requiring a motor benefit, a functional benefit and a corroborating biomarker. While a parallel group design might only permit approval indicating an anti-parkinsonian effect of an intervention, a complete description in the label of the underlying science and potential mechanism of action, and permitting companies to discuss these factors, might be sufficient for the community to make informed decisions as to how best to employ these agents and how they might be acting. This approach has the advantage that it would encourage more work in the basic science field to clarify mechanism, and the use of a clinical trial design that is much easier to implement, faster, and less expensive. A potential alternative is to only study Disability as measured by MDS-UPDRS Parts I + II. This alternative is similar but allows a more novel stance on meaningful clinical change by viewing motor improvement, per se, as optional. Evidence for sustained functional benefit--even without overt motor benefit--with an appropriate change in a relevant biomarker would be the evidence base.
- **Parallel Group Design in Treated PD without Motor or Non-motor Complications, Measuring Delay of Clinical Milestones/Complications Including Classic Motor Complications, Onset of Postural Stability, Falls with Injury, Urinary Incontinence or Dementia**: This study is in mid- to later-stage participants on treatment, where PD medications would be permitted for the study, and would not readily confound any treatment effect on most of the outcomes of interest. Such an approach focuses on the major clinical milestones PD that are highly disabling, which in turn would be of high interest to patients and caregivers as meaningful. Addition of a biomarker to this design may be more complex than the above strategies, as it is not clear what an optimal marker of disease state would be, although synuclein or DAT imaging may be a possibility. A biomarker of drug effect may also be useful.

Conclusion

We have described a practical and reasonable process to advance development of PD drugs that may be effective in slowing clinically meaningful PD outcomes. We think that the community interested in PD therapeutics will be motivated to invest time and money in novel treatments if the path forward is clear and rational. We also think that the development community is currently stymied by an unnecessary degree of complication and confusion about product labeling. Companies, clinicians, patients and families, and regulators all want treatments that slow the inexorable progression of PD. They also all want there to be a fair and accurate process for establishing the safety and effectiveness of such treatments. We think that a consensus about the kind of descriptive language that can be placed in product labels, the types of outcomes that

can be used to assess such effects, and the acceptable trial designs will significantly lower obstacles and advance the field. The recommendations herein are initial steps in building that consensus. The delayed start study design is the only clinical trial methodology that the agency has indicated would be acceptable for providing data to support a 'disease modifying' indication, but this is a long, expensive, and complex trial full of specific design problems. Alternatively, a parallel group design might permit approval indicating an anti-parkinsonian effect of an intervention with clear descriptive language in section 12 regarding the MOA and in section 14 describing the clinical benefits observed. Describing the clinical benefits that were observed potentially with additional biomarker data, and the underlying science and potential mechanism of action, would permitting companies to discuss these factors, and might be sufficient for the community to make informed decisions as to how best to employ these agents and how they might be acting. This approach has the advantage that it would encourage more work in the basic science field to clarify mechanism, and the use of a clinical trial design that is much easier to implement, faster, and less expensive.

Appendix 1 Parkinson's Disease

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, exceeded only by Alzheimer's disease (AD). Hallmark features for the disorder were first described by the English physician James Parkinson in 1817, for whom the disease is named. It is estimated that the frequency of PD is approximately 800,000 in North America, and 5,000,000 world-wide. Mean age of onset for PD is about 60 years, with a lifetime risk of approximately 2% for men and 1.3% for women; frequency increases with aging, but cases can be seen in individuals in their 20s and even younger, particularly in association with a gene mutation. Based on the aging of the population and increasing life expectancy, it is estimated that the frequency of PD will more than double in coming decades.

Clinically, PD was classically characterized by resting tremor, rigidity (stiffness), bradykinesia (slowing), and gait dysfunction with postural instability, known as the "cardinal features" of the disease. It is now appreciated that non-motor features are also common, and include autonomic disturbances, sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia. Pathologically, PD is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), reduced striatal dopamine, and intraneuronal proteinaceous inclusions in cell bodies and terminals known as Lewy bodies/neurites (Lewy pathology) that is primarily comprised of misfolded and pathologic forms of the alpha-synuclein protein. While interest has primarily focused on pathology of the dopamine system, neuronal degeneration with Lewy pathology can also affect cholinergic neurons of the nucleus basalis of Meynert (NBM), norepinephrine neurons of the locus coeruleus (LC), serotonin neurons in the raphe nuclei of the brainstem, and neurons of the olfactory system, cerebral hemispheres, spinal cord, and peripheral autonomic nervous system. This "non-dopaminergic" pathology is likely responsible for many of the non-motor features of PD. More recently, a body of pathologic, clinical and epidemiologic evidence suggests that there is a prodromal phase of PD which includes features such as constipation, REM behavior sleep disorder, hyposmia, and minimal motor features coupled with changes on dopamine imaging.

Levodopa has been the major therapy for PD since its introduction in the late 1960s and is particularly effective for treating the motor features of the disease. However, chronic levodopa treatment is associated with the development of motor complications (motor fluctuations, dyskinesias) that limit the utility of the drug and can be a source of major disability. Several anti-parkinsonian classes of pharmacologic agents (e.g. dopamine agonists, MAO-B inhibitors, COMT inhibitors, A2a antagonists) and surgical interventions (e.g. deep brain stimulation, continuous levodopa intestinal infusion) have been introduced in the past several decades. The effects of these medications can be dramatic. Levodopa and other dopaminergic agents can virtually eliminate early motor features, DBS and amantadine can lessen or eliminate dyskinesias, and pimavanserin can improve hallucinations. All of these medications have 2 additional features: 1) the benefits are lost when the intervention is stopped, and 2) the progression of clinical severity and subsequent disability continues despite their use. For these reasons, available medications are often called "symptomatic" because they improve clinical features but do not appear to fundamentally alter the underlying disease process nor the clinical progression of neurological impairment. For example, levodopa may reduce disability and the mortality rate in PD by

improving motor features, but this is not believed to be due to slowing of the underlying progression of the disease process. Despite the large number of effective medical and surgical treatments available today, the disease continues to be inexorably progressive and ultimately lead to intolerable disability. A great deal of effort has gone into identifying treatments that have the desired feature of slowing or stopping the progression of disability, i.e., to go beyond the apparent benefits provided by "symptomatic" treatments. A therapy that alters the naturally progressive course of the disease and prevents the development of disability remains the major unmet need in modern therapy for PD. At present, no such therapy has been to impact the disease process nor the progression of disability in PD, and no agent has received approval for such an indication.

Clinical Trials Aimed at Demonstrating Slowed Progression

Summary of Clinical Trials to Date

Multiple different study designs have attempted to determine if an intervention can delay PD progression (see Table 1). Among the trial designs that have been employed, the "delayed start" study has attracted the most attention, partly because of publications by FDA staff members, and also due to its mention in guidance on AD, with reference to 'disease-modifying' effects. This design aims to demonstrate that early treatment with an agent provides benefits that can't be achieved with delayed treatment using the same agent. Positive results in this type of study are consistent with a disease-modifying effect, but numerous issues must be considered when employing a delayed start design. Other types of designs in PD clinical trials include trials assessing time to a clinical milestone, for example delay in development of clinical deterioration requiring levodopa therapy. While delaying development of a disease milestone could reflect slowing of disease progression, these studies cannot definitively separate such an effect from benefits related to a short-term improvement in clinical features. Other studies have focused on slowing of motor progression (for example slowing of the change in UPDRS scores) as an index of slowing. However, improvement in UPDRS score from baseline might also be expected from a drug with a short-term improvement in clinical features. There is also interest in considering slope analyses, an approach looking at differences in slope rate of decline between active and placebo groups at various time segments during the trial. However, improvements in clinical features can be long-lasting, or slowly developing, and it has not been established that the rate of decline in UPDRS score is linear and adequately assessed by a slope. Efforts are underway to use quantitative modelling to establish disease progression trajectories in UPDRS for use in future studies. There has also been some interest in designs that look at long term, pragmatic outcomes in global measures of health impact. In this kind of design, participants in early or mid-stage disease are typically followed for as much as 5 years, and the primary endpoint is a measure of global impact, broadly defined. Important outcomes such as loss of ambulatory status, falls with fractures, and loss of independent living could be captured. Non-motor outcomes are also part of advancing PD. Cognitive dysfunction is an extremely important and common, is not controlled or prevented with available medications, and represents the major reason for nursing home placement. The heterogeneity of trial designs reflects an uncertainty about both the optimal and feasible pathways to identifying an intervention that favorably influences the progressive nature of clinical impairment in PD. While the two-period design has received the most attention, and

apparent regulatory acceptance, it remains an extremely difficult design to properly complete. Alternative designs that may have regulatory acceptance, and be practically feasible, would be very useful to identify. Two other intertwined areas which deserve attention are the populations to study and the outcome measure to utilize. Most studies have focused on individuals with early to mid-stage PD. As the field advances to identify even earlier PD (eg prodromal), trials should likely include such individuals. Clinical measures can be meaningfully supplemented by biomarkers of disease status, and such measures have been in prior trials of diseases other than PD with success, as discussed in Appendix 2. These two areas are also discussed with regard to PD in Appendix 3.

1. Prior Clinical Trial Designs for Progression of Motor Features

Several clinical trials using multiple different study designs have attempted to determine if an intervention can delay PD progression. The major trial designs and primary endpoints that have been employed in these studies are summarized in Table 1. To date, no intervention has been established to have disease modifying properties. Among the trial designs that have been employed, the "delayed start" study has attracted the most attention. This design aims to demonstrate that early treatment with an agent provides benefits that can't be achieved with delayed treatment using the same agent. Positive results in this type of study are consistent with a disease-modifying effect, but numerous issues must be considered when employing a delayed start design (see discussion below). This is the only design that the regulatory agencies have indicated could be acceptable for providing data to support a disease-modifying indication. However, this design has its own set of difficulties and limitations (see below). For the present, there is no clear roadmap for establishing that an intervention has disease modifying properties.

Table 1 lists some of the trials that have been performed attempting to determine if an agent has a disease modifying or neuroprotective effect and the study designs that have been used.

TABLE 1

Study Design	Description	Strengths | Opportunities	Assumptions | Challenges
Delayed start or two-period design	Demonstrate that early intervention with a compound offers benefit compared to providing the same compound later	• Regulator endorsement off this approach for a 'disease-modifying' indication	• Lack of consensus on duration needed for periods 1 and 2 to differentiate disease modifying from symptomatic benefit • Differential drop-out rates between early and delayed start groups may confound design and interpretation
Time to a clinically relevant milestone	Demonstrate an intervention's ability to delay development of a milestone of clinical significance	• Delay of clinical events is likely meaningful to patients	• Acceptance by regulatory authorities uncertain • Results may be confounded by symptomatic benefit of intervention
Slowing motor progression	Demonstrate an intervention reduces change from baseline to final visit UPDRS score; may include modeling of disease trajectories, or slope analysis	describes longitudinal course of core clinical features	• Not accepted by regulators, with concerns about linear assumptions of slope analysis • Results may be confounded by symptomatic benefit of intervention
Long-term pragmatic outcomes	Demonstrate an intervention reduces cumulative disability as measured by global measures	• Outcome measures are highly meaningful to patients	• Required follow-up duration is likely longer than other designs (≤5 years)

Clinical Trials to Assess Disease Modification in PD

Design	Rx	Endpoint	Agent	Result	Reference
Time to Milestone	no Rx	Time to need for levodopa	Deprenyl	positive	5-7
of disease progression[a]		(DATATOP)	Vitamin E	negative	
		Time to levodopa and disability	Lazabemide	positive	8,9
		Time to levodopa	CEP-1347	negative	10
Washout Design[b]	Rx	Δ UPDRS; untreated BL to FV post washout			
		14 months	Selegiline	positive	11
		12 months	L-dopa	positive	12
Slowing of UPDRS	No Rx	Δ UPDRS from BL to FV			
Progression[c]	No Rx	Δ UPDRS from BL to FV 16 mos	CO-Q10	pos/neg	15-17
	No Rx	Δ UPDRS from BL to FV 12-18 mos	TCH-346	pos	18
	No Rx	Δ UPDRS – 44 weeks	Piaglitazone	neg	19
	No Rx	Δ UPDRS – 12 months	Nicotine	neg	NP
	No Rx	Δ UPDRS – 12 months	Cogane	neg	NP
	No Rx	Δ UPDRS – 36 months	Inosine	*	NP
	No Rx	Δ UPDRS – 36 mos	Isradipine	*	20
Slow UPDRS Progression	Rx	Δ UPDS BL to FV -24 mos	Fetal Transplant	neg	22
In Practically-defined off[d]		Δ UPDS BL to FV -12-24 mos	Neurturin	neg	23,24
		Δ UPDS BL to FV -6 mos	DBS	neg	25
		Δ UPDS BL to FV -6 mos	GDNF	neg	26
		Δ UPDRS BL to FV + wo – 60wks	Exanatide	pos	27
		Δ UPDRS BL to FV – 16wks	GM1 ganglioside	pos	28
2 Period Design[g]	no Rx	a) UPDRS Slope - period 1	Rasagiline	pos/neg	35-38
		b) Separation early/delayed start			
		c) Non-inferiority slope - period 2			
	no Rx	a) separation early/delayed start	Pramipexole	neg	39
		b) Non-inferiority - slope period 2			

a) Time to Milestone of Disease Progression

Several studies have been designed to assess disease modification based on an intervention's ability to delay development of a milestone of disease progression. The classic example is the DATATOP study[5-7], which assessed the effect of deprenyl +/- selegiline vs. placebo in untreated PD patients on the time to clinical deterioration requiring levodopa therapy. While results were robustly positive for selegiline, the drug also demonstrated short-term symptomatic effects that confounded interpretation of the study and prevented distinguishing disease-modifying from symptomatic effects.

Fundamental assumptions in this approach include a clinical trajectory that is relatively linear (progression of motor features, changes in staging, need for treatment etc.). While delaying development of a disease milestone could reflect slowing of disease progression, these studies cannot definitively separate disease modification form benefits related to a symptomatic therapy that obscures ongoing disease progression, even if a clear symptomatic effect is not detected.

b) Washout Design

The Sindepar and ELLDOPA studies were designed to assess interventions in untreated PD patients by comparing changes in UPDRS scores between baseline and final visits performed after withdrawing the study intervention[11,12]. Both studies showed significantly positive results for the study intervention. However, it is not clear if adequate time had been provided to fully eliminate any symptomatic effect of the study intervention because of the long-duration effect that has been observed with symptomatic medication1[,13,14]. Thus, a difference between study drug and placebo could be related to the need for a prolonged washout to fully eliminate the symptomatic effect of a study intervention. Additional problems with this type of design are the potential medical and ethical concerns inherent in acutely withdrawing medication from PD patients, particularly for a sufficiently long period of time to eliminate symptomatic effects.

c) Slowing the Rate of UPDRS Progression

Multiple studies have evaluated change from baseline to final visit in UPDRS score as an index of disease-modification[15-20]. However, improvement in UPDRS score from baseline might also be expected from a drug with sustained symptomatic effects, and it is not possible to be certain that positive results in this design are due to a disease-modifying effect. There is interest in considering slope analyses, an approach looking at differences in slope rate of decline between active and placebo groups at various time segments during the trial. However, symptomatic effects can be long-lasting, and it has not been established that the rate of decline in UPDRS score is linear and adequately assessed by a slope. Efforts are underway to use quantitative modelling to establish disease progression trajectories in UPDRS for use in future studies[21].

d) Slowing of UPDRS Progression in Practically Defined Off-State

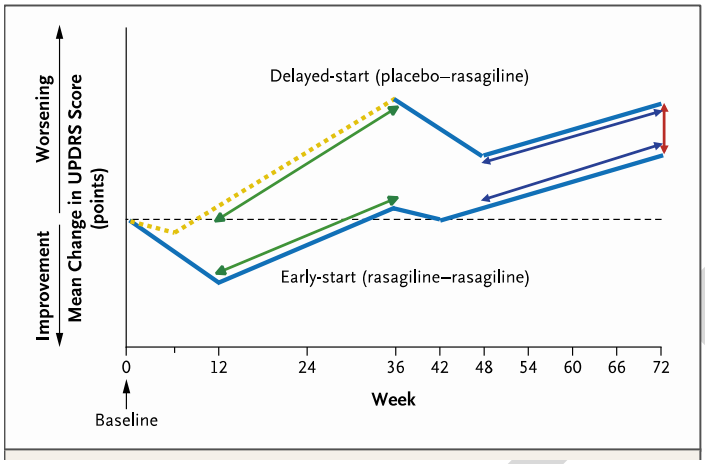
To address potentially confounding symptomatic effects of an intervention, some studies have used UPDRS change between baseline and final visit in the “practically-defined OFF state” as a primary endpoint. The practically defined OFF state represents the parkinsonian state (UPDRS score) in the early morning prior to taking any anti-parkinsonian treatment, approximately 12 hours after the last dose of dopaminergic medication. In advanced patients, UPDRS scores in the practically-defined OFF state are thought to reflect the underlying, untreated parkinsonian condition, as the long-duration effect tends to become minimized or disappear in this patient population. While intriguing, this design still suffers from uncertainty regarding its fundamental assumption that the practically-defined OFF state represents the underlying disease state devoid of a long-duration response or symptomatic effect. Further, this has proven to be a relatively high hurdle and difficult to achieve. It has thus not been established to the satisfaction of clinicians or regulatory authorities that benefit with respect to this endpoint represents a disease-modifying effect.

e) Two-Period Design

Perhaps the most important clinical trial design for evaluating a putative neuroprotective therapy in PD is the delayed-start design (see figure 1). This is a two-period design first described by Paul Leber[35]. In the first-period, patient are randomized to active treatment (early-start group) or placebo and followed for a defined period of time (approximately 6-9 months). In the second period, patients in the early start group are maintained on active treatment while those in the placebo group are switched over to the active treatment (delayed-start group)[36]. Thus, during the second period, both groups are on the same treatment. If there is a benefit of the study intervention at the end of the first period, it cannot be determined if this is due to a symptomatic and/or disease-modifying effect. If at the end of the second period there is no difference in the change from baseline between the early and delayed start groups, it can be concluded that the benefit seen in the early-start group at the end of period 1 was symptomatic. However, if the early-start group continues to have a benefit in comparison to the delayed start group at the end of the second period despite both groups being on the same treatment, and there is no evidence that the UPDRS slopes are converging, it can be concluded that early-treatment provides a benefit that cannot be achieved with delayed treatment. This finding is consistent with the intervention having a disease-modifying effect. Such a design was employed in the ADAGIO study[36-38]. There were 3 primary endpoints that had to be met in this trial: i) superiority of study drug vs placebo in the rate of UPDRS progression during the first period; ii) superiority of early-start vs delayed-start in change in UPDRS score between baseline and final visit of the 2nd period; and iii) non-inferiority between the early-start and delayed-start groups in the slope of the UPDRS scores during period 2, indicating that benefits are enduring and that UPDRS scores are not converging.

This design is currently thought to be most able to identify a disease-modifying or neuroprotective effect and is the only one that the FDA has to date indicated could be acceptable for approval with this indication. There are however several issues that need to be considered and agreed upon with regulatory agencies in designing such a trial; a) duration of period 1 sufficient to permit a disease modifying effect to be observed; b) duration of period 2 sufficient to permit full symptomatic effect to be achieved; c) the margins for non-inferiority between early and delayed start groups in the 2nd period; and d) how to manage any differential drop-out between early and delayed start groups at the end of Period and how to ensure that there is no imbalance between the groups entering period 2 that might confound interpretation of results.

Figure 1: Schematic of the delayed start study as employed in the ADAGIO trial (Adapted from Olanow et al, NEJM, 2009)



Patients are randomized to early-start of active intervention or placebo in Period 1. All patients receive the same active intervention in period 2. Benefits of early start at the end of period 1 could be due to symptomatic or neuroprotective effects. If benefits of early-start persist at the end of period 2 with no evidence that the UPDRS scores are converging, this indicates that early-start provides a benefit that cannot be achieved with delayed start and is consistent with a disease-modifying effect. The 3 primary endpoints utilized in the ADAGIO study are illustrated by the colored arrows in the figure and described in detail in the primary publication.

Thus, over the past decades there have been multiple strategic approaches trying to detect a disease modifying/neuroprotective effect with numerous interventions and several different study designs. To date, no intervention has been established to have a disease-modifying effect, and the only design which has been indicated as possibly being acceptable for a disease-modifying indication is the two-period design, which is long, expensive, and extremely difficult to perform. Taken together, there remains no clear road map for regulatory approval of an intervention for a disease-modifying indication in PD.

2. Studies to delay other motor and non-motor sources of disability

a) Quality of Life Measure

This design uses the effect of an intervention on quality of life as an endpoint in studies where subjects are randomly assigned to active treatment or a control[29,30]. There are different instruments that have been designed to assess quality of life; these include those focused on disease-specific factors, such as the PDQ 39, or those which assess overall well-being. This design has not been widely employed, as it is not at all clear that an improvement in quality of life is dependent on an intervention having disease- modifying as opposed to symptomatic or psychological properties. It has further not been established that this endpoint will be acceptable as a primary outcome measure for regulatory authorities.

b) Long-Term Simple Study

In this design, participants in early or mid-stage disease are randomly assigned to active treatment or placebo (or just natural history) and followed[31-34]. The study is typically long-term (5+ years), and the primary endpoint is a measure of cumulative disability. This can be measured with a global statistic that takes into account all or part of the UPDRS as well as other measures of disability such as falling, cognitive function, quality of life etc. The aim is to determine if the

intervention slows or prevents functional decline and the development of cumulative disability. An underlying assumption is that long-term clinical benefits and improved function likely represent disease modification and that symptomatic benefits would tend to wane over time. However, this assumption is by no means clear and symptomatic effects cannot be completely excluded even with long-term benefits. While any agent that provides long-term benefits with reduced cumulative disability would be a welcome addition to the PD armamentarium regardless of its mechanism of action, it is unlikely that even with positive results this design will alone be sufficient to receive a disease-modifying indication. Further, this design provides challenges in terms of the long duration, potentially high drop-out rate, and expense.

While much attention has focused on developing disease-modifying therapies that slow progression of the classical motor features of PD, there is also interest in developing therapies that slow or stop the development of other potentially disabling features of PD such as levodopa-induced motor complications and cognitive impairment.

Design	Rx	Endpoint	Agent	Result	Reference
Quality of Life Measure[e]	Rx	PDQ-39 – 2 years	DBS vs Nat Hx	pos	29
		Global Rating – 12mos	Fetal Transplant	neg	30
Long-term Simple Study[f]	Rx	Global statistic – 5 year	Creatine	neg	31
		Δ UPDRS, Motor comps - 5 year	selegiline	pos	32,33
		Δ UPDRS, Motor/ADL- 7 year	selegiline	pos	34

c) Delay of Motor complications

Motor complications (motor fluctuations and dyskinesia) affect the majority of PD patients, can be a source of considerable disability, and are the major reason for surgical intervention. A body of evidence indicates that motor complications are related to the non-physiologic replacement of brain dopamine with intermittent oral doses of standard levodopa[40]. Brain dopamine levels are normally maintained at a relatively constant level. Variable dopamine levels with pulsatile stimulation of dopamine receptors leads to molecular changes, physiologic changes, and the development of motor complications. This has led to the hypothesis that administering levodopa in a more continuous manner might be more physiologic and prevent the development of motor complications. Prospective double-blind studies confirm that higher doses of intermittent levodopa are associated with an increased risk of developing motor complications[41]. Furthermore, double-blind studies have demonstrated that continuous levodopa delivery can improve established motor complications[42]. However, only a few clinical trials have evaluated introduced therapy with a more continuous or long-acting form of dopaminergic therapy in an attempt to prevent the development of motor complications (Table 3). Studies with long-acting dopamine agonists consistently demonstrate a reduced frequency of motor complications in comparison to standard levodopa[43-47], but patients eventually require levodopa and motor complications ensue. The STRIDE-PD study tested initiating therapy with levodopa combined with the COMT inhibitor entacapone which extends the elimination half-life of the drug in an attempt to provide continuous delivery[48]. The combination failed to reduce

the risk of motor complications in comparison to standard levodopa, but the frequency of administration was likely not sufficient to provide continuous plasma levodopa levels. It is likely that studies delivering more continuous plasma levodopa levels from the start of treatment will be performed to determine if this strategy can reduce the frequency or prevent the development of motor complications. A trial design that assesses the time to development of motor complications as was used in STRIDE-PD should be sufficient to address this question. Limitations are that such studies are typically at least 18-24 months in duration, and it remains to be determined if regulatory agencies will accept this endpoint as an indication for labelling.

TABLE 2

Clinical Trials aimed at Preventing Motor Complications

Design	Rx	Endpoint	Agent	Result.	Reference
Prevent Motor complications		Time to onset of motor comps	Pramipexole	dyskinesia	44,45
			Ropinirole	dyskinesia	43,
			Cabergoline	motor comps	46
			Pergolide	motor comps	47
			Entacapone	motor comps	48
Clinical Trials aimed at Preventing Cognitive Impairment					
Prevent Dementia		ADIS-COG, CIBIC	Rivastigmine		49
			Donepezil		50
			Rasagiline		51

d) Cognitive complications

Cognitive dysfunction is an extremely important and common feature in advanced PD, is not controlled or prevented with available medications, and represents the major reason for nursing home placement. A small number of trials have been tested trying to treat cognitive dysfunction in PD (table 3). Two performed in advanced patients with dementia, had marginal benefits sufficient for approval, but results were likely due to symptomatic rather than disease modifying effects[49,50]. One study in PD patients with mild cognitive impairment looking to delay progression was negative[51]. Cognitive impairment and dementia are major causes of disability in PD, and it will be of great interest to see if therapies directed towards putative etiologic factors in PD provide benefit in this area as well. Toward that end studies providing information on the natural history of cognitive impairment in PD, particularly in early patients, are of great importance[52]**.** Falling is another major source of disability in progressing PD and another cause of nursing home placement. No studies have evaluated agents that attempt to reduce the risk of falling, but two recently published articles suggest that new onset of falls in moderately advanced PD is more common than was previously appreciated, and could serve as an endpoint in clinical trials.

Appendix 2 Regulatory Perspectives

1. Perspectives From Other Diseases

The development of drugs to slow or stop the clinical progression of neurological impairment in PD has been hampered by an uncertain regulatory environment. Drugs, biologics and devices

have been approved by showing an improvement in clinical features and associated individual functioning. That said, there is considerable precedent for the Food and Drug Administration (FDA) to consider study designs and outcomes--described in product labeling--that support a conclusion that a particular treatment has an effect on delaying (or slowing) the progression of, or preventing, a disease. Although these effects are not always included in the "Indications" section of labeling, they can be described in the Clinical Trials section. A review of FDA Guidance documents identified several different categories of diseases for which such effects are contemplated:

Treatments for Infectious Diseases, Cancer, and Other (Often Progressive) Chronic Diseases

Although guidance documents regarding the prevention of infectious diseases are not particularly relevant for the discussion of PD (for numerous reasons, including acute onset of symptoms, their frequent self-limited nature, and their well-known etiology), they do provide some concepts that could be considered in PD. For example, a Guidance about Cytomegalovirus (CMV) disease in transplant patients describes a specific period of risk after transplantation (6-12 months) during which the absence of clinical disease (and/or anemia) would support a conclusion that the treatment can be considered to be prophylactic. Similarly, a Guidance about systemic treatments to prevent Human Immunodeficiency Virus-1 (HIV-1) infection describes an observation period (in appropriately chosen subjects) of 12-24 months as being adequate to support a conclusion that infection has been prevented. Another example is a Guidance about the prevention of influenza, where a "flu season" is described as the period of risk during which the absence of clinical disease establishes prevention of influenza. The concept of a "period of risk" during which the absence of clinical signs and symptoms establishes prevention is potentially useful in the evaluation of treatments to prevent features of PD, or at least to prevent the appearance of specific clinical signs/symptoms. This may become especially important as their increasing evidence that a pre-motor form of PD may be detected based on a constellation of non-motor features (e.g REM behavior disorder, anosmia, constipation) with no discernible motor symptoms[53]. It must be stated that in order for this approach to be useful, an appropriate period of risk would need to be identified, which, at this point has not been defined for PD. There also remains the issue in neurodegenerative diseases such as PD of determining whether the avoidance of symptoms during the at-risk process could reflect a symptomatic effect of the intervention that simply masks the emergence of the classical motor features of the disease.

Although approaches using "period of risk" as a primary outcome measure to support a conclusion that a treatment can prevent PD may not be available at this time, various Guidance documents describe related outcomes that may have relevance for treatments of PD. These outcomes typically are defined by a period of time during which signs/symptoms of a disease do not appear, do not progress, or resolve completely. For example, numerous Guidance documents addressing treatments for various cancers describe outcomes like Disease-Free Survival (time from randomization until recurrence of tumor or death from any cause), Objective Response Rate (the proportion of patients with a reduction of tumor size of a certain amount over a certain period of time), Progression-Free Survival or Event-Free Survival (time from randomization to tumor progression or death, or time to development of some specific event), Time to Progression (time from randomization to tumor progression), and Complete Response (defined over a specific

period of time using criteria specific to the cancer-type [often including laboratory measures], but embodying the concept that disease is essentially no longer detectable or has not progressed in patients with manifest disease at entry. Overall survival is also considered an acceptable endpoint, although this is more relevant to diseases such as ALS than PD (see discussion below). Importantly, although there is no specific Guidance regarding disease modification in Multiple Sclerosis, Time to Sustained Disability Progression is a standard outcome measure described in product labeling (though not in the Indications section). These endpoints have in common the idea that *a treatment has an important effect on some aspect of the progression of the disease*, and, therefore, one or more of these outcomes may have considerable relevance in the detection of a similar effect in PD trials.

Guidance documents for other (often chronic) diseases also offer outcomes that are relevant for trials in PD designed to document a treatment's effects on disease progression. An outcome described as a "period of risk" approach used in infectious diseases is also described in a guidance for Delayed Graft Function in Kidney Transplantation, which defines the proportion of patients who do not require dialysis within 7 (and up to 30) days after transplant. A Guidance for developing treatments for Systemic Lupus Erythematosis (SLE) describes outcomes of Complete Clinical Response or Complete Clinical Remission, which should be observed for at least one year (interestingly, this guidance defines ***Response*** as the case if patients continue anti-SLE treatment, and ***Remission*** as the case where patients do not need to continue therapy; this distinction has relevance for PD and for approaches advocated by the Division of Neurology Products; see below. A Guidance describing treatments for patients with Type 1 or Type 2 Diabetes Mellitus (DM) describes an outcome of a delay in the diagnosis of DM for at least a year in high risk individuals as supporting a conclusion of prevention of DM. Elsewhere, a Guidance for Ulcerative Colitis describes a definition of Clinical Remission as requiring a composite endpoint of clinical and endoscopic criteria that establish that disease activity is essentially absent (though no time period is specified).

<u>Considerations for Biochemical or Imaging Outcomes</u>

In addition to the above described approaches endorsed by the FDA, several Guidance documents endorse the use of biochemical and/or imaging measures as supporting conclusions about the effects of treatments on the underlying progression of a particular disease.

FDA guidance on osteo-arthritis (OA) introduces the concept of treating the underlying pathophysiology and 'structural progression' of joint deterioration as seen on imaging. It acknowledges that approvals to date are based on the impact of the intervention on assessments of 'pain and function', and identifies the need for a treatment 'that inhibits structural damage or targets the underlying pathophysiology'. Such treatments would change the 'natural course' of the illness, and 'prevent long-term disability'. Complex issues identified include 1) the discordance of structural change with signs, symptoms and function; 2) multifactorial and complex pathogenesis; 3) lack of a standardized definition of disease progression; and 4) the absence of endpoints to reliably assess change in disease progression. They identify reduced pain, increased function, and increased time to 'end-stage disease' as potentially clinically meaningful. Additional outcome measures that could be employed include 'delay of joint failure', 'delay to need for joint replacement', less deterioration in function and less worsening of pain. A similar

example is the Guidance on treatments for Rheumatoid Arthritis (RA), which describes the use of radiographic evidence to support statements in labeling about "structural damage progression" or "structural joint damage", though currently this effect alone does not support approval. The community has identified a widely accepted definition of 'clinical response', namely the ACR20 (20% improvement in the number of painful or swollen joints and 3/5 considered to be improved in patient and physician global assessments), HAQ-DI, pain and acute phase reactants.

In some cases, language describing these types of findings is included in the Indications section; in other cases, it is described in the Clinical Trials section. Importantly, if it is present in either companies are permitted to discuss these findings. Likewise, numerous Guidance documents describe the use of imaging measures (e.g., tumor imaging) or biochemical markers (e.g., HIV-RNA levels), either alone or in combination with other clinical data, to support conclusions about prevention and/or effects on progression. In some cases, these measures are considered validated surrogate markers (that is, evidence demonstrates that an effect on the surrogate does predict the desired clinical effect), that support traditional approval; in other cases, these markers are considered "reasonably likely" to predict the desired clinical benefit and are used to support accelerated approval, *with a requirement to demonstrate the true clinical benefit after approval.* It is interesting to note that many treatments for Multiple Sclerosis-- unique among all approved treatments for neurologic disease--include data on several imaging markers considered to be clinically relevant, though labeling does not contain statements about the meaning of these findings, and, to date, imaging data alone are not considered sufficient to support approval or a disease-modifying indication.

2. Perspectives From Other Progressive Neurological Diseases

Finally, and most relevant for a discussion about treatments for PD, the FDA, with the support of the community, has produced Guidance Documents addressing the development of treatments for three progressive neurologic diseases: Early Alzheimer's Disease (AD), Amyotrophic Lateral Sclerosis (ALS), and Duchenne Muscular Dystrophy (DMD). The Guidance for early Alzheimer's Disease discusses the possibility of approving a treatment in patients with the pathophysiologic changes of AD but no symptoms on the basis of an appropriate surrogate marker that is reasonably likely to predict a clinical benefit (i.e., under the Accelerated Approval provisions). The document does not explicitly describe these results as supporting an effect of the treatment on the underlying progression of the disease. However, it does address potential approaches to establishing a treatment's effects on the underlying course of the illness. Specifically, it endorses the use of either randomized-start or randomized-withdrawal designs as being capable of supporting a conclusion that the treatment has a disease-modifying effect. Both of these designs can be interpreted to show that treating patients early produces a sustained benefit compared to patients treated later in their disease course (in particular, the randomized withdrawal design is intended to demonstrate that the effect of the drug persists after treatment is stopped, implying an effect on the underlying pathology). This document suggests that a similar interpretation would be made with respect to PD. However, the Guidance also states that an effect on biomarkers alone would not, at this time, support approval. The Division of Neurology Products has stated, however, that an effect on an appropriate clinical outcome(s) *as well* as an effect on (yet to be determined) biomarker(s) may possibly support a disease-modifying

conclusion. The guidance for ALS states that an effect on survival will support approval, though it requires attention to patients' respiratory support, since this alone can extend survival, without a specific effect on the underlying ALS. The guidance does not describe whether this effect would appear in the Indication section of labeling; riluzole, extended survival, but this is not described in the Indications section. The guidance on DMD does not explicitly discuss the demonstration of an effect on the progression of the disease but does raise the possibility that a surrogate marker could one day be validated (e.g., functional dystrophin). It should be noted that the validation of a surrogate marker does not necessarily support any conclusions about effects on disease progression (in any disease), though in many cases it likely will.

3. Perspectives on PD

In the only extant regulatory guidance on PD, the EMA specifically identifies the difference between 'disease modifying' and "symptomatic" treatments in the Executive Summary. The language becomes a bit more complicated when a distinction is made between the 'delay of disease progression' and 'disease modification'. The latter requires demonstrating the former, plus demonstrating an effect on the underlying disease pathophysiology (although no adequate measures to demonstrate that are felt to exist at present). There are also specific instances of what is meant by 'delay of progression' that vary according to trajectory: 1) Early PD- slowing progressive motor symptomatology; 2) Stable PD- slow further motor decline, progressive disability and prevent motor or non-motor complications; and 3) Advanced PD- prevent disability, autonomic failure, cognitive symptoms, or delay time to dementia or nursing home placement.

As there is no PD specific FDA guidance, there are only prior public meetings and analogous guidance to rely on, some of which are cited above. While not an official FDA position, a publication in 2009 presented the FDA's thinking about a delayed-start design trial in PD. This material was used in developing the design of the Adagio trial described previously. The material had been previously presented in a 2-day workshop hosted by the Fox Foundation and the AAPS, which was attended by representatives from academia, industry and government. In addition, there have been public Advisory Committee meetings on the design and the results of the Adagio study which provided an opportunity for discussion of the principles and complexities associated with a two-period design.

While the specific language of the different FDA guidance concerning other (perhaps analogous) diseases differ, there are some common themes, largely driven from the statutory basis of the regulation. First, there is often reference to 'clinical meaningfulness', namely that a treatment effect must have that quality. This is usually achieved by demonstrating an effect on a 'functional (or global)' measure (as distinguished from a quality of life measure). Second, this 'clinical meaningfulness' must be accompanied by an objective impact on the 'core symptoms' of the illness, which is usually targeted at measuring the specific illness feature of the disease (such as the UPDRS in the case of PD). Thirdly, there is often reference to the 'established' or 'characteristic' pathophysiology of the disease, although guidance often acknowledges that there is substantial heterogeneity of pathogenesis or frank uncertainty as to its nature. For all progressive diseases, guidance notes the priority of interventions aimed at such a 'characteristic pathophysiology' despite its apparently elusive nature, and the potential that it may not be the

same in all individuals – indeed there is increasing evidence that PD is a syndrome in which there are multiple primary causes.

In the recent FDA AD guidance, the classic requirement is described as an impact on cognition (core symptoms) and a 'functional (or global)' measure. However, it is acknowledged that an impact on cognition, if of sufficient breadth and magnitude, *can be clinically meaningful by itself*. In theory this could be similar for PD where a marked impact on UPDRS obtained under pre-defined conditions could be significant on its face. There is additional language in the AD guidance with terms such as 'alter(ing) disease progression', the 'continuum of progression', and the need for 'meaningful daily life impact' via subjective reports or those of a reliable observer (see above). The possibility of measuring the time until important events (such as a 'clinically meaningful' loss of function) is also discussed. Two-period designs (e.g., delayed start) are also discussed in the context of demonstrating a 'permanently altered course', which could be potentially sufficient for regulatory approval, and bolstered by biomarkers of pathophysiology.

Appendix 3 Trial Design Considerations in Assessing Therapy to Prevent or Delay Disability

1. Target Patient Population for Studies

In approaching the next-generation of trial designs, a crucial consideration is which participants to include. Recently, the criteria for diagnosing PD have come under scrutiny[54-56]. Pathology studies demonstrate that Lewy pathology is widespread and can be detected in the olfactory system, dorsal motor nucleus, cerebral hemispheres, upper and lower brain stem, spinal cord and in the peripheral autonomic nervous system in addition to the dopamine neurons of the substantia nigra pars compacta[57]. These non-dopaminergic pathologies can lead to a variety of non-motor features that expand the clinical picture of PD. These include autonomic dysfunction, sensory alterations, neuropsychiatric disturbances, and cognitive impairment with dementia. In addition, multiple different gene mutations have been discovered to cause, or increase the risk of developing PD[58], and most cases still occur sporadically with no evident genetic cause. These observations indicate that PD is a syndrome with multiple causes. Based on these developments the Movement Disorder Society has commissioned several papers that provide new clinical and research criteria for the diagnosis of PD to be used in clinical practice and research trials[53-56].

There is also evidence from recent pathology studies demonstrating that there is literally no staining for dopamine terminals in the dorsal striatum by 4 years after clinical diagnosis, and that dopamine terminals may have completely degenerated by this relatively early time point[59]. This finding implies that testing the effects of putative neuroprotective drugs on the motor features of PD is best conducted with patients in the earliest stage of the disease, at a time when there are still dopamine neurons available to be preserved or restored. The Movement Disorder Society has published specific criteria for diagnosing early PD in an attempt to increase accuracy of diagnosis at this early stage[60]. Braak and colleagues further suggested that alpha synuclein pathology in PD is first seen in the dorsal motor nucleus of the vagus and in the olfactory system, while involvement of the substantia nigra pars compacta occurs at a mid-stage of the disease[61]. Indeed, clinical, epidemiologic and pathology studies suggest that a prodromal or pre-motor form of PD can be detected based on a constellation of features including constipation, anosmia, rapid eye movement (REM) behavior sleep disorder, minimal motor features, cardiac denervation and

imaging abnormalities; indeed some of these features may precede the onset of the classic motor features of PD by years if not decades[62,63]. The concept that this may be the best population in which to test putative drugs to slow clinical progression has led to intense efforts to define patients with pre-motor PD with a high level of sensitivity and specificity. The Movement Disorder Society has also recently published on research criteria for the diagnosis of prodromal PD[64].

Attempts to identify therapies that can slow clinical disability would be facilitated through better understanding of the natural history of the disease in its various stages. The Parkinson Progressive Marker Initiative (PPMI) sponsored by the Michael J Fox Foundation, is a long-term study of different PD stages to assist in this endeavor[65]. In addition, there are several placebo-controlled studies that provide information on the rate of UPDRS decline in early untreated patients over approximately 9-12 months[37,38,66-68]. Longer-term information is not available on untreated patients after this time as the majority require symptomatic treatment by this time, thereby confounding appreciation of the natural rate of progression. Available studies indicate the average untreated patient declines by approximately 6-10 UPDRS Part III points per year, with deterioration occurring more rapidly for those with higher baseline UPDRS scores. Even more limited data is available for patients in the mid-stage of the disease who are on stable treatment [31,43,44,69-71]. These studies show a lower rate of UPDRS progression in the treated state than in the untreated state, likely reflecting masking by confounding symptomatic drugs. Interestingly, recent studies also suggest that falling occurs more frequently in this population than expected[31,69], raising the possibility that new onset of falls could potentially serve as an endpoint in testing these interventions. Finally, some studies are beginning to examine the rate of change of non-motor features in the pre-motor and early PD stages[72,73].

2. Outcome Measures for Studies

Clinical Measures

There is an abundance of clinical tools for assessing the core characteristics of PD. The most widely used measures are the UPDRS, the MDS-UPDRS, and home diary measures of motor activity (ON time, ON with dyskinesia, OFF time). These are all well-accepted by regulatory agencies and are frequently used as primary endpoints. While these scales capture many elements of PD and their functional impact in daily life, they do not assess other important features of the illness. Other scales that could be employed in an attempt to gain information on measures of function include those that assess activities of Daily Living, health related quality of life (PDQ-39), global outcomes, and patient related outcomes, as well as scales assessing depression, anxiety, and apathy. Important elements of the core symptoms of the disease that could potentially be used as outcome measures in more advanced patients include gait, postural stability, falls, cognitive function with measures of dementia, and nursing home placement.

Biomarkers

The development of a biomarker that provides an objective/quantitative measure of PD progression would be of enormous value in evaluating therapies to slow clinical progression. At the present time, no biomarker has been established to be a biomarker of PD, though an intensive search is underway. Dopamine imaging has been used as an endpoint in several clinical

trials, but results have been confusing (see table 3)[12,22,30,74,75]. Trials in PD patients have demonstrated positive clinical findings with negative imaging results[12], and negative clinical findings with positive imaging results[22,30]. Further, positive results in clinical trials have been challenged based on the potential of a drug intervention to downregulate receptors or induce confounding pharmacologic effects[76].

Alpha-synuclein has attracted particular attention as a possible biomarker because of its key role in the etiopathogenesis of PD, but here too results of CSF and blood/plasma analyses have been conflicting, and the significance of changes in this biomarker as they pertain to a measure of disease modification remain to be established[77]. The PPMI effort sponsored by the MJ Fox foundation is actively seeking biomarkers that correlate with the underlying disease and with disease progression that might serve as primary or confirmatory secondary endpoints in future studies[78].

TABLE 3

Biomarkers to Assess Disease Modification

Design	Endpoint	Agent	Result	Reference
DA imaging[a]	Δ FD-PET BL to FV – 2 yrs	Ropinorole	pos	74
	Δ β-CIT BL to FV – 46 mos	Pramipexole	pos	75
	Δ β-CIT BL to FV – 9 mos	Levodopa	neg	12
	Δ β-CIT BL to FV – 40 wks	CEP-1347	neg	10
	Δ FD-PET BL to FV – 2 yrs	Fetal Transplant	pos	22
	Δ FD-PET BL to FV – 1 yr	Fetal Transplant	pos	30
	Δ UPDS BL to FV -1 yr	Neurturin	neg	23
Blood and CSF[bc]	Urate	Inositol	NA	36,37
Alpha synuclein	CSF			77,78
	Peripheral			79
Oxidative stress				
Micro RNAs				
Proteomics				

a) Dopamine Imaging

Dopamine imaging provides a measure of the functional integrity of the nigrostriatal dopamine system. It has been used to confirm the diagnosis of PD, but also can be used to assess the integrity of the nigro-striatal system. Concern exists over whether treatments can artificially influence binding and create confounding pharmacological effects, and it remains to be determined how accurately dopamine imaging reflects changes in the number and function of nigrostriatal neurons and how closely they correlate to clinical observations. In some studies dopamine imaging was significantly improved though clinical outcomes were not[22,30], while in

others clinical benefit was associated with deterioration in measures of dopamine imaging[12]. Currently, DA imaging is not acceptable as a primary endpoint in regulatory studies but may prove to be of value in a positive trial with a traditional clinical endpoint in supporting an interpretation that the clinical benefit is due to novel mechanism of action.

b) Alpha-Synuclein

Given its proposed role in the etiology of PD, alpha-synuclein in its various conformational states has generated great interest as a potential biomarker of the underlying disease state, a marker of disease progression, and an index of the effect of treatment. There has been particular interest in determining if levels of aggregated or oligomeric alpha synuclein in CSF, blood, plasma, or peripheral tissue could serve as a biomarker of the disease state, but results have been inconsistent and conflicting[77-79]. While dose-dependent lessening of serum and CSF markers of alpha-synuclein have been reported in relatively short studies their clinical significance is unknown. Further, it has not yet been established how this biomarker might change over time during the natural course of the disease or the impact of interventions intended to slow clinical progression. While dose-dependent lessening of various serum and CSF alpha-synuclein species has been observed, and increased alpha synuclein deposits in peripheral tissues such as the GI tract and salivary glands have been reported, these changes are not consistently found, and their value as an index of disease progression remains to be established. Thus, despite the importance of alpha synuclein, it is premature to consider changes in an alpha synuclein biomarker as sufficient to serve as a surrogate endpoint of disease progression in clinical trials. Efforts are underway to develop a ligand for alpha synuclein imaging, but these are not as yet available for use in clinical trials.

c) Others

The antioxidant urate has been considered as a possible biomarker in PD and has been shown to correlate with clinical and imaging progression over 24 months[80]. Numerous convergent lines of data suggest an association of higher urate levels with slower clinical progression, although this hypothesis has not been prospectively tested using urate as a biomarker for another agent's biological activity. Further, urate itself may have therapeutic effects, and is currently being studied for this indication[81], which could confound its ability to serve as an independent measure of another compound's ability to influence clinical progression. PD specific changes in the pattern of CSF and blood proteomics, metabolomics, RNAs, and micro-RNAs have also been reported[82-84], but need to be confirmed as valid biomarkers and assessed in natural history studies. Studies have also assessed possible biomarkers of cognitive dysfunction in PD[85,86], but here too there is no clearly defined biomarker that is acceptable for use as a primary endpoint in clinical trials.

While a biomarker that can be used to identify PD with high specificity, track the progression of the disease, and serve as an endpoint for evaluating the effects of drugs intended to slow clinical progression is a major need in our attempt to develop novel therapies for PD, no such biomarker is currently available. Intensive efforts to define such biomarkers are underway.

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