FULL PROTOCOL TITLE
A Pilot Study of Terazosin for Parkinson's Disease

SHORT PROTOCOL TITLE
TZ-PD
Protocol Version: 2.0
Protocol Date: 12th November 2019

Protocol Principal Investigator (PPI);
Jordan Schultz, PharmD
Assistant Professor of Psychiatry and Neurology
Carver College of Medicine at the University of Iowa

Nandakumar Narayanan, MD, PhD
Associate Professor of Neurology
Assistant Director: Clinical Neuroscientist Training Program in Neurology
Assistant Director: Residency Program in Neurology
University of Iowa – Carver College of Medicine

NCT03905811

Supported by:
Institute of Clinical and Translational Science at the University of Iowa

LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

AE	Adverse Event
AZ	Alfuzosin
CCC	Clinical Coordination Center
CDE	Common Data Elements
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board
CRF	Case report form
CS	Clinically Significant
CSS PI	Clinical Study Site PI
DCC	Data Coordination Center
DM	Data Management
DSMB	Data Safety Monitoring Board
DZ	Doxazosin
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IMM	Independent Medical Monitor
MDS-UPDRS TMS	Movement Disorder Society Unified Parkinson's Disease Rating Scale Total Motor Score
MedDRA	Medical Dictionary for Regulatory Activities
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NINDS	National Institute of Neurological Disorders and Stroke
PD	Parkinson's Disease
Pgk1	Phosphoglycerate kinase 1
PPI	Protocol Principal Investigator
PPMI	Parkinson's Progression Markers Initiative
PSC	Protocol Steering Committee
SAE	Serious adverse event
SNc	Substantia nigra pars compacta
SOA	Schedule of Activities
TZ	Terazosin

SYNOPSIS

Rationale:
Parkinson's disease (PD) is a devastating neurodegenerative disease affecting ~1 million Americans with ~60,000 new diagnoses made annually[1]. There are no interventions that slow the inexorable progression of PD. Thus, there is a ***critical need*** to develop novel disease-modifying therapies for PD. We have discovered that activation of phosphoglycerate kinase 1 (Pgk1) can reverse energy deficits that contribute to the pathology of PD. More importantly, we have discovered that terazosin (TZ) can activate Pgk1 through a novel mechanism that is independent of its predicted α-adrenergic receptor antagonism and slow the progression of PD. The procedures outlined in the protocol will allow us to 1) quantify energy deficits in the brains of patients with PD and 2) determine if the administration of TZ can alter energy deficits over a short time period and longer time period. **This study will test the safety and tolerability of TZ in patients with PD as well as test the feasibility of this protocol while providing vital information to guide future clinical trials of TZ in PD.**

Study Title
A FeASibiliTy study of TeraZosin as a disease modifying treatment for PD: FAST TZ-PD

Objectives
Primary objective:
To assess the safety of TZ in patients with PD as well as the feasibility of the study protocol. The active treatment group (TZ 5mg daily) will be compared to a placebo group. The primary outcome measure will be the safety and tolerability of TZ in the select patient population. This will be assessed by comparing the number of participants in each group that experience drug-related adverse drug events as well as assessing the rate of drop out in each group.

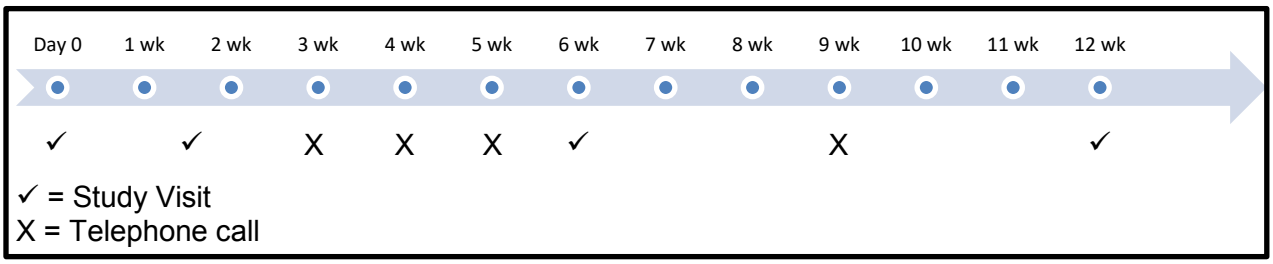
Secondary objective:
Orthostatic hypotension is more common in PD[2], so it is possible that TZ could exacerbate this symptom of PD. To assess the change in blood pressure (systolic and diastolic) from baseline to week 6 and from baseline to week 12.

Exploratory Objective:
To quantify ATP levels in 1) red blood cells and 2) in the brain before and after the administration of TZ and after taking TZ for 12 weeks.

Design and Outcomes
We will randomize 20 PD patients to receive TZ or placebo. Ten of the participants will be randomized to receive TZ 5mg daily for 12 weeks and 10 participants will be randomized to receive a daily placebo for 12 weeks. This aim will generate data on safety and tolerability of TZ in a population of patients with PD. As an exploratory outcome, we aim to determine if treatment with TZ in patients with PD improves markers of energy metabolism. Furthermore, we will determine if cellular and cerebral ATP levels correlate with disease severity and progression. Participants will also participate in an assessment that will include, but is not limited to a motor exam, a neuropsychological assessment, and functional assessments. Clinical findings will be used to guide future clinical trials.

Interventions and Duration

Participants in this study will be randomized to receive either TZ 5 mg by mouth once daily or a matched placebo once daily. Once randomized, each participant will receive their assigned treatment for 12 weeks. Participants will be assessed via telephone for 3 weeks after their 2 week visit, then 6 weeks months after their baseline visit, then via telephone 9 weeks after their baseline visit, and their last visit will occur 12 weeks from their baseline visit. We anticipate that this study can be completed (study open to end of data analyses) within 9 months.



Sample Size and Population

This study will randomize 20 participants: 10 participants will be randomized to receive 5mg of TZ daily and 10 participants will be randomized to the placebo group. It is anticipated that no more than 35 participants will need to be screened to enroll these participants.

This study will include participants who are ≥ 40 years old who have a confirmed diagnosis of PD made by a neurologist and a Hoehn & Yahr score at baseline of < 4. Participants will be excluded from this study if any of the following are true:

- Participants has orthostatic hypotension or a sitting blood pressure of ≤90/60
- Participant is pregnant
- Participant has a deep brain stimulation device implanted
- Participant has a known allergy or sensitivity to terazosin
- Participant is concomitantly taking doxazosin, alfuzosin, prazosin, urapadil, or tamsulosin
- Participant has active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements
- Participant is unable or unwilling to give written informed consent

1 STUDY OBJECTIVES

1.1 Primary Objectives

To assess the safety and efficacy of TZ in patients with PD as well as the feasibility of the study protocol. The primary outcome measure will be the safety and tolerability of TZ in the select patient population.

1.2 Secondary Objectives

To assess the mean change in systolic and diastolic blood pressures at 6 weeks and 12 weeks between the active and placebo groups.

1.3 Exploratory Objectives

1) To utilize magnetic resonance spectroscopy (MRS) to quantify ATP levels in the brain at baseline, after a single dose of study drug, and after 12 weeks of treatment with study drug
2) To explore the effect of TZ on ATP levels in red blood cells.

2 BACKGROUND

2.1 Rationale

Parkinson's disease (PD) is a devastating neurodegenerative disease affecting ~1 million Americans with ~60,000 new diagnoses made annually[1]. Patients with PD suffer debilitating motor symptoms affecting all aspects of their ability to function, communicate, and care for themselves[3]. In addition, PD patients can suffer non-motor symptoms including dementia, depression, sleep disorders, and a range of autonomic dysfunctions[4]. Because age is a primary risk factor for PD, PD-related morbidity and mortality will surge in the coming decades as Americans live longer[5]. There are no interventions that slow the inexorable progression of PD. Thus, there is a ***critical need*** to develop novel disease-modifying therapies for PD.

A key pathogenic factor in Parkinson's disease is impaired energy metabolism[5]. Several observations support this conclusion. a) Aging, a major risk factor for PD, impairs cerebral glucose metabolism, reduces mitochondrial biogenesis, and decreases ATP levels[6, 7]. b) Glycolysis and mitochondrial function and numbers are decreased in people with PD[8-12]. c) Mitochondrial toxins (MPTP & rotenone) induce PD and PD-like phenotypes in cells and animals, including humans[13]. d) Mutations associated with familial PD (*PINK1, Parkin, DJ-1, CHCHD2, α-synuclein, LRRK2*) disrupt various aspects of mitochondrial function and/or energy balance[14].

We recently discovered that terazosin (TZ) binds and activates phosphoglycerate kinase 1 (Pgk1), the first ATP-generating enzyme in glycolysis (Fig. 1)[15]. TZ is an α_1-adrenergic antagonist that is prescribed to treat benign prostatic hypertrophy and rarely hypertension[16]. However, biochemical and functional studies show that TZ has an additional target, Pgk1, that is independent of α_1-adrenergic antagonism[15]. Our earlier crystal structure of Pgk1 with TZ revealed that the 2,4-diamino-6,7-dimethoxyisoquinazoline motif of TZ binds Pgk1 adjacent to the ADP/ATP binding site[15]. In earlier work and our current unpublished data, we found that TZ increases glycolysis and cellular levels of ATP in cultured cells and *in vivo* in mice and rat brain[15]. Measurements of brain TZ levels also indicate that TZ readily crosses the blood-brain barrier. These findings and the impaired energy production in PD, suggested the possibility that TZ activation of Pgk1 might improve cellular energy metabolism, prevent progressive cell death, and restore dopamine production and motor function in PD. Of note, case reports have identified mutations in the *PGK1* gene that are associated with early onset PD[17].

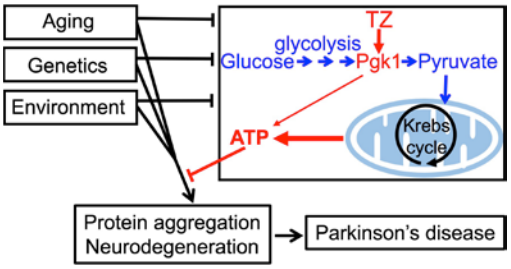


Fig. 1. Aging, genetic mutations & predispositions, and environmental factors contribute to PD in several ways. A common feature is energy deficits. Terazosin (TZ) enhances phosphoglycerate kinase (PGK1) activity to decrease energy deficits and halt neurodegeneration in models of PD.

Based on this information, we believe that TZ has the potential to be repurposed for use as the first disease modifying treatment of PD. This would have enormous implications for patients and society. TZ has the potential to provide a safe and low-cost treatment option for patients with PD. The information collected in this study will provide vital information to guide future clinical trials of TZ in PD.

Regarding the chosen treatment regimen, oral administration was chosen based on the existence of Phase 1 studies that have evaluated the safety of oral TZ in healthy subjects. The decision to utilize a dose of 5mg daily of TZ was primarily based on information obtained from human data (see Section 2.2). Two separate databases were evaluated (Parkinson's Progression Markers Initiative and Truven) to test the effect of TZ on PD. In both datasets, TZ was associated with improvements in progression and complications of PD. The mean dose of TZ being used by participants in both databases was approximately 5mg daily. Based on results from the Truven data, the use of TZ at this dose was not associated with a significantly increased risk of falls or orthostatic hypotension. TZ can be used at higher doses (up to 20 mg/day) for the treatment of benign prostatic hyperplasia and (rarely) hypertension. However, the antihypertensive action of TZ could potentially exacerbate the autonomic instability that can occur in PD[18]. Therefore, 5mg daily that was chosen represents a dose that is 1) already FDA approved, 2) is used safely in patients with PD, and 3) has been shown to provide benefit for the treatment of PD. After randomization, patients will remain on therapy for 12 weeks in this study.

2.2 Supporting Data

a) *Preclinical Data*

TZ increases brain ATP levels *in vivo*.

We recently discovered that terazosin (TZ) binds and enhances PGK1 activity in cell lines, thereby increasing ATP levels[15]. To test if TZ increases brain energy production *in vivo*, we administered it to mice. TZ increased levels of pyruvate, the product of glycolysis, increased oxidative phosphorylation, and elevated ATP levels (Fig. 2a-2c). Like previous *in vitro* data, the dose-response was biphasic; at low but not high concentrations, TZ may enhance ATP release from PGK1.

We also asked if TZ would increase energy production in mice that received 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is often used to model PD in mice. Seven days after administering MPTP to mice, ATP levels, pyruvate levels (Fig. 2d,2e), and mitochondrial numbers fell, consistent with impaired energy production. TZ partially prevented the energy deficits, and mitochondrial content was partially maintained. These data indicate that TZ activates glycolysis *in vivo*. Together with measurements of brain TZ levels, they also indicate that TZ readily crosses the blood-brain barrier.

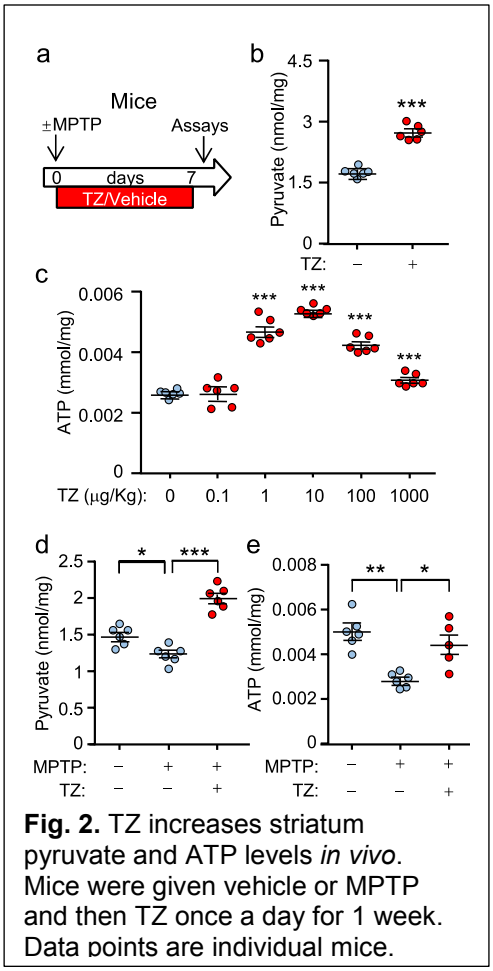


Fig. 2. TZ increases striatum pyruvate and ATP levels *in vivo*. Mice were given vehicle or MPTP and then TZ once a day for 1 week. Data points are individual mice.

TZ enhances PGK1 activity to protect dopamine neurons in toxin-induced models of PD.

MPTP causes PD in humans[19]. We delivered MPTP to mice, administered TZ for the next 7 days, and then assayed on day 7 (Fig. 3a). Because PD patients present after onset of neuron degeneration, we also asked if delayed TZ administration would slow neuron loss and functional decline. Therefore, we also delivered MPTP to mice, waited 7 days, then started 7 days of TZ treatment, and assayed on day 14 (Fig. 3a).

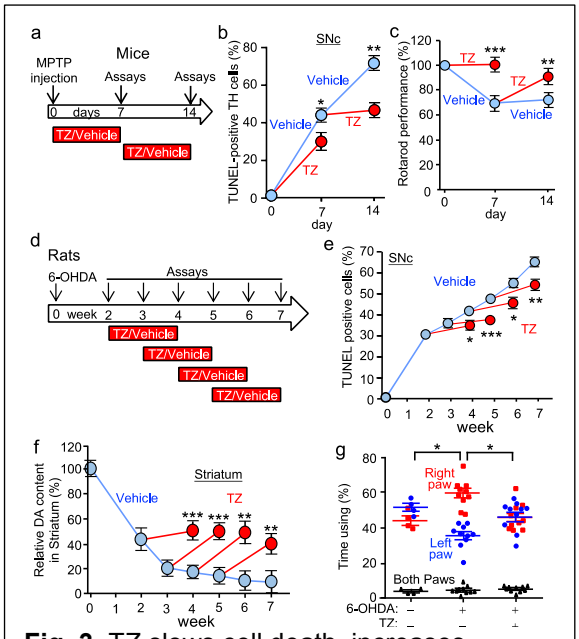


Fig. 3. TZ slows cell death, increases dopamine levels, and improves motor peformance in mice given MPTP (a-c) and rats given 6-OHDA (d-g).

Over the course of 14 days, MPTP progressively decreased levels of TH protein, dopamine content, numbers of TH-positive cells in the substantia nigra pars compacta (SNc), TH staining of their striatum projections, and increased apoptosis of the TH-positive SNc neurons in vehicle-treated mice (Fig 3b). Initiating TZ treatment when MPTP was delivered, attenuated these defects at day 7. Delayed TZ delivery also improved the day 14 abnormalities. Accordingly, TZ prevented deficits in motor function at day 7 and improved motor performance at day 14 after delayed administration (Fig. 3c).

6-hydroxydopamine (6-OHDA) is delivered to rats can model dopamine neuron degeneration[20]. We injected 6-OHDA into the right striatum, waited 2-5 weeks, and then initiated a two-week course of TZ (Fig. 3d). In vehicle-treated rats, evidence of SNc cell apoptosis progressively increased from 2 to 7 weeks (Fig. 3e). However, irrespective of the delay until beginning treatment, TZ protected against further cell loss. Correspondingly, dopamine content and TH reverted toward control values (Fig. 3f). Seven weeks after injecting 6-OHDA into the right striatum, use of the left forepaw had fallen (Fig. 3g). However, when rats received TZ between weeks 5 and 7, they used both forepaws equally.

As an additional model of PD, we treated *Drosophila* with rotenone, a mitochondrial complex I inhibitor implicated in sporadic PD[21]. Rotenone exposure reduced brain ATP levels and disrupted motor function. PGK1 is highly conserved in flies, and supplying TZ together with rotenone minimized decrements in ATP content and motor performance. Knocking-down *Pgk1* by RNAi in TH-neurons abolished the protective effect of TZ. Conversely, overexpressing PGK1 in *Drosophila* and rat TH neurons phenocopied TZ's energy effects[15, 22]. These *in vivo* results suggest that TZ slows or prevents neurodegeneration by enhancing PGK1 activity and increasing ATP[15, 22].

TZ prevents or slows neurodegeneration in genetic models of PD.

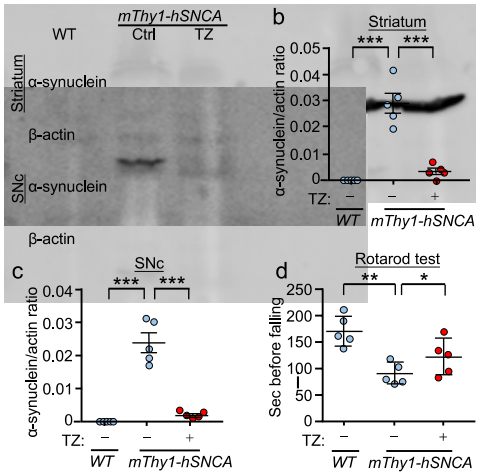


Fig. 4. TZ reduces accumulation of α-synuclein in transgenic mice over-expressing WT human α-synuclein.

We tested *Drosophila PINK1*[5] and *LRRK*[ex1] mutants; *PINK1* and *LRRK2* mutations cause PD in humans[23, 24]. TZ attenuated biochemical and motor deficits in these models.

Abnormal accumulation of α-synuclein, a major constituent of Lewy bodies, is a key feature of PD[25]. Transgenic mice overexpressing wild-type human α-synuclein (*mThy1-hSNCA*) exhibit PD-like neurodegeneration[26]. When they were 3 months-old, we began treating mice with vehicle or TZ. When 15 months old, vehicle-treated mice had substantial α-synuclein in the striatum and SNc and impaired motor performance on the rotarod and pole test (Fig. 4). TZ partially reversed these abnormalities.

We also tested the effect of TZ on dopamine neurons differentiated from induced pluripotent stem cells (iPSCs). *LRRK2*^{G2019S} is the most common *LRRK2* mutation and is associated with ~4% of familial and ~1% of sporadic PD[27]. Dopamine neurons derived from *LRRK2*^{G2019S} iPSCs recapitulate PD features including abnormal α-synuclein accumulation[28]. We studied such neurons generated from two Spanish patients. After thirty days of

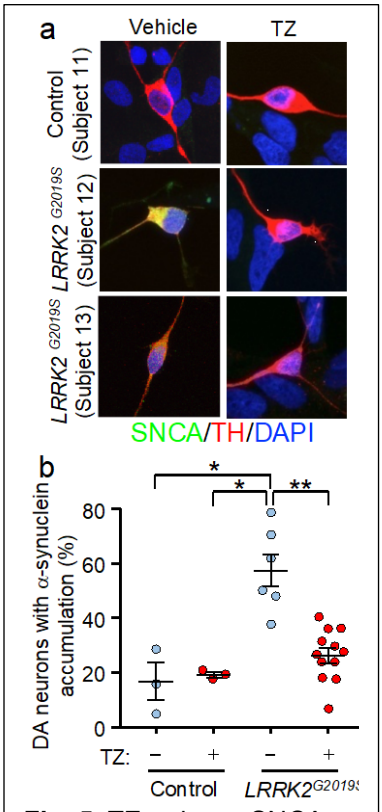


Fig. 5. TZ reduces SNCA aggregation in DA neurons derived from human iPSCs (*LRRK2*^{G2019S} and normal). 30-day old DA neurons received TZ and were studied 3d later.

differentiation, ~60% of the *LRRK2*^{G2019S} dopamine neurons had accumulated α-synuclein compared to ~15% of dopamine neurons from healthy individuals (Fig. 5). Adding TZ for 24 hr reduced the percentage of *LRRK2*^{G2019S} dopamine neurons with increased α-synuclein accumulation.

b) Clinical Data

TZ use is associated with slower disease progression in people with PD.

PD incidence increases markedly after age 60[29]. TZ is prescribed for benign prostatic hyperplasia, which also affects older men. Therefore, to determine if some patients with PD used TZ, we interrogated the Parkinson's Progression Markers Initiative (PPMI) database. Compared to PD patients not taking TZ (n=269), patients taking TZ had a slower rate of motor function decline assayed by the Movement Disorder Society's Unified Parkinson's Disease Rating Scale Part 3. Although statistically significant (P=0.039), only 7 patients with PD used TZ. To increase the sample size, we tested related drugs with quinazoline structures and found that doxazosin and alfuzosin increased glycolysis and tyrosine hydroxylase in MPTP-treated mice. In patients using TZ, doxazosin, or alfuzosin (TZ/DZ/AZ, n=13), progression of motor disability slowed (P=0.012) (Fig. 6). In contrast, the non-quinazoline α1-adrenergic antagonist tamsulosin did not rescue tyrosine hydroxylase levels in MPTP-treated mice and failed to slow motor function decline. These data also support the conclusion that enhanced glycolytic activity and attenuation of cell death are mediated by TZ's effect on PGK1 and not α1-adrenergic receptors.

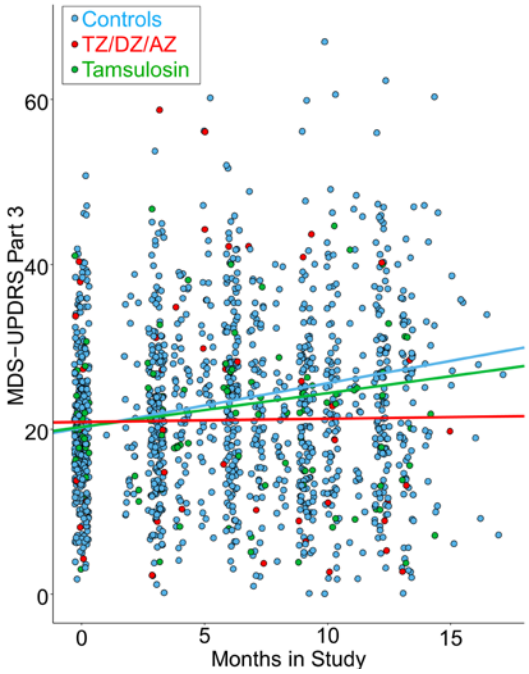


Fig. 6. TZ/DZ/AZ reduced motor function decline assayed by MDS-UPDRS Part 3. Data are scores at PPMI entry through ~1 year for patients taking TZ/DZ/AZ (n=13, red), tamsulosin (n=24, green), or neither (n=269, blue). Lines are linear mixed effect regression analyses. Slopes of TZ/DZ/AZ group differed by maximum likelihood estimation compared to controls (p=0.012).

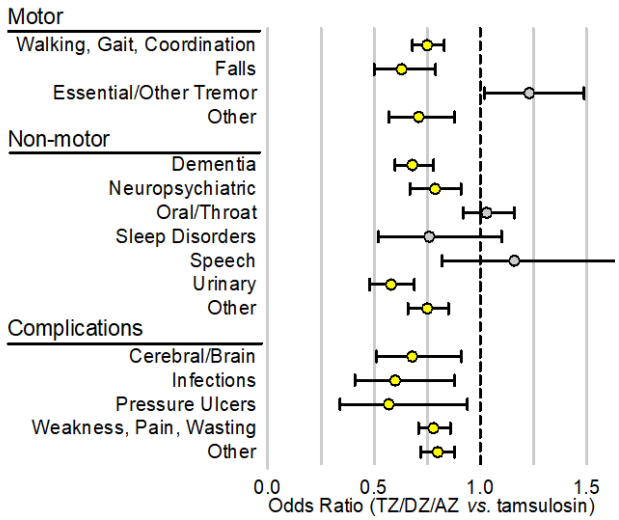


Fig. 7. TZ reduces risk of ICD9 diagnostic codes associated with PD. Data are means and confidence intervals for relative risk in PD patients taking TZ/DZ/AZ *vs.* tamsulosin. Codes were a curated set developed by physicians treating PD. 2,885 enrollees were taking TZ/DZ/AZ; 15,417 were on tamsulosin.

We also interrogated the IBM Watson/Truven Health Analytics MarketScan database from 2011 to 2016. The database includes longitudinal, de-

identified diagnoses (ICD-9/ICD-10 codes) and pharmaceutical claims. We identified 2,880 PD patients taking TZ/DZ/AZ and 15,409 taking tamsulosin. Among 79 PD-related diagnoses, we found a reduced relative risk in 69 codes among patients taking TZ/DZ/AZ *vs.* tamsulosin. Moreover 41 were significantly decreased, whereas only 2 were significantly increased. To estimate PD-related benefits/risks attributable to TZ/DZ/AZ *vs.* tamsulosin, we calculated the odds ratio for each of the 79 PD-related codes. Relative to PD patients taking tamsulosin, those on TZ/DZ/AZ had reduced clinic/hospital encounters for motor symptoms (odds ratio 0.77 (95% CI:0.70-0.84)), non-motor symptoms (odds ratio 0.78 (95% CI:0.73-0.83)), and PD complications (odds ratio 0.76 (95% CI:0.71-0.82)) (Fig. 7). These data suggest that under real-world conditions, TZ and related drugs that enhance PGK1 activity reduced PD signs, symptoms and complications.

Relationship between PGK1 enhancement and PD.
PGK1 mutations cause recessive hemolytic anemia, myopathy, seizures, and intellectual disability; Parkinsonism has also been reported[17, 30]. The authors speculated that reduced ATP generation in the SNc was responsible. It may also be worth noting that PD occurs 1.5 times more frequently in men than women[31], and *PGK1* is located on the X-chromosome.

Finding that TZ increases glycolysis and prevents progressive neurodegeneration supports the concept that energy deficits are a critical factor in the pathogenesis of PD[5, 14]. The increased ATP levels produced by TZ may be key. ATP has properties of a hydrotrope[32, 33]. It can prevent aggregate formation and dissolve previously formed protein aggregates, and the transition between aggregate stability and dissolution occurs in a narrow range of physiological ATP concentrations. We speculate that by elevating ATP levels, TZ facilitates solubilization of aggregates, including α-synuclein, and prevents the neurodegeneration of PD. However, other mechanisms are possible, including ATP-dependent chaperones (such as HSP90) and disaggregases[15, 32, 33].

Summary of supporting data.
It is uncertain which preclinical models of PD will accurately predict therapeutic benefit. These data have the advantage that they identify TZ efficacy in multiple different animal models of PD, including toxin-induced and genetic. Moreover, probing two independent databases suggested efficacy in humans with PD. As a potential PD therapeutic, TZ has the advantages of a defined mode of action, blood-brain barrier penetration, oral availability, and extensive safety experience in humans suggesting feasibility of long-term administration.

2.3 Risk/Benefit Assessment

As mentioned previously, TZ is associated with an increased risk for orthostatic hypotension (OH). This is especially important in the setting of PD where the prevalence of OH is significantly increased compared to healthy controls. Patients with PD are also more susceptible to calls, which could also be exacerbated by the presence of OH. The results from the Truven database outlined above demonstrated that patients with PD who were using TZ did not have significantly increased prevalence of ICD-9 codes related to falls compared to PD patients who were not using TZ. However, this study will directly assess whether or not the use of TZ in PD significantly increases the occurrence of orthostatic hypotension and related events, such as falls. TZ is associated with additional adverse effects, such as peripheral edema, palpitations, nausea, asthenia, dizziness, headache and somnolence. Despite these risks, the potential benefit that TZ may provide is significant given that there are no currently available treatments to slow the progression of PD.

3 STUDY DESIGN

3.1 Scientific Rationale for Study Design

The primary goal of this study is to assess the safety and efficacy of TZ in PD and to assess the feasibility of using TZ in patients with PD. Our hope is that the results of this pilot study will guide future clinical trials of TZ in PD.

3.2 Justification for Dose

Terazosin is used as an α1-adrenergic antagonist in humans with benign prostatic hyperplasia or, largely in the past, hypertension. The typical dosing range for use in these conditions is 1mg per day up to 20 mg/day. The average daily dose of TZ that participants from the PPMI and Truven databases were using was approximately 5 mg/day. In both of these databases, TZ was associated with beneficial outcomes for patients with PD. Therefore, it is reasonable to assume that a dose of 5 mg/day of TZ in patients with PD will provide benefit. This also represents a dose that will minimize antagonism of α-1 receptors that could lead to a decrease in BP, which could potentially exacerbate the autonomic instability that can occur in PD[18].

As outlined in Figure 2c, the dose of TZ that produced the optimal results was approximately 1 microgram/kg to 100 micrograms/kg. This translates into a dose of 0.001 mg/kg to 0.1 mg/kg. If we assume that the average participant will weight approximately 100 kg, a reasonable dose would be 0.1 to 10 mg/day. Figure 2c also demonstrates that the benefits of TZ are still significant at higher doses but begin to decrease. Taken together, our pre-clinical and clinical data suggest that the choice of optimal dose would most reasonably be between doses of 1mg, 5mg or 10mg daily. The choice to eliminate a dose of 10 mg/day was based on 1) the increased risk of orthostatic hypotension in PD at higher doses and 2) the fact that higher doses may blunt the potential benefit of TZ relative to lower doses. Because the average dose of TZ used in both the PPMI and Truven datasets was ~ 5mg/day, and this dose is very reasonable based on the pre-clinical data, this dose was chosen.

3.3 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Schedule of Activities (SoA).

4 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

1. Men or women aged 40 and older with the diagnosis of idiopathic PD per UK Brain Bank criteria
2. Hoehn-Yahr Stage I-III, on stable dopaminergic treatment regimen for ≥4 weeks prior to baseline.

4.2 Exclusion Criteria

1. Subjects unwilling or unable to give informed consent
2. Secondary parkinsonism (e.g., drug induced)
3. Parkinson-plus syndromes
4. History of brain surgery for PD such as deep brain stimulation
5. No confounding acute or unstable medical, psychiatric, orthopedic condition. Subjects who have hypertension, diabetes mellitus, depression, or other common age-related

illness will be included if their disease under control with stable treatment regimen for at least 30 days.

6. Neurogenic orthostatic hypotension defined as symptomatic decrease in BP > 20mmHg systolic or > 10mmHg diastolic and HR increase < 20bpm on supine to sitting or standing.
7. Clinically significant traumatic brain injury or post-traumatic stress disorder
8. Presence of other known medical or psychiatric comorbidity that in the investigator's opinion would compromise participation in the study
9. Presence of dementia per Movement Disorder Society Level I criteria
10. Major depression, bipolar affective disorder, or other mental health disorders that are sufficiently severe to increase adverse event risk or impact neuropathy assessment in the opinion of the responsible site principal investigator.
11. Current suicidal ideation within one year prior to the baseline visit as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS), Beck Depression score >21, Beck Anxiety score >22.
12. History of exposure to typical or atypical antipsychotics or other dopamine blocking agents within 6 months prior to the baseline visit
13. Use of investigational drugs within 30 days before screening
14. Subjects have to be on a stable regimen of central nervous system acting medications (benzodiazepines, antidepressants, hypnotics) for 30 days prior to the baseline visit
15. Use of doxazosin, alfuzosin, prazosin, or tamsulosin
16. For female participant, pregnancy, or plans for child-bearing during study period
17. Participant is restricted from traveling to and from the study site

4.3 Lifestyle Considerations

No specific restrictions on lifestyle and/or diet will be placed on the subject during the study. If a participant is prescribed an α-1 antagonist that is indicated for their care, they will be withdrawn early from the study to 1) avoid the risk for harmful side effects and 2) to maintain the integrity of blinding.

4.4 Subject Withdrawal Criteria

Subjects are free to withdraw from the study at any point. Subjects will be withdrawn from the study if they experience serious and/or persistent side effects during the study that, in the opinion of the site PI, are thought to be related to the study drug. Examples include but are not limited to persistent and symptomatic orthostatic hypotension, persistent peripheral edema, persistent drowsiness that significantly affects activities of daily living, significant weakness, or falls. If any of these side effects occur, the site PI will be asked to make a recommendation regarding whether continuation of the study treatment will place the subject at any undue risk. If so, the subject will be immediately withdrawn from the study.

Withdrawn subjects will not be replaced. Should a subject withdraw from the study despite all efforts to maintain follow-up every effort should be made to obtain an in-person final visit, which should include all assessments that would be obtained in the final drug visits (see Section 6).

4.5 Study Enrollment Procedures

Only subjects who meet all the inclusion and none of the exclusion criteria will be eligible for enrollment and subsequent randomization in the study. No protocol waivers will be allowed for eligibility criteria. Subjects will be deemed eligible for enrollment by the PI. If eligible for enrollment, the site investigators will review the informed consent documents with the subject. If

the subject signs the informed consent document, they will be considered as being enrolled in the study.

Once a participant has been enrolled, they will be assigned a Subject Identification Number by the site. After a subject is enrolled and has a Subject Identification Number, they will undergo a screening visit. If they fail the screening, their Subject Identification Number will be documented and their reason for screening failure will be documented. If a subject fails their initial screening visit, they will not be eligible for re-screening for the study. If a subject is deemed eligible after their screening visit, they will be randomized to treatment.

4.5.1 Subject Recruitment and Retention

Subjects will be recruited from the University of Iowa Neurology clinic as well as from referrals from other providers within the University of Iowa.

4.5.2 Screening Logs

Screening logs will be collected for all enrolled participants. Screening logs to document reasons for ineligibility and reasons for nonparticipation of eligible subjects will be stored by the PIs. Screening logs of all participants will include information regarding how the subject learned of the trial, reasons for screen failure (if applicable), and reasons for not participating in study (if applicable).

4.5.3 Informed Consent

Written informed consent will be obtained from each study subject before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The subject's willingness to participate in the study will be documented in writing in a consent form approved by the IRB at the University of Iowa, which will be signed by the subject with the date of that signature indicated. The investigator will keep the original consent forms and a copy will be given to the subject. It will also be explained to the subject that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the subject will be given to all subjects.

If a participant is unable to read the consent forms, the consent form will be read in its entirety to the subject. If the subject is willing and able to provide verbal consent to participate in the study, but is physically unable to provide their signature, the subject's authorized representative may sign the subject's name while also providing their name and relationship to the study participant.

4.5.4 Randomization/Treatment Assignment

Participants will be randomized in a 1:1 fashion to TZ 5mg daily and placebo. Randomization will be performed by NuCara Pharmacy in Coralville, Iowa. Randomization codes will be made available only to the dispensing pharmacist. The randomization code will not be made available to the investigators, study centers, study subjects, or other representatives. Only after the study is complete, will randomization codes be made available to the investigators.

5 STUDY INTERVENTIONS/STUDY MEDICATION/STUDY DRUG OR DEVICE

5.1 Study Medications/Interventions, Administration, and Duration

Once randomized, all participants will receive a one-month titration packet. For participants who are randomized to receive TZ, it is important to titrate the dose slowly to avoid higher incidences of orthostatic hypotension. All participants will undergo a dummy titration schedule to maintain blinding. The titration schedule is outlined below:

	Placebo	TZ 5mg per day
Week 1 (days 1-7)	P	A
Week 2 (days 8-14)	P + P	A + A
Week 3 (days 15-21)	P + P + P	A + A + A
Week 4 (days 22-28)	P + P + P + P	A + A + A + A
Day 28 and beyond	P	AA

P = 1 Placebo Capsule
A = 1 capsule containing 1mg of TZ
AA = 1 capsule containing 5mg of TZ

Participants will be informed of the titration schedule at randomization and all participants will be informed that they will be switched to a single capsule starting on Day 28 and beyond. This will maintain blinding and avoid the need for participants to have a 4 capsule pill burden for the remainder of the study.

Participants will be provided with the entire study supply of 1mg and 5mg terazosin or placebo. The first bottle will contain a one month supply of 1mg capsules for the titration period. The second bottle will contain a two month supply of 5mg capsules. The participant will be instructed to take their dose of medication once daily. The participant will be instructed to take their dose of medication before bedtime to maintain the same dosing schedule, as doses should be separated by at least 23 hours. Each treatment will be administered by the participant in their home by mouth. Each participant will be maintained on their dosage schedule for the duration of the study (3 months). Dose escalation schedules will not be employed.

5.2 Handling of Study Medications/Interventions

Study treatment will be compounded and shipped to the University of Iowa IDS Pharmacy by NuCara Pharmacy. All treatment capsules will be compounded to have similar appearance, color, taste, and markings between active treatment capsules and placebo capsules. The NuCara Pharmacy will be responsible for all regulatory requirements for dispensing of treatment, including packaging and labeling requirements. Additionally, the NuCara Pharmacy will be responsible for documenting the codes of the treatment bottles that are dispensed.

On Day 1 of the study, the participant will be given a 1 month supply for their initial titration medication, either terazosin or placebo per randomization, and a 2 month supply of the 5mg capsules. At each visit, participants will bring their medication bottles to the investigator who will be responsible for counting the reamining capsules and checking medication compliance.

An investigator is responsible for ensuring product accountability records are maintained throughout the course of the study. The inventory will include details of treatment bottles received and dispensed to subjects, batch, and ID numbers. All unused capsules must be kept until reconciliation of delivery records with accountability logs by the monitor. An accounting must be made of any drug deliberately or accidentally destroyed. Discrepancies between the number of capsules received and dispensed drug must be reconciled.

5.3 Concomitant Interventions

5.3.1 Required Concomitant Medications/Interventions

No specific concomitant medications/interventions are required for this study. Participants will continue to receive their normal level of care from their providers, and any concomitant medications initiated by outside providers will be dispensed by the subject's preferred pharmacy. Any time that a new medication is prescribed to a participant, they are to contact their site to report this change in therapy to ensure that it is allowed.

5.3.2 Prohibited Medications/Interventions

Subjects are prohibited from taking doxazosin, alfuzosin, prazosin, terazosin, urapadil, or tamsulosin during this study. If one of these medications is prescribed during the course of the study, the participant will be informed that initiation of any of these treatments will result in their immediate withdrawal from the study. They may decide if they wish to receive the prescribed treatment from their outside provider. If the subject decides to not initiate the prohibited treatment, they may remain in the study.

5.4 Subject compliance

Subject compliance will be assessed at each study visit via pill counts. Specifically, study intervention will be dispensed in prescription bottles and subjects will be asked to bring their bottles to each visit so that compliance can be assessed. See section 5.2 for additional information.

6 CLINICAL AND LABORATORY EVALUATIONS/STUDY PROCEDURES

6.1 Schedule of Activities

Evaluation	*Screening (-90 days)*	*Day 1*	*2 wks*	*3 wks*	*4 wks*	*5 wks*	*6 wks*	*9 wks*	*12 wks*
Written Informed Consent	*X*								
Inclusion/Exclusion Review	*X*	*X*							
Documentation of Disease/Disorder	*X*	*X*							
Hoehn & Yahr	*X*	*X*	*X*				*X*		*X*
Medical History • *Overall Medical History* • *Medical History of PD*	*X*	*X*					*X*		*X*
Concomitant medication review	*X*	*X*	*X*				*X*		*X*
Orthostatics[a]	*X*	*X*	*X*				*X*		*X*
MDS-UPDRS Motor assessment[b]	*X*	*X*	*X*				*X*		*X*
Physical examination	*X*	*X*					*X*		*X*
Randomization[c]		*X*							
Dispense Study Drug[d]		*X*							
Blood Draw		*X*[c]					*X*		*X*
MRI		*X*[c]							*X*
Neurological examination	*X*	*X*					*X*		*X*
Body weight and height	*X*	*X*	*X*				*X*		*X*
Vital signs	*X*	*X*	*X*				*X*		*X*

Finger Tapping Assessments		*X*	*X*				*X*		*X*
Behavioral Assessments • *Columbia Suicide Severity Rating Scale Questionnaire for Compulsive Disorders (C-SSRS)* • *Beck Anxiety Inventory* • *Beck Depression Inventory* • *Parkinson's Disease Questionnaire (PDQ-39)*	*X*[e]	*X*	*X*[f]				*X*		*X*
Sleep assessment • *Pittsburgh Sleep Quality Index*		*X*					*X*		*X*
Recent Falls			*X*	*X*	*X*	*X*	*X*	*X*	*X*
Cognitive Assessments • *Hopkins Verbal Learning Test (HVLT)* • *Symbol Digit Modalities Test (SDMT)* • *MoCa*		*X*					*X*		*X*
Auditory/Speech Assessment		*X*	*X*				*X*		*X*
Pregnancy Test for Women of Child-Bearing potential	*X*	*X*	*X*				*X*		
Timed Up and Go Assessment		*X*	*X*				*X*		*X*
Drug Accountability/ Compliance			*X*	*X*	*X*	*X*	*X*	*X*	*X*
Adverse Event Review			*X*	*X*	*X*	*X*	*X*	*X*	*X*

a) Participants will lie in the supine position for 5 minutes and have their blood pressure checked. The patient will then sit up for 1 minute and have their blood pressure re-checked. The patient will then stand for 3 minutes and have their blood pressure checked. If the participant has a decrease in the systolic blood pressure by 20 or more mmHg after standing for 3 minutes, or a decline of 10 or more mmHg in the diastolic blood pressure, they will be considered to have orthostatic hypotension.

b) *All MDS-UPDRS Motor Assessments will be collected when the participant is in the practically defined OFF state, meaning they have not taken their dopaminergic PD medications for > 6 hours at the time of assessment; this assessment will be video recorded to ensure rater reliability*
c) *Baseline assessments on day 1 will occur PRIOR to randomization or the study drug being dispensed after the site coordinator has determine the subject is still eligible for participation.*
d) *This will be performed twice at the baseline visit: prior to administration of TZ and 3 hours after administration of TZ*
e) *Only the Beck Depression, Beck Anxiety, and C-SSRS will be assessed at the screening visit, per exclusion criteria*
f) *At the Week 2 visit only the PDQ-39 will be assessed.*

6.2 Timing of Study Activities

6.2.1 Screening/Pre-Randomization Evaluations/procedures

Individuals identified at each site to potentially be eligible for inclusion will first be informed about the study and asked if they wish to receive more information. If the subject answers in the affirmative, approved staff will first go through the informed consent document with the subject and answer any questions that the subject may have. Specifically, the participant will be informed that signing this informed consent document does not guarantee that they will included in the study. It simply allows the study sites to perform the necessary screening procedures to determine if the participant is eligible for randomization. If the participant signs the informed consent document, the participant will then be screened. This will include the following assessments:

- Review of inclusion/exclusion criteria
- Documentation of PD
- Hoehn & Yahr
- Review of concomitant medications/prohibited medications
- Orthostatics
- Medical history
- A physical exam
- Neurological exam
- Body weight and height
- Vital signs
- MDS-UPDRS Motor assessment
- Beck Depression Inventory, Beck Anxiety Inventory, Columbia-Suicide Severity Rating Scale

If the participant is found to be eligible for randomization based on this screening visit, their first baseline visit will be scheduled. The baseline visit must be scheduled within 90 days of the initial screening visit. If the participant is unable to schedule their baseline visit within 90 days of the screening visit, they may still be eligible for inclusion, but they will need to be re-screened.

After all assessments are completed, the site investigator will review the available data and ensure that the participant is eligible for randomization. If so, the participant will be randomized at Day 1. They will then be dispensed their study treatment packs. The participants will then have their blood drawn and then have their MRI. Immediately following this initial MRI, they will take their first dose of TZ 1mg or placebo. They will then wait 3 hours from that time, during which the other study assessments may be completed. After three hours from the time that they took their TZ, they will have their blood drawn again, and will then undergo another MRI study.

6.2.2 On-Study/On-Interventions Evaluations/procedures

At each study visit, subjects will undergo the following assessments:

- Hoehn & Yahr
- Concomitant medication review
- Orthostatics
- Height and weight
- Vital signs
- Physical examination
- Neurological examination
- MDS-UPDRS Motor Assessment
- Cognitive Assessments
- Behavioral Assessments
- Sleep Assessments
- Fall Assessments
- Speech Assessments
- Motor Assessments

- Blood Draw
- Drug accountability/compliance
- Adverse Event Review

The likelihood of adverse events is highest near the initiation of study drug or at the time of dose escalation[34]. Therefore, subjects will be contacted via telephone the following 3 weeks (weeks 3, 4 & 5) after starting study drug and after the 2 week visit. They will then be seen halfway through the study at 6 weeks. They will again be contacted 9 weeks after their baseline visit via telephone by the research coordinator, and their final visit will be 12 weeks after their baseline visit.

6.2.3 Study Medication Discontinuation Evaluations/procedures

Study medication discontinuation will occur under the following circumstances:

- Completion of study
- Presence of orthostatic hypotension
- Blood pressure of ≤90/60
- Participant initiates prohibited medication
- Participant reports unwillingness to continue with study due to intolerable side effects

If any of the above occurs, participants will be asked to come in for an end-of-study visit as soon as possible. All assessments outlined in the SoA will be performed at the end-of-study visit. Participants will not be required to continue for future follow-up appointments after discontinuation of treatment. Participants who experience adverse effects will immediately discontinue study treatment and will not be considered for inclusion in further evaluations.

6.2.4 On Study/Off-Intervention Evaluations

This trial will follow an intention-to-treat design. Subjects who discontinue study medication (see section 6.2.3) will be asked to continue to be followed for the remainder of the study, but will not be taking a study intervention. The following assessments will be performed at all on study/off-intervention visits:

- Hoehn & Yahr
- Concomitant medication review
- Orthostatics
- Height and weight
- Vital signs
- Physical examination
- Neurological examination
- MDS-UPDRS Motor Assessment
- Cognitive Assessments
- Behavioral Assessments
- Sleep Assessments
- Fall Assessments
- Speech Assessments
- Motor Assessments
- Blood draw

If participants are unable or unwilling to continue with the regularly-scheduled assessments after discontinuation of the study intervention, they will be encouraged to return to the study site for a final evaluation that will include the same assessments as listed above.

6.2.5 Final On-Study Evaluations

The final On-Study Evaluation will be comprised of the following assessments:

- Hoehn & Yahr
- Concomitant medication review
- Orthostatics
- Height and weight
- Vital Signs

- Physical examination
- Neurological examination
- MDS-UPDRS Motor Assessment
- Cognitive assessments
- Behavioral Assessments
- Sleep assessments
- Fall Assessments
- Speech Assessment
- Motor Assessments
- Blood draw
- Drug accountability/compliance
- Adverse Event Review

6.2.6 Off-Study Requirements

No off-study requirements after the final evaluation will be employed for this study.

6.2.7 Pregnancy

Per the exclusion criteria, female who are pregnant will be excluded from this study. Terazosin has been designated a pregnancy category C medication by the FDA. Therefore, if a subject were to become pregnant while taking the active treatment, it is unclear if this would pose a risk to the developing fetus. As a result, females who are capable of becoming pregnant during the study should be screened with a urine-dipstick pregnancy test at their screening visit, prior to randomization, and at their 6-week visit. Females participants must also practice a highly effective method of contraception (i.e., oral contraceptives, a barrier method of birth control such as condoms or a diaphragm, intrauterine devices, partner with vasectomy, or sexual abstinence).

6.3 SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS

6.3.1 Informed Consent

Written informed consent will be obtained from each subject before any study-specific procedures or assessments are performed and after the aims, methods, anticipated benefits, and potential hazards are explained. Written informed consent will be obtained from each participant by authorized personnel prior to undergoing screening and prior to randomization. The subject's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the subject with the date of that signature indicated. The investigator will keep the original consent forms and copies will be given to the subjects. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the subject will be given to all subjects. HIPAA guidelines for confidentiality and the principles of medical ethics will be adhered to during the study.

6.3.2 Protocol Violations

Protocol violations will be defined as any of the following:

- Inadequate or delinquent informed consent
- Inclusion/exclusion criteria not met
- Unreported serious adverse events
- Improper breaking of blinding
- Use of prohibited medications
- Missed visits
- Inadequate record keeping
- Non-compliance with study requirements

6.3.3 Documentation of Parkinson's Disease

Participants must have a documented diagnosis of PD that fits with the UK Brain Bank Diagnostic Criteria (Appendix A).

6.3.4 Medical History

As part of the initial screening for inclusion in the study, participants will provide all comorbidities and their approximate time of diagnosis (Appendix B). At each visit, the participant will be asked to provide any newly diagnosed comorbidities.

6.3.5 Treatment History

Participants will be asked to provide a full history of any medications, over-the-counter products, herbal supplements, nutraceuticals, or devices that have been used for the treatment of PD or PD-related symptoms. They will also be asked to recollect (to the best of their knowledge) the timing of these treatments (i.e. when did they start the medication, when were dosage adjustments made, when was the treatment stopped). For medications that were used specifically for the treatment or relief of symptoms of PD, participants will be asked what the reason for discontinuation was, if applicable. Participants will also be asked to provide information about dosages, dosage form (capsule, tablet, etc) route of administration, dosing schedule (Appendix C)

6.3.6 Concomitant Medications/Treatments

In addition to PD-related treatment history, all concomitant medications they are currently taking. Participants will also be asked to provide information about dosages, dosage form (capsule, tablet, etc) route of administration, dosing schedule(Appendix D).

6.3.7 Protocol Amendments and Study Termination

All revisions and/or amendments to this protocol must be approved in writing by IRB. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the IRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

Any revisions to the protocol that will change the number or frequency of evaluations that a participant undergoes will require the participant to sign an updated written informed consent.

6.3.8 Clinical Assessments

- Hoehn & Yahr
    - Collected to measure disease severity as well as progression throughout study
- Orthostatics
    - Collected to measure if participants are having worsening orthostatic hypotension.
    - If orthostatic hypotension is present, this assessment will NOT be able to determine if it is secondary to the study medication or autonomic failure that occurs in PD.
- Physical examination
    - This will be a simple physical exam to measure the general health of the participant independent of their PD
- MDS UPDRS Part 3
    - This portion of the MDS-UPDRS specifically measures motor function. This will only be collected when subjects are in the practically defined "off-period" meaning that they have not taken their PD medications within 6 hours of the assessment
- MDS-UPDRS Part 4
    - This portion of the MDS-UPDRS will use historical and objective information to assess the motor complications of dyskinesia and motor fluctuations including off-state dystonias
- Vital signs/Height & Weight

- Participants will have their heart rate, respiratory rate, blood pressure, and core body temperatures measured as well as their height and weight
- Neurological Exam

6.3.9 Laboratory Evaluations

Women of child-bearing potential will have a urine-dipstick pregnancy test performed at their screening visit, their baseline/randomization visit, and at their 6 week visit. The site PI must verify each result and indicate that the results are "Negative" or "Positive". If the results are "negative", this indicates that the subject is not pregnant. If the results are "positive" this indicates that the subject is pregnant and must discontinue study drug.

The MRI studies are being conducted to perform MR Spectroscopy in an attempt to quantify ATP levels in the brain.

The blood draws are being conducted to collect red blood cells. These samples will be sent immediately to the lab of Dr. Michael Welsh, where they will be analyzed to quantify ATP levels in the red blood cells.

6.3.10 Pharmacokinetic Studies

N/A

6.3.11 Other Laboratory Studies

All randomized participants will have the option of having their blood drawn at each visit. Within the informed consent documents, subjects will have the option to donate blood or not. The subjects will be informed that the blood samples are being collecting for the sake of bio-banking meaning that the blood is being collected without a specific assay in mind. It is possible that these samples will be used for genome-wide studies in the future as well as assays aimed at quantifying ATP levels in red blood cells.

6.3.12 Questionnaires

- MDS-UPDRS Part 1
  - This will measure Non-motor experiences of daily living
- MDS-UPDRS Part 2
  - This will measure Motor experiences of daily living
- The following cognitive assessments will be performed
  - Hopkins Verbal Learning Test (HVLT)
  - Symbol Digit Modalities Test (SDMT)
  - Montreal Cognitive Assessment (MoCA)
- Pittsburgh Sleep Quality Index
  - Assessment of sleep quality
- The following behavioral assessments will be performed to test depression, compulsiveness & anxiety
  - Beck Depression Inventory (BDI)
  - Beck Anxiety Inventory (BAI)
  - Columbia Suicide Severity Rating Scale (C-SSRS)
  - Parkinson's Disease Questionnaire (PDQ-39)

6.3.13 Subject Adherence Assessments

The site pharmacies will document subject adherence at each visit by pill count.

7 MANAGEMENT OF ADVERSE EXPERIENCES

The expected adverse experiences from use of TZ include orthostatic hypotension, palpitations, peripheral edema, nausea, asthenia, dizziness, headache, somnolence, nasal congestion, syncope, intraoperative floppy iris syndrome, and priapism. Participants who experience side effects that are found to be intolerable by the subject or the site investigator will discontinue study drug. If discontinuation of the study drug occurs in between visits, subjects will be encouraged to return to the site for their end of study assessment.

8 CRITERIA FOR INTERVENTION DISCONTINUATION

Study medication discontinuation will occur under the following circumstances:

- Completion of study
- Presence of orthostatic hypotension
- Blood pressure of ≤90/60
- Participant initiates prohibited medication
- Participant reports unwillingness to continue with study due to intolerable side effects

Participants who discontinue study medication will be encouraged to undergo all remaining study assessments.

9 STATISTICAL CONSIDERATIONS

9.1 Outcomes

9.1.1 Primary Outcome (including definition)

The primary outcome measure will be the safety and tolerability of TZ in the select patient population. This will be assessed by comparing the number of participants in each group that experience drug-related adverse drug events as well as assessing the rate of drop out in each group.

To assess the mean change in systolic and diastolic blood pressures at 6 weeks and 12 weeks between the active and placebo groups.

9.1.2 Secondary Outcome(s)

- Mean change in systolic and diastolic blood pressure from baseline to 6 weeks and 12 weeks
- Prevalence of falls between placebo and active group
- Prevalence of intolerable side effects between placebo and active group
- Prevalence of study discontinuation between placebo and active group
- Differences in overall compliance between placebo and active group

9.1.3 Exploratory Outcome(s)

- Difference in ATP levels in red blood cells and brain within subjects before and after taking study drug on day 1
- Difference in ATP levels in red blood cells and brain within subjects at 6 and 12 weeks compared to baseline reading
- Difference in ATP levels in red blood cells and brain between groups at 6 weeks and 12 weeks
- Slope of change over 12 weeks of the MDS-UPDRS Part 1
- Slope of change over 12 weeks of the MDS-UPDRS Part 2
- Slope of change over 12 weeks of the MDS-UPDRS Part 3 (OFF)
- Slope of change over 12 weeks of the MDS-UPDRS Part 4 (OFF)
- Absolute change over 12 weeks of the MDS-UPDRS Parts 1, 2, 3, 4, and TMS (OFF)

- Slope of change over 12 weeks of MDS-UPDRS TMS (OFF) (direct comparison for efficacy)
- Slope of change over 12 weeks of the Hoehn & Yahr Score
- Slope of change over 12 weeks of all cognitive assessments between placebo and active group
- Slope of change over 12 weeks of sleep assessments between placebo and active group
- Slope of change over 12 weeks of behavioral assessments between placebo and active group

9.2 Sample Size and Accrual

This is a pilot study and the sample size was chosen based on available funding and resources

9.3 Data Monitoring

All aspects of the study will be monitored by the PI of the study. Monitoring will be conducted according to Good Clinical Practice and applicable government regulations. The investigator agrees to allow monitors access to the clinical supplies, dispensing and storage areas, and to the clinical files of the study subjects, and, if requested, agrees to assist the monitors.

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device. FDA and Office of Human Research Protection (OHRP) requirements for reporting AEs will be followed. Subjects will be monitored for AEs from the time they sign consent until 30 days following permanent discontinuation of study drug. At that point, all ongoing AEs will be followed to resolution, but no new AEs will be recorded.

The PI and research team (co-Investigators, research nurse, clinical trial coordinator) are responsible for identifying and reporting AEs and determining the relationship of the event to the study drug/study procedures.

9.4 Data Analyses

The following outcome measures will be analyzed under an intention-to-treat protocol. All randomized individuals will be included regardless of their final treatment status.

- Primary Outcome
    - Rate of drop out between groups
        - Chi-square
    - Rate of adverse events between groups
        - Chi-square
- Secondary outcomes
    - Prevalence of orthostatic hypotension between placebo and active group
        - Chi-square
    - Prevalence of falls between placebo and active group
        - Chi-square
    - Differences in overall compliance between placebo and active group
        - Linear mixed effect models that includes compliance at each study visit for each participant
- Exploratory outcomes
    - Difference in ATP levels in red blood cells and brain within subjects before and after taking study drug on day 1
        - Paired samples t-test
    - Difference in ATP levels in red blood cells and brain within subjects at 6 and 12 weeks compared to baseline reading

        - Paired samples t-test
    - Difference in ATP levels in red blood cells and brain between groups at 6 weeks and 12 weeks
        - Independent samples t-test
    - Slope of change over 12 weeks of the MDS-UPDRS Part 1
        - LMER
    - Slope of change over 12 weeks of the MDS-UPDRS Part 2
        - LMER
    - Slope of change over 12 weeks of the MDS-UPDRS Part 3
        - LMER
    - Slope of change over 12 weeks of the MDS-UPDRS Part 4
        - LMER
    - Absolute change over 12 weeks of the MDS-UPDRS Parts 1, 2, 3, 4, and TMS
        - Independent samples t-tests
    - Slope of change over 12 weeks of MDS-UPDRS TMS (direct comparison for efficacy)
        - LMER
    - Slope of change over 12 weeks of the Hoehn & Yahr Score
        - LMER
    - Slope of change over 12 weeks of all cognitive assessments between placebo and active group
        - LMER
    - Slope of change over 12 weeks of sleep assessments between placebo and active group
        - LMER
    - Slope of change over 12 weeks of behavioral assessments between placebo and active group
        - LMER

10 DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

10.1 Data Management

Site personnel will collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The PI will monitor clinical sites to ensure compliance with data management requirements and Good Clinical Practices. The PI is responsible for developing, testing, and managing clinical data management activities.

10.1.1 Data Entry

Data will be entered in RedCap. Data quality assurance and analyses will be performed by the PI.

Data collection for this study will be accomplished with paper forms that will be transcribed into RedCap. The paper forms will be stored in a locked filing cabinet in a locked office, in a badge-access area.

10.2 Role of Data Management

Data Management (DM) is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with University of Iowa policies, and applicable Sponsor and regulatory requirements.

10.3 Adverse Experience Reporting

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and International Conference on Harmonization (ICH) guidelines. The PI will carefully monitor each subject throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Receipt will be kept in the investigator's study file.

An adverse event is defined as: "an unfavorable and unintended sign, symptom, or disease associated with a subject's participation in this research trial."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

Unexpected adverse event is defined as any adverse experience…the specificity or severity of which is not consistent with the risks described in the protocol.

Expected adverse events are those that are known to be associated with or have the potential to arise as a consequence of participation in the study.

On-line Adverse Event Reporting System

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The PI will prepare a Medwatch safety report for submission to the FDA.

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the PI within 24 hours.

10.3.1 Definitions of Adverse Events, Suspected Adverse Drug Reactions & Serious Adverse Events

10.3.1.1 Adverse Event and Suspected Adverse Drug Reactions

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the

trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

Clinical → symptoms reported by the subject or signs detected on examination.

Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures: the results of which are not being captured as AEs).

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the Site Investigator.

An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with the current Investigators Brochure or package insert or described in the protocol. An unexpected, suspected adverse drug reaction is any unexpected adverse event that, in the opinion of the Site Investigator or Sponsor, there is a reasonable possibility that the investigational product caused the event.

10.3.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study subject, in the view of the Site Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled “procedure” or a “treatment” is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This serious criterion applies if the “disability” caused by the reported AE results in a substantial disruption of the subject’s ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an *adverse* experience, and will therefore, not be considered an SAE. An example of this would include a social admission (subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE that, in the opinion of the Site Investigator or Sponsor, suggests a reasonable possibility that the investigational product caused the event.

The Site Investigator is responsible for classifying adverse events as serious or non-serious.

10.3.1.3 Assessment and Recording of Adverse Events

Assessment of Adverse Events

At each visit (including telephone interviews), the subject will be asked "Have you had any problems or symptoms since your last visit?" in order to determine the occurrence of adverse events. If the subject reports an adverse event, the Investigator will determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the Site Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.
3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject. (suspected ADR)
4. Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state. (suspected ADR)
5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (suspected ADR)

Recording of Adverse Events

All clinical adverse events are recorded in the Adverse Event (AE) Log in the subject's study binder. The site should fill out the AE Log and enter the AE information into the online Adverse Event Reporting System within 5 working days of the site learning of a new AE or receiving an update on an existing AE.

Please Note: Serious Adverse Events (SAEs) must be reported to the NeuroNEXT Data Coordinating Center within 24 hours of the site learning of the SAE.

Entries on the AE Log (and into the online Adverse Event Reporting System) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

Adverse Events and Serious Adverse Events - Reportable Events

The following are considered reportable events and must be reported to the PI within 24 hours of the site being notified of the event.

- All events that meet the above criteria for Serious Adverse Events (SAEs)

All occurrences of Serious Adverse Events (SAEs) must be reported within 24 hours of discovery of the event. All other Adverse Events (AEs) must be reported within *insert timeline for reporting* (of discovery of the event).

11 HUMAN SUBJECTS

Documented approval from the IRB will be obtained for all participating centers prior to clinical trial start, according local laws, regulations and organization. When necessary, an extension, amendment or renewal of the IRB approval must be obtained.

Evidence of training in responsible conduct of research shall be on file for each PI and co-investigator.

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix A) and any subsequent modifications will be reviewed and approved by the University of Iowa IRB responsible for oversight of the study. A signed consent form, approved by the IRB, will be obtained from the subject. For subjects who cannot provide consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the clinical study site will be identified only by the study specific Subject Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using study specific SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the OHRP, the sponsor, or the sponsor's designee.

11.2.1 Certificate of Confidentiality

To further protect the privacy of study subjects, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to subjects.

11.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected. If the study is terminated or suspended, the PI will promptly inform study subjects, the IRB, and sponsor and provide the reason(s) for the termination or temporary suspension.

12 FUTURE USE OF STORED SPECIMENS AND DATA

Within the informed consent documents, participants will have the options to either opt in or opt out of having their blood drawn and stored for future use. For subjects who opt to have their blood drawn and stored, the biospecimens will be stored at the University of Iowa. The tubes will be stored with only the subject's ID number to protect confidentiality. Future studies that will require use of clinical data that was obtained during the course of this study will require review by the institutional IRB to ensure proper actions are taken to protect confidentiality. All clinical data will be deidentified and include only the subject ID as the primary identifier. Samples will be stored for up to five years.

13 STUDY RECORDS RETENTION

All records pertaining to this study will be made publicly available, in accordance with NIH Policies. Therefore, all available data will be made electronically available for a time period specified by the NIH. In addition, all records related to this study will be kept for a minimum of five years by the investigator. Destruction of records after five years will be done only after permission has been requested and granted from the NINDS.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies of the ICTS at the University of Iowa.

15 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NINDS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

16 REFERENCES

1. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. The Lancet Neurology 2006;5:525-535.
2. Senard JM, Rai S, Lapeyre-Mestre M, et al. Prevalence of orthostatic hypotension in Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;63:584-589.
3. Chaudhuri KR, Odin P. The challenge of non-motor symptoms in Parkinson's disease. Prog Brain Res 2010;184:325-341.
4. Collier TJ, Kanaan NM, Kordower JH. Ageing as a primary risk factor for Parkinson's disease: evidence from studies of non-human primates. Nat Rev Neurosci 2011;12:359-366.

5. Saxena U. Bioenergetics failure in neurodegenerative diseases: back to the future. Expert Opin Ther Targets 2012;16:351-354.
6. Cunnane S, Nugent S, Roy M, et al. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition 2011;27:3-20.
7. Hoyer S. Brain glucose and energy metabolism during normal aging. Aging (Milano) 1990;2:245-258.
8. Firbank MJ, Yarnall AJ, Lawson RA, et al. Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study. J Neurol Neurosurg Psychiatry 2017;88:310-316.
9. Hattingen E, Magerkurth J, Pilatus U, et al. Phosphorus and proton magnetic resonance spectroscopy demonstrates mitochondrial dysfunction in early and advanced Parkinson's disease. Brain 2009;132:3285-3297.
10. Schapira AH, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem 1990;54:823-827.
11. Pyle A, Anugrha H, Kurzawa-Akanbi M, Yarnall A, Burn D, Hudson G. Reduced mitochondrial DNA copy number is a biomarker of Parkinson's disease. Neurobiol Aging 2016;38:216 e217-216 e210.
12. Mortiboys H, Johansen KK, Aasly JO, Bandmann O. Mitochondrial impairment in patients with Parkinson disease with the G2019S mutation in LRRK2. Neurology 2010;75:2017-2020.
13. Blesa J, Phani S, Jackson-Lewis V, Przedborski S. Classic and new animal models of Parkinson's disease. J Biomed Biotechnol 2012;2012:845618.
14. Schapira AH. Mitochondria in the aetiology and pathogenesis of Parkinson's disease. The Lancet Neurology 2008;7:97-109.
15. Chen X, Zhao C, Li X, et al. Terazosin activates Pgk1 and Hsp90 to promote stress resistance. Nat Chem Biol 2015;11:19-25.
16. Achari R, Laddu A. Terazosin: a new alpha adrenoceptor blocking drug. J Clin Pharmacol 1992;32:520-523.
17. Sakaue S, Kasai T, Mizuta I, et al. Early-onset parkinsonism in a pedigree with phosphoglycerate kinase deficiency and a heterozygous carrier: do PGK-1 mutations contribute to vulnerability to parkinsonism? NPJ Parkinsons Dis 2017;3:13.
18. Kaufmann H, Goldstein DS. Autonomic dysfunction in Parkinson disease. Handb Clin Neurol 2013;117:259-278.
19. Heikkila RE, Hess A, Duvoisin RC. Dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine in mice. Science 1984;224:1451-1453.
20. Ungerstedt U. 6-Hydroxy-dopamine induced degeneration of central monoamine neurons. Eur J Pharmacol 1968;5:107-110.
21. Coulom H, Birman S. Chronic exposure to rotenone models sporadic Parkinson's disease in Drosophila melanogaster. J Neurosci 2004;24:10993-10998.
22. Boyd PJ, Tu WY, Shorrock HK, et al. Bioenergetic status modulates motor neuron vulnerability and pathogenesis in a zebrafish model of spinal muscular atrophy. PLoS Genet 2017;13:e1006744.
23. Clark IE, Dodson MW, Jiang C, et al. Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. Nature 2006;441:1162-1166.
24. Lee SB, Kim W, Lee S, Chung J. Loss of LRRK2/PARK8 induces degeneration of dopaminergic neurons in Drosophila. Biochem Biophys Res Commun 2007;358:534-539.
25. Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M. alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. Proc Natl Acad Sci U S A 1998;95:6469-6473.
26. Rockenstein E, Mallory M, Hashimoto M, et al. Differential neuropathological alterations in transgenic mice expressing alpha-synuclein from the platelet-derived growth factor and Thy-1 promoters. J Neurosci Res 2002;68:568-578.
27. Lill CM. Genetics of Parkinson's disease. Mol Cell Probes 2016;30:386-396.

28. Nguyen HN, Byers B, Cord B, et al. LRRK2 mutant iPSC-derived DA neurons demonstrate increased susceptibility to oxidative stress. Cell Stem Cell 2011;8:267-280.
29. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology 2009;72:432-438.
30. Sotiriou E, Greene P, Krishna S, Hirano M, DiMauro S. Myopathy and parkinsonism in phosphoglycerate kinase deficiency. Muscle Nerve 2010;41:707-710.
31. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry 2004;75:637-639.
32. Patel A, Malinovska L, Saha S, et al. ATP as a biological hydrotrope. Science 2017;356:753-756.
33. Hayes MH, Peuchen EH, Dovichi NJ, Weeks DL. Dual roles for ATP in the regulation of phase separated protein aggregates in Xenopus oocyte nucleoli. Elife 2018;7.
34. Lowe FC. Safety assessment of terazosin in the treatment of patients with symptomatic benign prostatic hyperplasia: a combined analysis. Urology 1994;44:46-51.

17 Appendix A

UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.

18 Appendix B

Medical History of PD

Date Medical History Taken (m m/dd/yyyy):

1. Year of first symptoms as confirmed by history obtained by the physician?
2. Year of Initial Diagnosis?
3. Diagnostic Features/Criteria (as evident on clinical assessment of the patient):
   a. 4-6 Hz Rest Tremor: ☐ Present ☐ Absent ☐ Unknown
   b. Bradykinesia: ☐ Present ☐ Absent ☐ Unknown
   c. Rigidity: ☐ Present ☐ Absent ☐ Unknown
   d. Asymmetric Onset: ☐ Present ☐ Absent ☐ Unknown
   e. Substantial Response to Dopaminergic Therapy: ☐ Present ☐ Absent ☐ Unknown
4. Degree of Certainty of Diagnosis of PD:
   ☐ 90-100% Certain ☐ 50-89% Certain ☐ 10-49% Certain ☐ 0-9% Certain
   Other important diagnostic alternative(s) (give reason):
5. Initial motor symptoms, i.e., as described by the patient (Please check all that apply):
   ☐ Tremor (including internal tremor)
   ☐ Stiffness
   ☐ Change in facial expression
   ☐ Disturbances of dexterity
   ☐ Micrographia
   ☐ Weakness
   ☐ Dystonia (specify symptoms)
   a. Ambulatory/Axial Difficulties:
      ☐ Freezing
      ☐ Lack of arm swing
      ☐ Leg Dragging
      ☐ Shuffling of gait
      ☐ Postural imbalance (excluding falls)

☐ Falls
☐ Slowness of gait
☐ Other abnormality of posture or gait (other, specify)

6. Side of Body of Initial Symptoms:
   ☐ Right ☐ Left ☐ Bilateral ☐ Midline ☐ Unknown
7. Motor symptoms developing over the course of illness (Please check all that applies):
   ☐ Tremor (including internal tremor) - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
   ☐ Stiffness - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
   ☐ Micrographia - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
   ☐ Change in facial expression - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
   ☐ Disturbances of dexterity - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
   ☐ Weakness - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
   ☐ Dystonia - Approximate date of onset (m m/dd/yyyy): ☐ Unknown

   a. Ambulatory/Axial Difficulties:
      ☐ Freezing - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
      ☐ Lack of arm swing - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
      ☐ Leg Dragging - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
      ☐ Shuffling of gait - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
      ☐ Postural imbalance (excluding falls) - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
      ☐ Falls - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
      ☐ Slowness of gait - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
      ☐ Stooped posture - Approximate date of onset (m m/dd/yyyy): ☐ Unknown
      ☐ Other abnormality of posture or gait (other, specify) – Approximate date of onset (m m/dd/yyyy): ☐ Unknown

General Instructions

Medical history data are collected to help verify the inclusion and exclusion criteria (e.g., no history of cognitive disabilities), ensure the participant/subject receives the appropriate care, and describe the study population. The Parkinson's disease Medical History CRF captures conditions specifically related to PD as opposed to a more general Medical History which captures conditions that occurred at some point in time within a protocol-defined period.

Important note: None of the data elements included on this CRF Module are classified as Core (i.e., strongly recommended for all Parkinson's disease clinical studies to collect). The remaining data elements are classified as supplemental (i.e., non Core) and should only be collected if the research team considers them appropriate for their study. Please see the Data Dictionary for element classifications.

Specific Instructions

Please see the Data Dictionary for definitions for each of the data elements included in this CRF Module. History can also be obtained from a family member, friend, or chart/ medical record. If the informant is unable to answer the question or is deemed unreliable (e.g., the participant/ subject has dementia) the history should be obtained from the medical record.

Additional instructions for the elements are already included on the CRF.

19 Appendix C

PD Medication History

Did the subject ever take any non-study PD medications?

☐ Yes (Follow instructions below) ☐ Unknown

☐ No

Please record all PD medications the subject has ever taken (including PD medications the subject has taken while participating in the study). Enter each dose change on a new line. All other medications (i.e., non-PD medications) should be recorded on the Non-PD Medications Log.

PD Medication Class Reference

Parkinson's Disease-Medication Class Reference.

Class Reference Table

Levodopa	Dopamine agonists	MAO-B inhibitors	COMT inhibitors	Antiglutamat agents	Anticholinergics	Other, specify

PD Medication Name Reference

Parkinson's Disease Medication Name Reference

Name Reference Table

1 Alpha-Dihydroergocryptine	Budipine	L-Dopa Methylester	Lisuride	Pramipexole	Selegiine standard oral
Amantadine	Cabergoline	L-Dopa Slow Release	Mematine	Rasagiline	Selegiline patch
Apomorphine	Entacapone	L-Dopa Soluble	Pergolide	Ropinirole	Selegiline sublingual
Bromocriptine	L-Dopa Duel Release	L-Dopa Standard	Piribedil	Rotigotine	Tolcapone

Parkinson's Disease Medication Log.

Medication Log Table

Line #	Medication Class	Medication Name (Trade or generic name)	Maximum Dose (Specify units)	Estimated Total Duration of Exposure (Check units)	Medication Use Ongoing?	If Applicable, Reason for Discontinuation
Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	☐ Years ☐ Months ☐ Weeks ☐ Days	☐ Yes ☐ No ☐ Unknown	☐ Lack of efficacy ☐ *Side Effect: ☐ Other:
Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	☐ Years ☐ Months ☐ Weeks ☐ Days	☐ Yes ☐ No ☐ Unknown	☐ Lack of efficacy ☐ *Side Effect: ☐ Other:
Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	☐ Years ☐ Months ☐ Weeks ☐ Days	☐ Yes ☐ No ☐ Unknown	☐ Lack of efficacy ☐ [1]Side Effect: ☐ Other:
Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	☐ Years ☐ Months ☐ Weeks ☐ Days	☐ Yes ☐ No ☐ Unknown	☐ Lack of efficacy ☐ [2]Side Effect: ☐ Other:
Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	☐ Years ☐ Months ☐ Weeks ☐ Days	☐ Yes ☐ No ☐ Unknown	☐ Lack of efficacy ☐ [3]Side Effect: ☐ Other:

[1] Common Side Effects
[2] Common Side Effects
[3] Common Side Effects

Line #	Medication Class	Medication Name (Trade or generic name)	Maximum Dose (Specify units)	Estimated Total Duration of Exposure (Check units)	Medication Use Ongoing?	If Applicable, Reason for Discontinuation
Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	☐ Years ☐ Months ☐ Weeks ☐ Days	☐ Yes ☐ No ☐ Unknown	☐ Lack of efficacy ☐ [4]Side Effect: ☐ Other:
Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	Data to be filled out by site	☐ Years ☐ Months ☐ Weeks ☐ Days	☐ Yes ☐ No ☐ Unknown	☐ Lack of efficacy ☐ [5]Side Effect: ☐ Other:

Side Effects Table

AA = Motor offs (including wearing off and sudden off)	DD = Cognitive impairment – not dementia	GG = Autonomic dysfunction	JJ = ICD (including Gambling, Hypersexuality, Binge eating, Shopping)	MM=Dopamine agonist withdrawal
BB = Dyskinesia	EE= Non-motor offs, specify:	HH= Daytime sleep abnormalities	KK=Punding	OT = Other important side effects, specify
CC = Hallucination/psychosis	FF - Behavioral disturbances specify:	II = Nighttime sleep abnormalities	LL=Dopadysregulation syndrome	

[4] Common Side Effects
[5]Common Side Effects from Medication

General Instructions

The Parkinson's disease medication log provides information about current non-study PD medications the participant/ subject has taken in his/her lifetime. Study PD medications should not be listed on this CRF.
The PD Medication Log was created as an alternative to the Prior and Concomitant Medication CDEs that are available under the General CDE Data Standards. For example, in a PD population, patients may be able to recall 'duration' with greater accuracy than they can recall specific medication start and stop dates.
Important note: Three of the data elements included on this CRF Module are classified as Core (i.e., strongly recommended for all Parkinson's disease clinical studies to collect). The remaining data elements are classified as supplemental (i.e., non Core) and should only be collected if the research team considers them appropriate for their study. Please see the Data Dictionary for element classifications.

Specific Instructions

Please see the Data Dictionary for definitions for each of the data elements included in this CRF Module.
The majority of the data elements on the CRF have the following instructions:
History can be obtained from participant/ subject, family member, friend, or chart/ medical record. In some studies it may be possible to ask the subject/ participant or a family member to bring in the pill bottles for all current medications.
Medication name – Please refer to the PD Medication Name Reference Chart. Additionally, please include the genric name or trade name of the medication.
Side effects – Please refer to the Common Side Effects chart for the codes of the possible side effects experienced from PD medications. Only capture the side effects code on this form. Specifics of the side effect (i.e., Severity, Relatedness, Outcome, etc) should be recorded on the General Adverse Events form if they occur during the study.
There are no other specific instructions for the data elements not already included on the CRF.

20 Appendix D

Non-PD Medication Log

Note: This is a template form. Please consider whether your study needs to collect additional data (e.g., exact timing for PRN medications) and if additional data are required add fields to this template or capture them on a separate form.

Did the subject take any medications before or during the study? (days***):***

☐ Yes (Follow instructions below)
☐ No
☐ Unknown

In the table below please record all non-Parkinson's Disease medications the participant/subject was taking at the time of the protocol-specified period indicated above. These can include prescription medications, over the counter drugs, vitamins, supplements, minerals, complementary/alternative medications etc.

Table 1: Non-Parkinson's Disease medications

Line #	Medication Name (Trade or generic name)	Total Daily Dose or PRN Dose (with units)	Start Date (M M/D D/Y Y Y Y)	End Date (M M/D D/Y Y Y Y)	Medication Use Ongoing?	*PRN Med?	If PRN, Average Frequency (with units e.g., times per month)	Indication
Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown	Data to be filled in by site	Data to be filled in by site
Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown	Data to be filled in by site	Data to be filled in by site
Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown	Data to be filled in by site	Data to be filled in by site
Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown	Data to be filled in by site	Data to be filled in by site
Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	Data to be filled in by site	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown	Data to be filled in by site	Data to be filled in by site

* "PRN Med?" asks whether the medication is taken on an as needed basis. NO should be answered for chronic medications that are taken on a regular basis.

General Instructions

The non-Parkinson's disease medication log provides information about non-PD medications the participant/ subject was taking prior to or during the study. Collecting non-PD medications taken prior to the study in a defined time window is important when there may be potential interactions with the study intervention. Thus, a potential subject may need to stop a medication prior to starting the study intervention (washout period). The study exclusion criteria may identify drugs that cannot be taken during the study and so prior medications are identified to determine whether an individual may be eligible for the study.

Important note: None of the data elements included on this CRF Module is classified as Core (i.e., strongly recommended for all Parkinson's disease clinical studies to collect). All data elements are classified as supplemental (i.e., non Core) and should only be collected if the research team considers them appropriate for their study. Please see the Data Dictionary for element classifications.

Specific Instructions

Please see the Data Dictionary for definitions for each of the data elements included in this CRF Module.

The majority of the data elements on the CRF have the following instructions:

History can be obtained from participant/ subject, family member, friend, or chart/ medical record. In some studies it may be possible to ask the subject/ participant or a family member to bring in the pill bottles for all non-PD medications.

There are no other specific instructions for the data elements not already included on the CRF.