Project Summary

**Title:** A double-blinded, randomized, placebo-controlled trial of pramipexole for Essential Tremor.

Essential tremor (ET) is one of the most prevalent neurologic disorders in the world that affects people of all ages. While treatment options are available the multifaceted nature of ET suggests there are several other ways to approach therapies. Dopaminergic medications, while not thoroughly investigated in ET, may be one area of research, providing ET patients with a different avenue for treatment. In this double-blind, randomized, placebo-controlled trial subjects will be given either pramipexole up to a dose of 4.5 mg per day or matching placebo in order to assess its effectiveness on tremor. The Essential Tremor Rating Assessment Scale (TETRAS) will be used to assess changes between baseline and study endpoint after 6 weeks of stable maintenance dose of study medication. Subjects will be allowed to titrate up to the highest tolerated dose of pramipexole to avoid unwanted side effects. The expected outcome of this project is to see an improvement in tremor as assessed by the essential tremor rating assessment scale (TETRAS). Other outcomes of interest include improvements in patient and clinician impression of change and improvements in activities of daily living.
clarify the possible link between a DRD3 variant and the pathogenesis of ET.

Developing ET, especially in women (21). Thus, given the current controversy, a dopaminergic probe is warranted to
receptor located on chromosome 3q13 (16). Only two association studies have associated the Ser9Gly variant with
Ser9Gly-ET association studies actually supports an association between the DRD3Gly variant and increased risk of
segregates with ET in the Icelandic families used to identify the ETM1 locus (20). Additionally, a meta-analysis of all
inherent heterogeneity of ET itself (19). To date, analyses have not been performed to determine if the DRD3 variant
suggested that the functional relevance of the DRD3 variant in the pathogenesis of ET may be of a synergistic effect with
failed to support the positive associations found in the two preliminary analyses (17-20). Even still, Vitale et al has
locus, a documented genetic marker of familial ET in Icelandic families (16). Attempts at replicating these results have
block of strong linkage disequilibrium in the Ser9Gly polymorphism in these studies was found to be similar to the ETM1
ischemia and methamphetamine administration by reducing the elevation of dopamine turnover and hydroxyl radical

As such, we are interested in exploring the possible connection between the DRD3 receptor and ET through the use
of the D3-selective dopamine agonist pramipexole. Using single photon computed emission tomography (SPECT) in
cerebellum of ET patients (7). Furthermore, it is known that the DRD3 receptor is expressed in cerebellar Purkinje cells
with Lewy bodies, labeled cerebellar ET; whereas 25% were found to harbor Lewy bodies predominantly in the locus coerulesus, dubbed Lewy Body Variant of ET (LBVET) (7). However, despite the recent increase in concern for identification of pathological abnormalities in ET, few clinical trials are accounting for the possible connection between genetic biomarkers and pathological evidence.

Preliminary Data

Dopaminergic medications have not been thoroughly investigated for the treatment of ET. Even still, support for
such therapy in the present study is derived from genetic and neuroimaging studies of ET, as well as pharmacologic analysis of pramipexole in other neurodegenerative diseases involved with Purkinje cell function. With respect to the genetics of ET, several loci have been identified thus far. More than half of reported cases of ET have identified an autosomal dominant mode of inheritance via FET1/ETM1 and ETM2 genetic variants on chromosomes 3q13 (8) and 2p24.1, respectively (9-12). In addition, another study found that roughly 16% of ET subjects compared to 0% of controls were heterozygous for the HS1-BP3 (hematopoietic-specific protein 1-binding protein 3) gene also found on chromosome 2 (13). A fourth possibility that has produced conflicting results thus far is the homozygous Ser9Gly variant of the DRD3 receptor located on chromosome 3q13.3 (16). Only two association studies have associated the Ser9Gly variant with earlier onset of ET and more severe ET symptoms than heterozygous individuals (14,15). Furthermore, the haplotype block of strong linkage disequilibrium in the Ser9Gly polymorphism in these studies was found to be similar to the ETM1 locus, a documented genetic marker of familial ET in Icelandic families (16). Attempts at replicating these results have failed to support the positive associations found in the two preliminary analyses (17-20). Even still, Vitale et al has suggested that the functional relevance of the DRD3 variant in the pathogenesis of ET may be of a synergistic effect with other genes associated with ET susceptibility with incongruence between association studies being possibly due to the inherent heterogeneity of ET itself (19). To date, analyses have not been performed to determine if the DRD3 variant segregates with ET in the Icelandic families used to identify the ETM1 locus (20). Additionally, a meta-analysis of all Ser9Gly-ET association studies actually supports an association between the DRD3Gly variant and increased risk of developing ET, especially in women (21). Thus, given the current controversy, a dopaminergic probe is warranted to clarify the possible link between a DRD3 variant and the pathogenesis of ET.

Additional support is provided by neuroimaging and pharmacologic studies in patients with ET and PD. The pathological relationship of these two diseases is rendered significant by the reported loss of Purkinje cells in the cerebellum of ET patients (7). Furthermore, it is known that the DRD3 receptor is expressed in cerebellar Purkinje cells (14). As such, we are interested in exploring the possible connection between the DRD3 receptor and ET through the use of the D3-selective dopamine agonist pramipexole. Using single photon computed emission tomography (SPECT) in conjunction with tracer ligands for visualizing dopamine transporters, two studies in particular have shown that up to 80% of ET patients may have reduced DAT binding of tracers in the striatum (22,23). For PD patients, who experience significant loss of DAT binding in the striatum, pramipexole was shown to significantly reduce the amount of striatal loss of tracer uptake; this effect was greater than that observed in a levodopa group for up to 46 months (24). This continued efficacy is important for the treatment of ET patients, as the acute and chronic side effects of primidone and propranolol are well-documented. Pharmacologic studies of pramipexole have already started identifying additional benefits of treatment. One study found that pramipexole conferred neuroprotection to striatal dopamine neurons following induced ischemia and methamphetamine administration by reducing the elevation of dopamine turnover and hydroxyl radical formation, suggesting the possibility of antioxidant properties of pramipexole (25). Ling et al has suggested

Specific Aims

Aim 1: To assess the effectiveness of pramipexole on changes in tremor rating as assessed by the TETRAS total score before and after study medication is given.
Aim 2: To assess PGIC and CGI at baseline and at study endpoint.
Aim 3: To assess the effects of pramipexole on activities of daily living, at baseline and at regularly scheduled intervals for each study phase.
Aim 4: To minimize the occurrence of adverse events or side effects throughout the course of the study. These will be measured as changes in the following scales between baseline and study end-point: Columbia Suicide Severity Rating Scale (C-SSRS), Sudden Onset of Sleep (SOOS), and Modified Minnesota Impulse Disorders Inventory (mMIDI).

Rationale and relevance to ET

Essential Tremor (ET) is one of the most prevalent neurologic disorders in the world that affects people of all ages. The overall prevalence of ET is approximately 0.9%, with those 65 years of age or older being 4.6% (1). Clinical features of ET consist of postural, kinetic, and rest tremor in the limbs, head, and voice. However, this historically monosymptomatic characterization does not consider recent evidence proposing a more holistic clinical profile of both motor and non-motor manifestations of ET. In the past decade, evidence of hearing loss (2), olfactory deficits (3), and depression and anxiety (4,5) have all been reported in ET subjects at a higher degree of prevalence than in controls. Additionally, evidence supporting the presence of a tandem gait disorder in advanced ET suggests an involvement of the cerebellothalamicortical circuitry in the manifestation of cerebellar-derived clinical features (6). Overall, this suggests that a multifaceted profile exists with respect to identifying clinical manifestations of ET.

Linking structural abnormalities in the brain to physiologic deficits is a daunting task. Nevertheless, to date one such study (7) has filled in part of the void, demonstrating that of 33 brains from those with ET two distinct groups could be discerned with respect to anatomical abnormalities. Most brains (75%) possessed predominantly cerebellar degeneration of Purkinje cells without Lewy bodies, labeled cerebellar ET; whereas 25% were found to harbor Lewy bodies predominantly in the locus coerulesus, dubbed Lewy Body Variant of ET (LBVET) (7). However, despite the recent increase in concern for identification of pathological abnormalities in ET, few clinical trials are accounting for the possible connection between genetic biomarkers and pathological evidence.

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neuroprotection is provided by pramipexole through the combined action of its antioxidant and D₃ selective properties (26). Several studies confirming the antioxidant properties of pramipexole demonstrate that reactive oxygen species production (27), mitochondrial permeability (27), lipid peroxidation (28), and the release and aggregation of cytochrome c and alpha-synuclein (29) are all reduced following administration of pramipexole. Furthermore, pramipexole was shown in one study to promote adult neurogenesis in an acute Parkinsonian model through direct stimulation of dopamine receptors (30). Given the mounting evidence underlying the neurodegenerative mechanisms of ET, pharmacological exploration is necessary to identify additional strategies of improving the functional outcomes and quality of life of those suffering from ET.

**Research methods and procedures**

This proposed study will be a prospective, double-blinded, placebo-controlled trial of the clinical safety and efficacy of pramipexole for monotherapeutic treatment of essential tremor. During this one year trial we will test 10 subjects with ET, with the option of extending the trial to 2 years and 20 subjects should additional funds become available. Duration per subject will be approximately 19 weeks: up to 30 days screening, up to 49 days of titration, 42 days of maintenance dose drug treatment, 7 days of down-titration, and up to 7 days for follow-up. Subjects must meet all inclusion and exclusion criteria below for participation in the study.

**Inclusion Criteria**

1. An Institutional Review Board (IRB)-approved written Informed Consent form is signed and dated by the subject prior to study procedures.
2. Subject understands the investigational nature of the study and is willing and able to comply with the study requirements. Subject is willing to accept that he/she might be treated with placebo during the treatment period.
3. Subject is male or female, and is ≥18 and ≤70 years of age.
4. Subject has essential tremor with a tremor severity score of ≥ 2 in the dominant hand/arm as measured by the Essential Tremor Rating Assessment Scale (TETRAS) (tremor is a minimum of 1 cm in amplitude).
5. Normal standing blood pressure (systolic 90-140 and diastolic 60-90).
6. Serum creatine kinase, complete metabolic panel, complete blood count with differential and platelets, liver function tests, renal function tests, and ECG are within normal limits (results obtained from primary care physician and dated within the past 6 months or obtained at screening visit). Any discrepancies are at the discretion of the investigator.
7. Ability to ambulate with or without assistance.
8. Stable doses of all medications for 30 days prior to study entry and for the duration of the study. (Any medications not discussed in exclusion criteria).

**Exclusion Criteria**

1. Any unstable illness or concomitant medical condition that, in the investigator’s opinion, precludes participation in this study. This includes other disorders that may affect gait or balance (stroke, arthritis, etc).
2. Hypersensitivity to study medication (pramipexole dihydrochloride monohydrate) and/or inactive ingredients: hypromellose, corn starch, carbomer homopolymer, colloidal silicon dioxide, and magnesium stearate.
3. Pregnancy or lactation. Women of child-bearing potential must use a reliable method of contraception and must provide a negative pregnancy test at entry into the study.
4. Participation in another study of an investigational medicinal product (IMP) or a medical device within the last 30 days prior to Visit 1, or is currently participating in another study of an IMP or a medical device.
5. Concurrent treatment with any dopamine antagonists (phenothiazines, butyrophenones, thioxanthenes), metoclopramide, MAOIs, Wellbutrin, sulfonamides and other antibiotics causing neuromuscular blockade, nicotine patches, as well as any other medication that, in the investigator’s opinion, precludes participation in this study.
6. Dementia or other psychiatric illness that prevents the patient from giving informed consent (Mini-Mental State Exam score of ≤24).
7. Legal incapacity or limited legal capacity.
8. Subjects on hemodialysis or those having severe renal disease (BUN 50% greater than normal or creatinine clearance <30 mL/min) or hepatic disease. Subjects with moderate renal impairment (creatinine clearance between 30 and 50mL/min) may require lower doses.
9. Abnormal creatine kinase and/or platelet count in the past 6 months (as determined by lab reports obtained from primary care physicians or conducted at screening).
10. Previous lack of response to other ET therapies (propranolol and primidone).
11. Patients who have a history of deep brain stimulation (DBS).
12. Subject currently has severe depression or a history of suicide attempts.
13. Subjects with symptomatic orthostatic hypotension at the screening visit (20 drop in systolic BP or 10 point drop in diastolic BP accompanied by severe dizziness or fainting upon standing).
14. Subjects with evidence of and Impulse Control Disorder (ICD) according to the modified Minnesota Impulse Disorders Inventory (mMIDI) at the screening visit confirmed by a positive structured clinical interview.
15. Concomitant treatment with pramipexole – except the IMP.

**Study Protocol**

Subjects will be screened for up to 30 days prior to being randomized to either treatment or placebo groups (1:1 ratio using SAS 9.2). The investigational medicinal product (IMP) will be slowly titrated up over a course of 7 weeks as
described below. After subjects reach their maximum tolerated dose (defined as the dose at which no AEs or SAEs occur) they will maintain a stable dose of the IMP for six weeks. Subjects will be assessed for changes in tremor, activities of daily living and PGI/CGI at baseline and end of maintenance period. Changes in these endpoints will be compared between treatment and placebo groups.

**Table 1 - Schedule of Assessments**

<table>
<thead>
<tr>
<th>Study Day (±3 days)</th>
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<td>M2/EW</td>
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</table>

**Screening Period**

At the screening visit, subjects will be evaluated for their suitability for enrollment. The screening visit will be conducted up to 30 days prior to baseline assessments. A full explanation (both verbal and written) of study procedures and risks will be given to the subject by the investigator (or designee). Prior to starting any study procedures the subject will sign and date the IRB-approved informed consent if he/she agrees to participate in the study. The subjects eligibility for the study will be determined on the basis of the inclusion/exclusion criteria, signature of an informed consent prior to any study related procedures or evaluations, and the results of the assessments listed in Table 1.

**Baseline Period**

Baseline assessments, as listed in Table 1, will be performed prior to randomization to treatment groups.

**Treatment Period**

Subjects will be titrated slowly from a dose of 0.375 mg/day to 4.5mg/day over a period of 7 weeks (week 1 = 0.125mg TID; week 2 = 0.25 mg TID; week 3 = 0.5 mg TID; week 4 = 0.75 mg TID; week 5 = 1.0 mg TID; week 6 = 1.25 mg TID; week 7 = 1.5 mg TID). Subjects will be held at their maximum tolerated dose for 6 weeks before down-titrating over a period of 7 days by reducing their study medication by 0.75 mg QD until they reach a dose of 0.75mg QD, after which they will reduce the dose in half (0.375 mg QD) and discontinue the following day. Any study-related side effect (e.g., nausea) requiring medication management must be approved by the site-specific investigator prior to consumption.

Subjects will be frequently monitored for the occurrence of sleep attacks (SOOS), suicide (C-SSRS), and impulse control disorders (m-MIDI). If subjects experience adverse events they will be given the option of discontinuing the trial agent or returning to the highest dose of agent that did not produce discomfort. If they undergo dose reduction, then they will enter into the maintenance phase. If AE/SAEs occur that require the withdrawal of the IMP the subject will complete an early withdrawal visit as described below.

**Study completion/early withdrawal**

Any subjects withdrawn early from the study will be required to return to the clinic for an early withdrawal visit to receive medication so they may down-titrate safely. Assessments performed during early withdrawal will include those performed during the maintenance 2 visit. All subjects, regardless of completion status, will receive a safety follow-up phone call 1-2 weeks after discontinuing the study medication. A subject is considered to have completed the study if
he/she has fulfilled all study requirements. If a subject does not complete a phase, their data will be used only for safety analysis.

Whenever a subject decides to withdraw or is withdrawn for whatever reason, all efforts will be made to complete and report the observations as thoroughly as possible. A final evaluation must be completed for that subject, including all endpoint evaluations if possible, and stating the reasons why the subject was withdrawn from the trial.

**Anticipated Results and Statistical Considerations**

The expected outcome of this project is to see an improvement in tremor as assessed by the essential tremor rating assessment scale (TETRAS). Other outcomes of interest include improvements in patient and clinician impression of change and improvements in activities of daily living.

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). The primary efficacy endpoint will be the change in the TETRAS total score and the change in TETRAS and ADL subscales between baseline and endpoint. Secondary endpoints will include the change in the Clinical Global Impression (CGI) and Patient's Global Impression of Change (PGIC).

Data will be analyzed using non-parametric paired samples analysis and unconditional growth curve modeling to compare the change in outcomes before and after treatment with pramipexole. For all analyses, α will be set at 0.05. No correction for multiple comparisons is planned because this is a pilot study.

All subjects entered into the study at assessment will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs will be described in detail. AE incidence will be summarized along with the corresponding 95% confidence intervals.

We are planning a study of a continuous response variable from independent control and experimental subjects with 1 control(s) per experimental subject. In a previous study the response within each subject group was normally distributed with standard deviation 13 (31). If the true difference in the experimental and control means is 20, we will need to study 10 experimental subjects and 10 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05.

**Detailed budget and justification**

**Table 2 - Procedures Budget**

<table>
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<th>Procedures</th>
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Table 3 - Drug costs and dosing

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<th>week</th>
<th>dose (mg)</th>
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<th># pills</th>
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**Total cost per subject**: $236.37

**Total drug cost**: $2,363.70

**Drug kit preparation costs**: $456.30

**TOTAL STUDY COSTS**: $25,000

The budget outlined in Tables 2 and 3 represents total study costs for a 1 year trial of 10 subjects. Should this study be funded, a second year of funding would be applied for at the same rate, resulting in a total of 20 subjects in this double-blind, placebo-controlled trial.
References


BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FOUR PAGES.

NAME
Zesiewicz, Theresa A.

POSITION TITLE
Professor – Department of Neurology
Professor – Department of Molecular Pharmacology

eRA COMMONS USER NAME
Zesiewicz

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>St. Peter's College; Jersey City, New Jersey</td>
<td>B.S.</td>
<td>1978</td>
<td>Biology</td>
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<tr>
<td>University of Medicine and Dentistry of New Jersey; Newark, New Jersey</td>
<td>M.D.</td>
<td>1984</td>
<td>Medicine</td>
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<td>University of Medicine and Dentistry of New Jersey; Newark, New Jersey</td>
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<td>1988-1989</td>
<td>Internship</td>
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<td>State University of New York Health Science Center; (SUNY) Brooklyn, New York</td>
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<td>1989-1992</td>
<td>Neurology Residency</td>
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<td>State University of New York Health Science Center (SUNY), Brooklyn, NY</td>
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<td>1991-1992</td>
<td>Chief Resident</td>
</tr>
<tr>
<td>Fellow, Movement Disorders Center; University of South Florida, Tampa, Florida</td>
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<td>1993-1995</td>
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A. Personal Statement. As a Professor of Neurology at the University of South Florida in Tampa, I have specialized in clinical research and patient care for 20 years, examining close to 2,500 patients with movement disorders per year. I have over 100 peer reviewed papers in movement disorders, many of which have focused on essential tremor, and 5 books. My team and I are active in clinical pharmaceutical research for Parkinson’s disease, essential tremor, Restless Legs Syndrome, Tardive dyskinesia, Spinocerebellar Ataxia and Friedreich’s ataxia. I have also been the topic chair of the American Academy of Neurology for the past 4 years, reviewing all abstracts and forming the scientific program for the meeting, and am a member of the Quality Standards Subcommittee for the American Academy of Neurology for the past 10 years, a committee designated to establishing evidence based medicine guidelines for the treatment of neurologic conditions. The guidelines include papers on early treatment of Parkinson’s disease, alternative therapies for Parkinson’s disease, and treatment of non-motor issues. My clinical and research expertise strongly support my role as principle investigator of the proposed project.

B. Positions and Honors.

Positions and Employment
1995-2001  Assistant Professor of Neurology, University of South Florida, Tampa, Florida
1996-present  Associate Director, Parkinson’s Disease and Movement Disorders Center, University of South Florida
2001-2008  Associate Professor of Neurology (tenured), University of South Florida, Tampa, Florida
2006-present  Associate Professor, Department of Pharmacology and Molecular Therapeutics, University of South Florida
2007-present  Director, Parkinson’s Disease Clinic, PADRECC, James A. Haley Veterans Hospital
2008-present  Professor of Neurology (tenured), University of South Florida, Tampa, Florida
2008-present  Director of Clinical Research, Parkinson’s Research Foundation, Tampa, Florida
2008-present  Director, University of South Florida Ataxia Research Center, Tampa, Florida

Other Experience and Professional Memberships
1993-2002  Director of Neurology, Health Park Specialty Clinic
1996-2004  Director, 2nd Year Medical Student Neurology Course, University of South Florida
2001-2010 Member of Quality Standard Subcommittee, Review of Parkinson’s Disease for AHRQ (Agency for Healthcare Research and Quality)

2001-present Member, Promotions and Tenure Committee for Department of Neurology, University of South Florida

2001-present Chair, Promotions and Tenure Committee for Volunteer Faculty, Department of Neurology, University of South Florida

2001-present Chair, American Academy of Neurology Quality Standard Subcommittee (QSS) to develop a Practice Parameter on Essential Tremor

2002-present Member, Chair Search Committee, Department of Neurology, University of South Florida

2002-present Director, 4th Year Medical Student Neurology Course, University of South Florida

2002-present Member, American Academy of Neurology Quality Standard Subcommittee to develop Practice Parameter in Parkinson's Disease

2003-present Reviewer, National Board of Medical Examiners, 4th year Medical Student Examination

2005-present Director of Research, Southeast Parkinson’s Disease Association

2008 Abstract Reviewer Movement Disorders for American Academy of Neurology Annual Meeting

2008-present Facilitator, American Academy of Neurology Quality Standards Subcommittee to develop Evidence Based Medicine on Tardive Dyskinesia

2008-present Facilitator, American Academy of Neurology Quality Standards Subcommittee to develop Evidence Based Medicine on Fragile X–associated tremor/ataxia syndrome (FXTAS)

2008-present Topic Chair, Movement Disorders, American Academy of Neurology Annual Meeting

2010-present Director, US Fight PD Foundation

C. Selected peer-reviewed publications (in chronological order).

(Publications selected from peer-reviewed publications)


D. Research Support

Ongoing Research Support (selected studies)

Sponsor: UCB BIOSCIENCES GmbH

Title: A multicenter, multinational, double-blind, placebo-controlled, 2-arm study to evaluate the efficacy of rotigotine on Parkinson’s disease-associated pain.

Goals: The major goals of the study are 1) to assess the effects of rotigotine over placebo on improvement of Parkinson’s disease-associated chronic pain in subjects with advanced-stage PD experiencing disease-associated chronic pain; and 2) to demonstrate that rotigotine is effective on Parkinson’s disease-associated chronic pain intensity and characterization, quality of life, depression, anxiety, and motor function in these subjects.

Role: PI
**Dates:** October 2013 - Present

**Sponsor:** GlaxoSmithKline  
**Title:** A fixed dose, dose response study for ropinirole prolonged release (PR) as adjunctive treatment to L-dopa in patients with advanced Parkinson's disease.  
**Goals:** The major goals of the study are 1) to characterize the dose response of fixed doses of ropinirole PR as adjunctive treatment to L-dopa in patients with advanced Parkinson's disease; and 2) to investigate the tolerability of fixed doses of ropinirole PR as adjunctive treatment in patients with advanced Parkinson's disease.  
**Role:** PI  
**Dates:** March 2012 - Present

**Sponsor:** GlaxoSmithKline  
**Title:** A fixed dose, dose response study for ropinirole prolonged release (PR) in patients with early stage Parkinson's disease.  
**Goals:** The major goals of the study are 1) to characterize the dose response of fixed doses of ropinirole PR as monotherapy in patients with early stage Parkinson's disease; and 2) to investigate the tolerability of fixed doses of ropinirole PR as monotherapy in patients with early stage Parkinson's disease.  
**Role:** PI  
**Dates:** October 2011 - Present

**Sponsor:** Astellas Pharmaceuticals US, Inc. (Investigator Initiated)  
**Title:** A Multi-site, Double-blind, Randomized, Placebo controlled trial of Solifenacin succinate (VESIcare) for the Treatment of Overactive Bladder in Parkinson's disease.  
**Goals:** The major goals of the study are 1) to measure the efficacy of solifenacin succinate (VESIcare) in reducing the mean number of micturitions per 24 hour period in Parkinson’s disease (PD) patients as measured by voiding diaries; and 2) to examine the effect of solifenacin succinate (VESIcare) on urinary incontinence severity and Parkinson’s disease severity.  
**Role:** PI  
**Dates:** December 2009 – Present

**Sponsor:** Edison Pharmaceuticals, Inc.  
**Title:** Safety and Efficacy Study of EPI-743 (Vincerinone™) on Visual Function in Patients with Friedreich’s Ataxia.  
**Goals:** The major goals of the study are 1) to measure the effects of EPI-743 in Friedreich’s Ataxia subjects on visual field tests and visual acuity; and 2) to measure the effects of EPI-743 in Friedreich’s Ataxia subjects on color vision, neurologic function, quality of life, activities of daily living, cardiac function, upper extremity function, patient perception of clinical improvement, hearing function and disease blood biomarkers.  
**Role:** PI  
**Dates:** December 2012 - Present

**Sponsor:** Friedreich’s Ataxia Research Alliance (Investigator Initiated)  
**Title:** Natural History Biomarkers in Friedreich’s Ataxia.  
**Goals:** The major goal of this study is to test a series of biomarkers for sensitivity in detecting progression in Friedreich’s ataxia.  
**Role:** PI  
**Dates:** 2011 – 2013

**Sponsor:** Friedreich’s Ataxia Research Alliance (Investigator initiated)  
**Title:** Natural History Biomarkers in Friedreich’s Ataxia  
**Goals:** The primary objective of this study is to test a series of biomarkers for sensitivity in detecting progression in Friedreich’s Ataxia.  
**Role:** PI  
**Dates:** 2011 - 2013

**Title:** Clinical Outcome Measures in Friedreich’s Ataxia  
**Goals:** The primary objective of this study is to find out ways to follow progression of Friedreich’s Ataxia (FRDA) and be able to measure clinical and biochemical changes over a short period of time.  
**Role:** PI  
**Sponsor:** Friedreich’s Ataxia Research Alliance
Dates: 2010 - 2016

**Completed Research Support (past three years):**

**Sponsor:** UCB Biosciences, Inc.

**Title:** A phase 3B, Double-blind, randomized, placebo-controlled study of rotigotine and its effect on all-day functioning and quality of life in subjects with moderate to severe idiopathic restless legs syndrome.

**Goals:** The major goals of the study are 1) to demonstrate that rotigotine improves RLS symptom intensity in subjects with moderate to severe idiopathic RLS during both day and evening and 2) to investigate the effects of rotigotine on other aspects related to RLS, including sleep, mood, and QOL.

**Role:** PI

**Dates:** June 2012 – June 2013

**Sponsor:** Allon Therapeutics Inc.

**Title:** A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Davunetide for the Treatment of Progressive Supranuclear Palsy.

**Goals:** The primary objectives of this study are to evaluate davunetide vs placebo given over 52 weeks for efficacy and safety.

**Role:** PI

**Dates:** July 2011 - January 2013

**Sponsor:** Baxter Healthcare Corporation & USF Department of Neurology (Investigator initiated)

**Title:** A Pilot, Open-label Study to Determine the Safety and Efficacy of Intravenous Immune Globulin in Treating Friedreich's Ataxia and Spinocerebellar Ataxia.

**Goals:** The primary objective of this study is to test if intravenous immunoglobulin (IVIG) helps reduce symptoms of Spinocerebellar ataxia type 3 (SCA 3).

**Role:** PI

**Dates:** 2011 – 2012

**Sponsor:** National Institutes of Neurological Disorders and Stroke (NINDS)

**Title:** Natural history of and genetic modifiers in Spinocerebellar Ataxias (SCA).

**Goals:** The primary objective of this study is to bring together a group of experts in the field of SCA for the purpose of learning more about the disease, finding out how the disease progresses over time and what may be the best way to measure the progression.

**Role:** PI

**Dates:** 2010 – 2013

**Sponsor:** Pfizer and Bob Allison Ataxia Research Center (Investigator Initiated)

**Title:** A Pilot, Randomized Double-blind, Placebo-controlled Phase I Study to Determine the Safety and Tolerability of Varenicline (Chantix®) in Treating Spinocerebellar Ataxia Type 3.

**Goals:** The major goal of this study was to evaluate the efficacy of varenicline in patients with SCA type 3.

**Role:** PI

**Dates:** April 2008 – December 2011

**Sponsor:** Pfizer and Friedreich’s Ataxia Research Alliance (Investigator Initiated)

**Title:** Double-blind, Randomized, Placebo-Controlled pilot study of Varenicline (Chantix®) in the Treatment of Friedreich’s Ataxia

**Role:** PI

**Dates:** 4/2008 - ongoing
Grant Application Form

Please complete the following form for IETF grant applications. This form and all the attachments below must be combined into one document before submitting electronically. Grant submissions will not be accepted otherwise.

Attachments Required
1. Specific aims of the proposal (1 page maximum).
2. Rationale of the proposal and relevance to essential tremor (1-2 pages maximum).
3. Preliminary data, if available should be incorporated into the Rationale/Relevance section. Preliminary data are not required for a proposal. However, if preliminary data are referred to in the proposal rationale, or have been used to formulate the hypotheses to be tested, such information must be formally presented in this section.
4. Research methods and procedures (1-2 pages maximum).
5. Anticipated results (half-page maximum).
6. Detailed budget and justification (1 page maximum).
7. Biographic sketch of principal investigator and all professional personnel participating in the project (standard NIH format, including biosketch and other support).
8. Copies of relevant abstracts and/or articles that have been published, are in press, or have been submitted for publication.
9. Completed conflict of interest questionnaire.

Project Title: A double-blinded randomized placebo-controlled trial of primigenius for ET.

Sponsoring Institution: University of South Florida

Principal Investigator:
Last Name: Desai First Name: Manasa Middle Initial: A

Degree(s): M.D. Current Title/Position: Professor

Department: Neurology

Address: 12901 Bruce B. Downs Blvd, M665
City: Tampa State: FL Postal Code: 33612
Country: USA E-mail address: tae@health.usf.edu
Phone: 813-974-5707 Fax: 813-974-8032

All grant applicants acknowledge that the Board of Directors of the IETF is the only entity authorized to award grants on behalf of the IETF and the amounts of and occasions for awarding such grants, if any shall be awarded at all, shall be wholly within the sole and exclusive discretion of said Board and its judgment shall be final and conclusive and not subject to review for any reason judicial or otherwise.

GrantApp5222013

PO Box 14005 | Lenexa, Kansas 66285-4005 | USA | 888.387.3667 (toll free) | 913.341.3880 (local) | essentitremor.org
Grant Proposal - Conflict of Interest Policy

PURPOSE
The International Essential Tremor Foundation (IETF) is a nonprofit, tax-exempt organization. Maintenance of its tax-exempt status is important both for its continued financial stability and for public support. Therefore, the IRS as well as state regulatory and tax officials view the operations of the IETF as a public trust, which is subject to scrutiny by and accountable to such governmental authorities as well as to members of the public.

Consequently, there exists between the members of the Medical Advisory Board, officers and members of the IETF Board of Directors, IETF employees and the public a fiduciary duty, which carries with it a broad and unbounding duty of loyalty and fidelity. The officers and members of the IETF Board of Directors and IETF employees have the responsibility of administering the affairs of the IETF honestly and prudently, and of exercising their best care, skill, and judgment for the sole benefit of the IETF. Those persons shall exercise the utmost good faith in all transactions involved in their duties, and they shall not use their positions with the IETF or knowledge gained for their personal benefit. The interests of the organization must be the first priority in all decisions and actions.

PERSONS CONCERNED
This statement is directed to those persons who may submit grant proposals to the IETF Medical Advisory Board. For the purposes of this policy, a relative is any person who is related by blood or marriage, or whose relationship is similar to that of persons who are related by blood or marriage.

AREAS IN WHICH THERE IS A DIRECT CONFLICT
1. A direct conflict arises if an individual is a member of the IETF Board of Directors or an employee of the IETF. Therefore, individuals who serve on the IETF Board of Directors or who are employees of the IETF are not permitted to submit grant proposals.

2. A direct conflict arises when an individual who is employed by a firm(s) that provide funding to the IETF such as, but not limited to pharmaceutical and medical device companies submit grants. Therefore, these individuals are not permitted to submit grant proposals.

AREAS IN WHICH A CONFLICT MAY ARISE NECESSITATING A REVIEW
A conflict of interest, direct or indirect, may be considered to exist in some instances when individuals submit a grant:

1. There may be a conflict if an individual is a member of the board of a competing organization(s)
2. There may be a conflict if an individual is an employee of an agency, organization, or association which affect the operations of the IETF
3. There may be a conflict if an individual is a relative of a member of the IETF Board of Directors, IETF Medical Advisory Board or IETF employee
4. There may be a conflict if an individual receives gifts, gratuities, entertainment or remuneration for services with respect to individual transactions involving the IETF

A conflict of interest can arise in other instances. While it is impossible to list every circumstance giving rise to a possible conflict of interest, the above will serve as a guide to the types of activities which do as well as possibly cause conflict.

Full disclosure of any situation that might raise an actual or potential conflict of interest will be reviewed by the IETF Board of Directors in order to permit an impartial and objective determination. It should be particularly noted that this disclosure relates not only to you, but also relatives.

Individuals who submit grant proposals are to read, review and sign a Conflict of Interest Questionnaire when submitting a grant.
CONFLICT OF INTEREST QUESTIONNAIRE
Grant Proposal Submissions

Pursuant to the purposes and interests of the policy adopted by the IETF Board of Directors requiring disclosure of certain interests, a copy of which has been furnished to me, I hereby state that I or relatives have the following affiliations or interests and have taken part in the following transactions which, when considered in conjunction with my relationship to the International Essential Tremor Foundation (IETF) might create or be a conflict of interest. (Write "none" where applicable).

1. Advisory Board or Panel Affiliation
   IETF Medical Advisory Board member

2. Consulting, Speakers Bureau or Contractual Services
   none

3. Research/Grant Support
   none

4. Financial or Material Support not otherwise listed.
   none

I hereby acknowledge the information given is complete and accurate to the best of my knowledge and belief. I understand that failure to accurately disclose a potential interest may cause revocation of my grant award if approved. I also understand that if any of the above circumstances change, that I am to complete a new questionnaire.

Signature [Signature]

Date [2/27/14]

GrantConflict2222013

PO Box 14005 | Lenexa, Kansas 66285-4005 | USA | 888.387.3667 (toll free) | 913.341.3880 (local) | essentialtremor.org