Meaningful Behavioral Change as an Efficacy Outcome in a Clinical Trial of Istradefylline for Apathy in Parkinson's Disease

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Objective

This poster describes a novel clinical trial of istradefylline treatment on physical activity and other motivated behavior in Parkinson's disease (PD). Behavioral measurements may provide more meaningful and reliable indices of apathy in PD and related conditions than self-report. NCT05182151

Background

Apathy is a common troublesome symptom in PD, associated with diminished quality of life for both the patient and care partner[1,2]. Because apathy reduces engagement in physical and social activities, it may accelerate disease progression and cognitive decline[3]. Prior studies suggest reduced apathy with istradefylline (ISD) in PD[4]. Enhanced mesolimbic dopamine via adenosine A2A receptor antagonism is proposed as a mechanism[5].

Measurement of apathy in clinical trials is typically based on Patient Reported Outcomes (PROs). This is problematic in Parkinson's disease and related conditions, as lack of insight and poor memory impact rating validity. Study partner reports can also be biased. The Lille Apathy Rating Scale (LARS)[6] is a clinician rated outcome (CRO) that is more objective but does not directly measure behavior and is confounded by expressive language deficits common in PD. Functional measures of motivated behavior may prove more effective in measuring apathy and response to treatment than subjective rating scales[6].

Study Design Overview

- 12-week, single site, investigator-initiated, open-label trial of ISD (40mg daily) in PD
- Study drug and funding by grant from Kyowa-Kirin

Major Inclusion:

- Motor fluctuations warranting treatment with ISD
- Clinically significant apathy (LARS>-22)

Major Exclusion:

- Dementia / Psychosis / Moderate-Severe Depression
- Inability to participate in light physical activity.

Primary Efficacy Outcome

Physical Activity Scale for the Elderly Physical Activity Scale for the Elderly (PASE) [7] is a well-validated survey that is administered weekly by telephone. Participants are asked to report frequency of various physical activities, including work, exercise, walking, housework, and recreation.

- 12 Items, approximately 5 minutes to complete
- Formalized scoring system (intensity x frequency)
- Age & gender adjusted normative data from large US Sample

Example Item #3

#3 Over the past 7 days, how often did you engage in light sport or recreational activities such as bowling, golf with a cart, shuffleboard, fishing from a boat or pier or other similar activities?

[0] Never

[1] Seldom (1-2 days)

[2] Sometimes (3-4 days)

[3] Often (5-7 days)

3.a What were these activities? (open ended question)

3.b On average, how many hours did you engage in these light sport or recreational activities?

[0] Less than 1 hour

[1] 1 but less than 2 hours

[2] 2 - 4 hours

[3] more than 4 hours

Example Weekly Report

ITEM	TYPE OF ACTIVITY	WEIGHT	FREQUENCY (HOURS/DAY)	WEIGHT x FREQUENCY
1	Walk outside of home	20	0.43	8.6
2	Light sport/recreation	21	0.75	15.75
3	Moderate sport/recreation	23	0.32	7.36
4	Strenuous sport/recreation	23	0	0
5	Muscle strength/endurance	30	0.11	3.3
6	Light housework	35	(yes/no)	25
7	Heavy housework or chores	25	(yes/no)	0
8	Home repairs	30	(yes/no)	0
9	Lawn work or yard care	36	(yes/no)	36
10	Outdoor gardening	20	(yes/no)	20
11	Caring for another person	35	(yes/no)	0
12	Work for pay or volunteer	21	0 (hours/day)	0
			TOTAL:	116.01

Secondary Outcomes

Engagement in Meaningful Activities Scale (EMAS) [8]

- 12-item self-report scale to measure perception of meaning, purpose, and value in daily activities
- Items rated 1 (rarely) – 4 (always), higher is better
- Example: "The activities I do give me a sense of satisfaction."
- Administered weekly via telephone interview

Apathy Evaluation Scale (AES) [9]

- 18-item scale to measure apathy, validated in PD over past 4 weeks
- Items rated 1 (not at all) – 4 (a lot), lower scores indicated more apathy
- Example: "I am interested in learning new things."
- Self-report and informant-report administered at baseline, midpoint, and final visit

Unified Parkinson's Disease Rating Scale (UPDRS)

- Structured rating scale of motor and non-motor symptoms in Parkinson's disease
- Parts II (motor and non-motor experiences), III (motor examination) and IV (motor complications of treatment) will be used to characterize the population sample.
- Administered at baseline, midpoint (week 6), and final visit (week 12)
- Exploratory analyses will examine the extent to which improvements in motor symptoms and reduction of treatment complications are associated with changes in apathy.

Statistical Plan

Hierarchical Linear Modeling (HLM) with imputation to measure change over 12 weeks on PASE and EMAS.

Power considerations

- Mean (SD) PASE scores in older adults = 115 (60)
- 10 repeated measurements after 2 weeks of treatment (where changes would be expected), a linear increase over time of .8 SD (large effect size) using the LEAR correlation matrix model (base=.5, decay=.05)
- Proposed sample n=32. With n=26, B=.80 to detect group differences with two-tailed a=.05 Six additional subjects are recruited to control for early withdrawal or attrition.

Progress Update

Study discontinued prematurely due to recruitment challenges as single site study.

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