Journal of Parkinson's Disease 9 (2019) 3–4
DOI 10.3233/JPD-190002
IOS Press

Clinical Trial Highlights: Phase III Study in Spotlight

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TITLE: A Phase 3 study of isradipine as a disease modifying agent in patients with early Parkinson's disease (STEADY-PD III):

STATUS: Study completed, results pending.
CLINICALTRIALS.GOV ID: NCT02168842.
SPONSOR: NINDS.
ENROLMENT: 336.
ESTIMATED COMPLETION DATE: Winter 2019.

OBJECTIVE: To assess the efficacy of isradipine, a dihydropyridine calcium channel antagonist to slow the progression of Parkinson's disease (PD).

BACKGROUND: Isradipine, a dihydropyridine calcium channel antagonist (DHP) that is approved for the treatment of hypertension, is being tested as a potential disease modifying intervention in early PD. Isradipine was shown to be neuroprotective in *in vitro* and *in vivo* models of parkinsonism[1]. The mechanism of neuroprotection is linked to selective vulnerability of substantia nigra pars compacta neurons that preferentially express L-type calcium channels. Neuroprotective effects of isradipine are achieved at a plasma concentration that is obtained within the safe dose range for human administration and consistent with the tolerable dosage identified in the phase II study of isradipine in PD (STEADY-PDII)[2]. A number of epidemiological studies have demonstrated a reduced risk of development of PD in individuals treated with DHPs compared to other antihypertensive agents.

STUDY DESIGN and OUTCOMES: STEADY-PD III is an NINDS funded Phase 3, parallel group, placebo-controlled 36 months study evaluating the efficacy of isradipine 10mg daily as a disease-modifying agent in early PD[3]. The study is being conducted at 54 Parkinson Study Group sites in US and Canada. The study recruited 336 participants with *de novo* PD not requiring symptomatic therapy and followed them prospectively for 36 months. The primary outcome is the change from baseline in the Unified Parkinson Disease Rating Scale (UPDRS) Part I-III score as measured in the ON state at month 36, in the active arm compared to the placebo arm. Secondary outcome measures include: 1) Time to initiation and utilization of dopaminergic therapy; 2) Time to onset of motor complications; 3) Change in non-motor disability and other PD motor and non-motor outcome measures

CURENT STUDY STATUS: Enrolment was started in November 2014 and was completed in 12 months, 6 months ahead of schedule, including 10% minority recruitment. The last partiicpant completed the study in November 2018. Study retention rate is 95%, 297 have initiated PD symptomatic therapy. Data lock is scheduled for January 2019 and final data analysis will be available February 2019.

Comments:
STEADY-PD III final results will be presented at the American Academy of Neurology May 2019 meeting. The study has a number of unique design features, including the longest duuration disease modifying interventional study (3-year) in a *de novo* PD population and assessment of the primary outcome in the medication ON state. Retention and completion rates have been higher than expected for such a long duration study.

REFERENCES:
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3. Biglan, K.M., et al., *A novel design of a Phase III trial of isradipine in early Parkinson disease (STEADY-PD III).* Ann Clin Transl Neurol, 2017. **4**(6): p. 360-368.