Novel Outcome Measures For Proof-of- Concept Clinical Trial of the Immunomodulatory and Dopaminergic Neuroprotective RXR Agonist IRX4204 in PD

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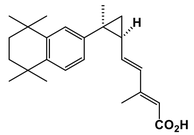
Abstract

- Objectives: IRX4204 is a highly potent, highly selective, brain penetrant, RXR nuclear receptor agonist compound. IRX4204 has immunomodulatory effects of promoting Tregs, and inhibiting Th17 cells and their production of IL-17. It also has anti-inflammatory effects of inhibiting production of IL-6, nitric oxide, and other inflammatory mediators by microglia and monocytes. It has neuroprotective effects on dopaminergic neurons, mediated by activation of heterodimers with Nurr1 and Nur77. IRX4204 has been evaluated in a previously unpublished open label dose ranging clinical trial in early PD patients, in which it demonstrated tolerability and safety of oral dosing at 5 mg/day, brain penetrance, and improvement in UPDRS Total Scores and Motor Scores in 13 of 15 patients.
- Methods: We are initiating a follow-on phase II, randomized, double-blind, placebo-controlled proof of concept clinical trial in PD patients using an expanded panel of novel assessments of efficacy. The trial utilizes biomarkers, including quantitation of brain derived exosomes for RXR, Nurr1, Nur77, DAT, and DDC, all of which are promoted by IRX4204 in preclinical studies; CSF and plasma assays for IL-17, IL-6, and other cytokines; a newly developed multi-symptom questionnaire, the University of Rochester PD Health Index; and quantitative recording of patient motor activities by a wearable device; in addition to the UPDRS. The trial will be conducted with IRB and regulatory agency approvals.
- Results: It is expected the trial conclusion will not have been reached at the time of the presentation and the trial blinding will not have been broken.
- Conclusions: It is expected that the trial will provide placebo-controlled proof-of-concept evidence of safety and efficacy of IRX4204 for treatment of PD by utilizing multiple new types of assessments of biologic and clinical outcomes.

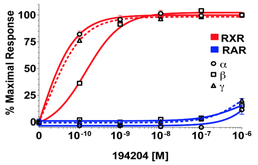


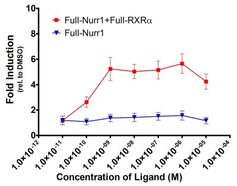
IRX4204 Chemical Structure

IRX4204 has two chiral centers; only one of the four stereoisomers is pharmacologically active. Manufactured IRX4204 has 99% chiral purity of the active stereoisomer.

IRX4204 Nuclear Receptor Agonism

IRX4204 Is a Potent and Highly Selective RXR Homodimer Agonist with agonist activity on RXR Nurr1 and Nur77 Heterodimers





IRX4204 does not activate RXR heterodimers with RAR, PPARγ, or LXRs at nanomolar concentrations

IRX4204 Previous Clinical Development

- 100 patients have been treated with IRX4204, including 85 with various cancers and 15 with early Parkinson's disease.
- IRX4204 was well-tolerated for up to 20 months of continuous oral treatment.
- PK in humans is consistent with once daily oral dosing.
- Common side effects include known RXR agonist activities of dose related reversible suppression of thyroid stimulating hormone, with resultant treatable hypothyroidism; mild to moderate reversible increased triglycerides; and mild to moderate reversible leukopenia.
- Oral dosing with 5 mg/day appears to be safe and potentially effective for PD.
- In an open-label Phase I/II safety and activity clinical trial of IRX4204 in early Parkinson's disease patients, improvements in Total UPDRS and Total Motor Score were observed in 13 of 15 patients with 2 weeks of treatment.

Mean Changes from Baseline to Week 2 in Total Motor Score, UPDRS, and TSH

Dose	Total Motor Change*^	Total UPDRS Change*^	Changes in TSH
20 mg/day	-14.5%	-6.6%	-98.8%
10 mg/day	-11.7%	-13.6%	-36.6%
5 mg/day	-31.4%	-18.7%	-28.9%

*Reduction in UPDRS and Total Motor scores represent clinical improvement

^Mean changes, n=5 per group

TSH Reduction is a class effect of RXR agonists, caused by inhibition of hypothalamic TRF synthesis, and is a biomarker of brain penetrance of IRX4204 in humans.

IRX4204 Cellular and Animal Models Pharmacology for PD

IRX4204 protects dopaminergic neuron survival and functions *in vitro* (1).
IRX4204 is effective in the 6-OH dopamine rat model of PD and preserves survival of TH positive neurons in tissue histopathology.
IRX4204 promotes RXR homodimer and RXR-Nurr1 activation *in vivo*.
IRX4204 promotes expression of DAT and DDC and increases dopamine *in vivo*.
IRX4204 inhibits α-synuclein aggregation and PFF-induced fibrillar structures.
IRX4204 is brain penetrant in multiple mouse and rat models.
IRX4204 is immunomodulatory, promoting Treg differentiation while inhibiting Th17 differentiation and IL-17 production (2).
IRX4204 inhibits microglia and macrophage inflammatory production of IL-6.
IRX4204 inhibits astrocyte inflammatory astrocyte expression of IL-1β (3).
IRX4204 promotes oligodendrocyte differentiation, *in vivo* axon protection, and myelin repair in cuprizone demyelination models and EAE models (3).

Design of IRX4204 Phase II Randomized, Double-blind, Placebo-controlled Clinical Trial in Early PD Patients

The clinical trial will use a randomized, double-blind, placebo-controlled, crossover design. Each patient will be randomized to receive oral IRX4204 5 mg/day or matching placebo, for a blinded first treatment period of 28 days, followed by an open-label washout period of 14 days, followed by a second blinded treatment period of 28 days during which each patient will receive the alternative treatment.

The trial will be conducted under a US FDA-allowed IND, and IRB approvals. All patients choosing to participate in the trial must sign an IRB-approved informed consent. The sponsoring company will request allowance from the FDA to continue open-label treatment with IRX4204 for at least 6 months for all patients who safely complete the blinded trial and who consent to continued open-label treatment and continued evaluations.

The trial will enroll 20 patients with early PD, giving a total of 40 treatment periods for analysis, 20 for IRX4204 and 20 for placebo. Statistical analyses will be conducted on all patients as a group, as well as on dosing subgroups to evaluate for potential dosing sequence effects on the outcomes.

Patients will have safety evaluations including physical examinations, clinical laboratories, ECGs, and recording of adverse events. Patients will complete various written symptom questionnaires for both safety and efficacy evaluations.

Patients will wear a watch like device for various periods for measurement of walking pace, tremors, balance, and sleep.

Novel Outcome Measures for PD Clinical Trial

The primary efficacy outcome for the trial will be the University of Rochester Parkinson's Disease Health Index (UR PD-HI). The UR PD-HI is a recently developed highly validated outcome measure usable for PD clinical trials. Developed at the University of Rochester, the UR PD-HI has 13 *independently* validated symptomatic subscales consisting of: fatigue; sleep & daytime sleepiness; mobility & ambulation; activity participation; central sensory function; pain; gastrointestinal function; hand & arm function; social health; emotional health; cognitive function; communication; and abnormal movements. We will also collect the Total UPDRS and Total Motor Scores as secondary outcome measures and compare their data to the UR PD-HI.

Recently, wearable devices measuring patients' motion have been used in PD clinical trials (4). These wearable devices, many of which resemble a wristwatch, continuously measure multiple parameters. We plan to collect and analyze, as secondary outcome measures, data on walking pace, tremors, balance, and sleep, using a commercially available wearable motion sensing hardware system and its analytical software.

Patients will have blood drawn at multiple time points for evaluation of a panel of biomarkers. Patients will be requested to consent to lumbar punctures for CSF collection at the beginning and end of the first blinded treatment period, for measurements of CSF biomarkers.

The biomarkers will include:
Brain derived exosomes for documenting target engagement and quantitation of RXR, Nurr1, Nur77 activation (assays to be performed by Neurodex)
α-synuclein seeding CSF assays for clinical trial analysis stratification and evaluation of possible treatment effects
Neurofilament light chains, GFAP, α-synuclein calpain-cleaved peptides, tau caspase-cleaved peptides (assays to be performed at Nordic Bioscience)
Inflammatory cytokine assays in plasma and CSF including IL-17s and IL-6
Mass spectroscopic proteomic analysis of plasma and CSF for drug treatment-associated changes in protein profiles (assays to be performed at Inoviv).

Conclusions

Historically, phase II clinical trials in PD have required large sample sizes of patients observed for 6-12 months, in attempts to observe rigorous evidence of drug benefit using relatively insensitive clinical measures such as the UPDRS. The newer outcome measures in this trial, including the UR PD-HI, motion assessments with a wearable sensor, and a substantial panel of biomarkers in blood and CSF, may allow an earlier decision to be made for further development of IRX4204 for PD.

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COI Disclosures

Martin Sanders and Vidyasagar Vuligonda are directors, officers, shareholders, and patent inventors of Io Therapeutics, Inc.