#5_A Phase 1b Double Blind Multiple Ascending Dose Study of the Safety and Pharmacokinetics of NTRX-07

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Background: NTRX-07 is an orally administered, brain-permeable, selective cannabinoid receptor type 2 (CBR2) agonist under development for treating neuroinflammatory-related diseases, including neuropathic pain (NP) and Alzheimer's Disease (AD). Preclinical studies of NTRX-07 have demonstrated decreased inflammatory changes in the brain, decreases in pain response in NP models, and improved clearance of A-beta proteins, improved long-term potentiation, and improved learning and memory in rodent AD models.[1] A previous Phase 1a study of NTRX-07 demonstrated no significant adverse effects with single doses up to 2 mg/kg in healthy volunteers.[2] The objectives of the present study were to study the safety and pharmacokinetics (PK) of repeat dosing in older volunteers and a cohort of subjects with AD. Exploratory endpoints included a food effect cohort and plasma biomarkers of inflammation.
Methods: The IRB approved study procedures, and informed consent was obtained. Three cohorts of volunteers 45-80 years of age with well-controlled comorbidities and one cohort of AD patients diagnosed with cognitive impairment consistent with prodromal AD per International Working Group criteria or mild AD per National Institute on Aging - Alzheimer's Association criteria (n=6 active, 2 placebo per cohort) were enrolled. Participants were admitted to the site for the dosing duration and returned 7-12 days after the last dose for a safety visit. Participants received NTRX-07 (10, 30, or 90 mg) or a placebo in a double-blinded randomization orally once daily for seven days. Subjects were assessed for changes in vital signs, including maneuvers to induce lightheadedness, electrocardiograms, electroencephalograms (EEG), and laboratory studies. The second cohort returned and received a single repeat dose after a standard high-fat meal. The AD cohort also underwent cognitive testing and had blood samples for biomarkers drawn. Subjects had PK sampling done after the first and final dose of the study drug.
Results: There were no dose-limiting or serious adverse events during the trial. One subject withdrew from the trial due to social reasons. Five participants had orthostatic changes in blood pressure, three of whom were asymptomatic, and none required treatment. No participants had changes in the timed get-up and go, Nystagmus test, or Romberg test. No participants had abnormalities on the EEG. No clinically meaningful changes in ECG or safety labs were observed. PK at the high dose was similar between Non-AD and AD participants with an average of AUC0-24h (h•ng/mL) of 1291 and 1556, and Cmax (ng/ml) of 439 and 477, respectively. A decrease in levels on Day 7 suggested a change in clearance. The high-fat meal decreased Cmax, but AUC was comparable. No significant changes in cognitive scores were observed, though there was an interesting trend toward improvement in the AD participants. No significant changes in biomarkers were observed.
Conclusions: NTRX-07 was safely administered for 7 days at doses up to 90 mg/day. The primary side effect observed was mild transient orthostatic changes in blood pressure, usually with early doses. Plasma levels were within the target ranges based on the allometric scaling of preclinical data.
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References:
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