THE NMDAR MODULATOR NYX-458 DOES NOT WORSEN MOTOR SYMPTOMS OR INTERFERE WITH L-DOPA'S ANTI-PARKINSONIAN EFFECT IN A IN A NON-HUMAN PRIMATE PARKINSON'S DISEASE MODEL

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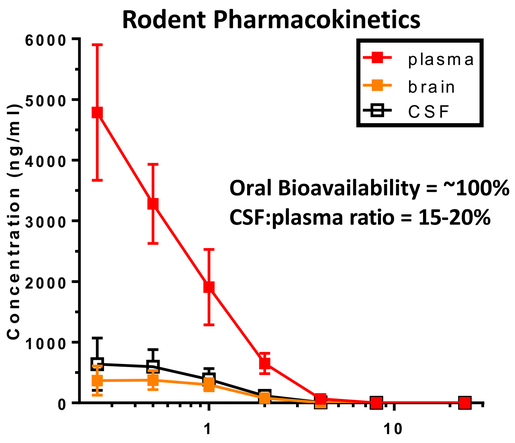
521

INTRODUCTION: NYX-458 is an orally available NMDAR modulator that demonstrates an attractive safety and pharmacokinetic profile. In animal models of cognitive dysfunction, including a non-human primate chronic low-dose MPTP model of Parkinson's disease (PD; see poster 522), NYX-458 reverses cognitive deficits. To understand whether NYX-458 administration negatively impacts motor function in PD, NYX-458 was evaluated as a monotherapy or in combination with low- or high-dose L-Dopa in primates with high-dose acute MPTP-induced motor impairment.

NYX-458 is orally bioavailable and a CNS penetrant with a favorable toxicology profile in rats and dogs

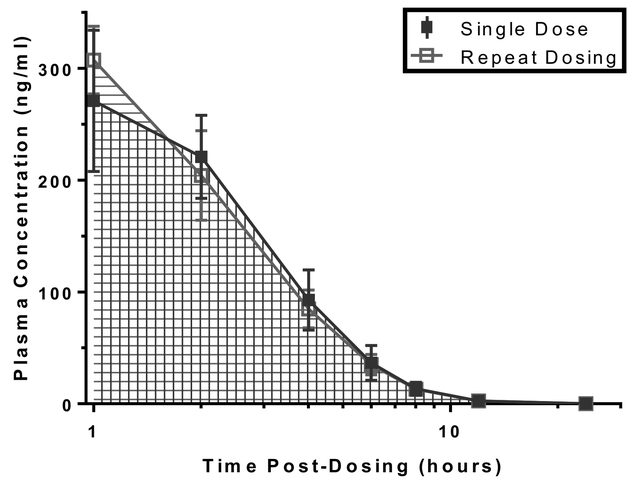


Parameter	Single-Dose Toxicology Studies (rat)
Doses (mg/kg)	750, 1000
N / group	3 male, 3 female
Maximally tolerated dose	1000 mg / kg
Noteworthy Findings	No treatment related findings at max dose

Parameter	28-Day Repeat Dose Toxicology Studies (rat and dog)	
Species	Rat	Dog
Doses (mg/kg)	50 - 250 mg/kg	5 - 75 mg/kg
N / group	13 male, 13 female	5 male, 5 female
NOAEL	250 mg / kg / day	75 mg / kg / day
Noteworthy Findings	No treatment related findings in either species	

Pharmacokinetic and toxicology data following acute or 28-day repeat exposure with NYX-458 in the rat and dog. *(Left panel)* Three male Sprague-Dawley rats each received administration of 10 mg/kg NYX-458 (PO). The Tmax was 0.25 hours with a Cmax of 4784, 638, and 374 ng/ml in plasma, CSF, and brain, respectively. *(Right panel)* In toxicology studies, Animals were observed for behavioral changes, mortality, body weight, food consumption, gross pathology, and histopathology.

Pharmacokinetics following repeat dosing with NYX-458 (0.5 mg/kg, PO) in non-human primate



Parameter	Single Dose	After 8 days repeat dosing
tmax	1 hr	1 hr
Cmax (ng/ml)	271	307
$AUC_{0\text{-}inf}$	913	904

Plasma pharmacokinetic data following acute and repeated oral administration of NYX-458 in the macaque. Three male macaques each received administration of 0.5 mg/kg NYX-458 for 8 days with samples analyzed on Days 1 and Day 8.

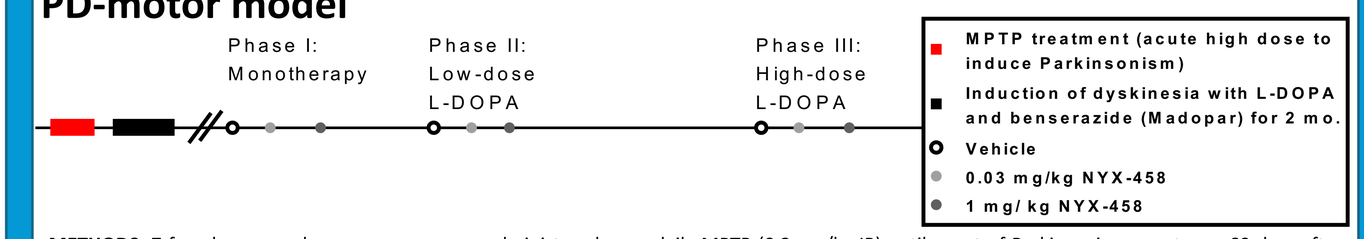
Rating Scales for Parkinsonian Disability and Dyskinesia

Category	Parkinsonian Disability Rating
Range of Movement	0: normal locomotion 1: walking on the floor of the cage only 2: movement of limbs and/or trunk; no locomotion 3: movement of head only; no locomotion 4: no movement
Bradykinesia	0: normal speed and initiation of movement 1: mild slowing of movement 2: moderate slowing, difficulty initiating and maintaining movement, freezing 3: marked slowing or unable to move, with prolonged freezing episodes.
Postural Abnormality	0: normal balance, upright, holds head up 1: hunched body, holds head up 2: hunched body and neck, face down, may lose balance
Checking Behavior	0: present, looking around, observant 1: absent

Rating	Dyskinesia
Severe (4)	Abnormal movement are continuous and present >70% of the time
Marked (3)	Abnormal movement are continuous and present <70% of the time
Moderate (2)	Able to perform motor tasks. Abnormal movement are intermittent or continuous and present >30% of the time
Mild (1)	Able to perform motor tasks. Abnormal movement are intermittent or continuous and present <30% of the time
Absent (0)	No abnormal movements

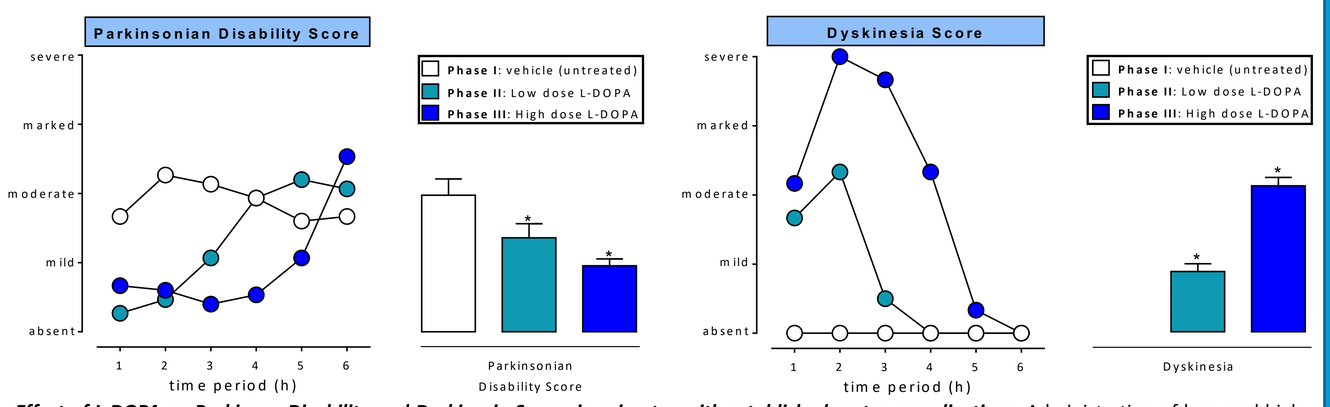
Non-human primate Motor Impairment Rating Scale. Parkinsonian disability score is the sum of range of movement, bradykinesia, postural stability, and alertness. Dyskinesia rating is rated for chorea and dystonia for each assessment period. All ratings were made for 5 min every 10 min for a 6 hour period post-dosing with either vehicle or LDOPA (The sum of 36 ratings total).

PD-motor model



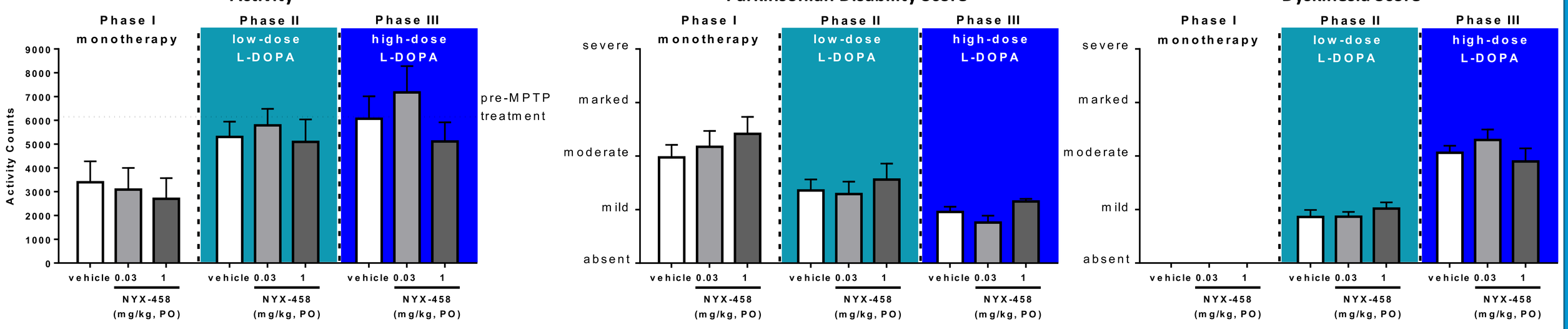
METHODS: 7 female cynomolgus macaques were administered once daily MPTP (0.2 mg/kg IP) until onset of Parkinsonian symptoms. 60 days after commencing MPTP treatment, animals were orally dosed with L-DOPA (Madopar; 25 mg/kg) twice daily for at least 2 months until the onset of L-DOPA induced dyskinesia. Two dose levels of NYX-458 (0.03 and 1 mg/kg) were assessed, first as a monotherapy, then in combination with low-dose L-DOPA, and finally in combination with high-dose L-DOPA.

L-DOPA Decreases Parkinsonian Disability but Increases Dyskinesia in the MPTP Primate



Effect of L-DOPA on Parkinson Disability and Dyskinesia Scores in primates with established motor complications. Administration of low- and high-dose L-DOPA reduced mean PD scores and increased mean dyskinesia scores relative to vehicle (untreated Parkinsonism). Data are median scores for each hour post dosing with L-DOPA (line graphs), or the mean + SEM for all 6 hours (bar graphs, N = 7; * $p < 0.05$, one-way ANOVA, Holm-Sidak).

NYX-458 has No Effect on Activity, Parkinsonian Disability, or Dyskinesia, in the Presence or Absence of L-DOPA in MPTP Primate



Effect of NYX-458 on activity levels and Parkinsonian and Dyskinesia Scores in primates with established motor complications. As a monotherapy, NYX-458 (0.03 and 1 mg/kg, PO) did not alter mean activity, parkinsonian disability, or dyskinesia as compared to vehicle (untreated Parkinsonism) treatment. NYX-458 (0.03 and 1 mg/kg, PO) also did not influence the anti-parkinsonian effect of low-dose, or high dose, L-DOPA: activity, Parkinsonian disability, and dyskinesia scores remained unchanged compared to vehicle (untreated Parkinsonism). Total activity was determined based on the number of beam crosses, and Parkinson disability and dyskinesia scores were based on blinded post-hoc ratings (see above). All data are mean + SEM across all 6 hours (N= 7, * $p < 0.05$, two-way ANOVA, Holm-Sidak multiple comparison for each measure).

CONCLUSIONS

- NYX-458 is highly orally bioavailable, has high brain penetration and a favorable toxicology profile.
- NYX-458 administration reverses cognitive deficits seen in the MPTP treated non-human primates (see poster 522).
- **At doses that reverse cognitive impairment, NYX-458 does not exacerbate motor disturbances or interfere with the anti-Parkinsonian activity of L-dopa in non-human primates with MPTP-induced PD motor symptoms.**
- **NYX-458 may be an effective therapeutic for Parkinson's disease cognitive impairment**

FINANCIAL DISCLOSURES

A. Barth, J. Moskal, and C. Cearley are employees of Aptinyx Inc.