# NYX-458, A NMDA RECEPTOR MODULATOR, IMPROVES COGNITIVE DEFICITS IN A NON-HUMAN PRIMATE MPTP MODEL OF COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

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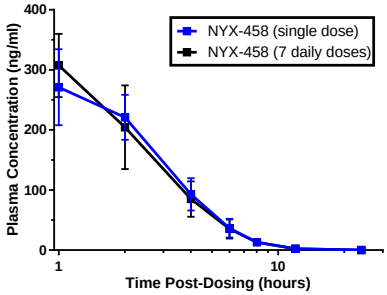
## INTRODUCTION

Aptinyx has developed a novel class of small molecule orally bioavailable N-Methyl D-Aspartate Receptor (NMDAR) modulators with broad applicability across CNS disorders. NYX-458 enhanced cognition in multiple rodent models with no toxicity or safety pharmacology concerns at all doses tested. NYX-458 preferentially binds NMDAR2B and 2D subtypes, which may be applicable to cognitive impairment in Parkinson's Disease (PD).

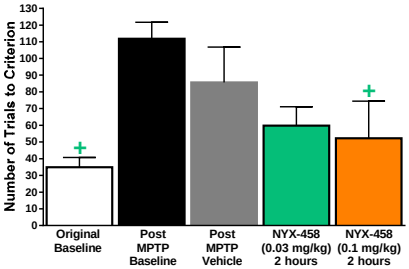
In the present study, NYX-458 was evaluated in a chronic low-dose MPTP (CLD-MPTP) non-human primate (male Cynomolgus macaque) model of cognitive impairment in PD. Five macaques were trained to perform cognitive tasks including: continuous performance task (sustained attention/impulsivity), variable delayed response task (spatial working memory), and visual discrimination/reversal learning task (cognitive flexibility). After training, chronic low doses of MPTP were administered until stable cognitive deficits appeared. Animals were then assessed for improvement in performance following treatment with NYX-458 (0.03 – 0.1 mg/kg, PO).

## NYX-458 was orally bioavailable and well tolerated



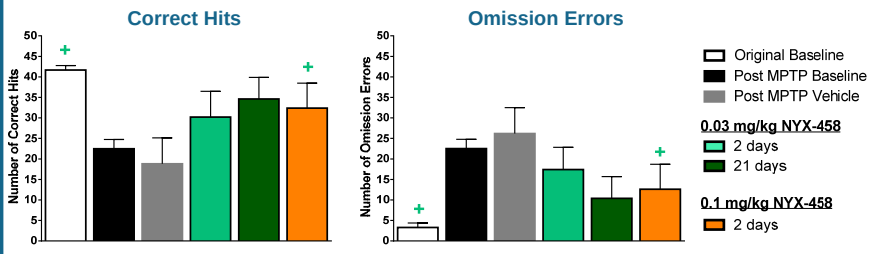

***Plasma exposure levels of NYX-458 (0.5 mg/kg, PO) in Cynomolgus macaques.*** There was no significant difference in plasma level profile between a single acute dose and 7 daily doses. The Cmax was 270 ng/ml at 1 hr and plasma levels were below 2 ng/ml at 24 hours; AUC of 900 ng/ml (LC/MS/MS). NYX-458 showed no signs of adverse events.

## NYX-458 improved cognitive flexibility in the simple discrimination reversal (SDR) assay




***Effect of NYX-458 (0.03 – 0.1 mg/kg, PO) in SDR assay.*** Macaques were presented with two images and required to identify correct image on 14/16 consecutive trials to meet criteria. Animals were then required to shift responses to the other image; with 14/16 consecutive correct responses. Data are mean ±SEM (N=5). + p<0.05, compared to MPTP vehicle (two way ANOVA, FSLD).

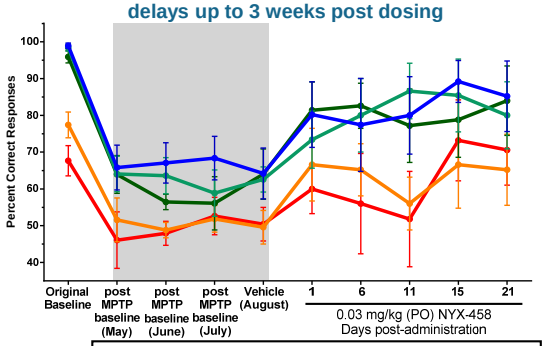
## NYX-458 reduced omission errors in the continuous performance task (CPT)




***Effect of NYX-458 (0.03 – 0.1 mg/kg, PO) on CPT response.*** Macaques were trained to associate a target (yellow rectangle) with a reward. Touch of a non-target rectangle (white or black) was not rewarded. The target appears 30% of the time. In an omission error the target appears, but is not touched. Commission errors (number of touches to a non-target) was also scored but there were not significant changes between groups, Data are mean ±SEM (N=5). + p<0.05, compared to MPTP vehicle (one way ANOVA, FSLD).

## NYX-458 improved attention and spatial working memory in the variable delayed response (VDR) task

### A single dose of NYX-458 improved VDR performance across all time delays up to 3 weeks post dosing

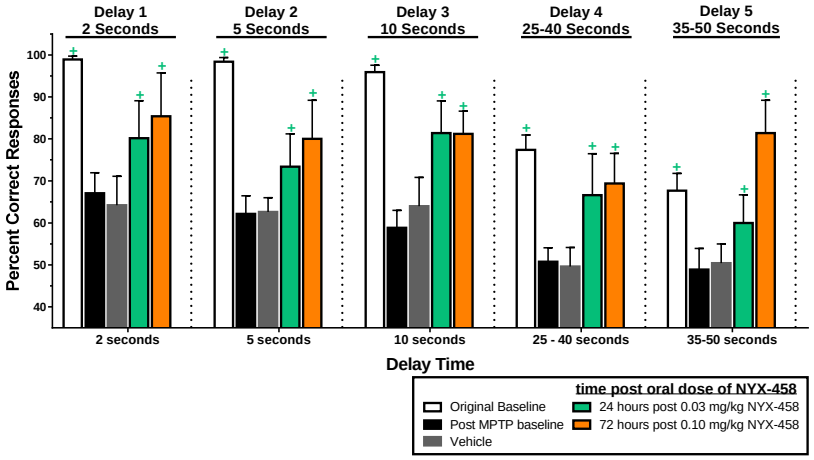



Percent correct responses vs. post MPTP treatment vehicle control:

| Delay | 1 day | 6 days | 11 days | 15 days | 21 days |
|---|---|---|---|---|---|
| 2 seconds | + | + | + | + | + |
| 5 seconds | ns | + | + | + | + |
| 10 seconds | + | + | + | + | + |
| 25-40 seconds | + | + | ns | + | + |
| 35-50 seconds | ns | ns | ns | + | + |

Increasing need for sustained attention

### All doses of NYX-458 tested (0.03 – 0.1 mg/kg, PO) improved VDR performance




***Effect of NYX-458 (0.03 – 1 mg/kg, PO) on VDR performance.*** During the trial, a white circle (cue) appears (screen location can vary) and the animal must remember the location of the cue. After a delay (variable duration) the animal must select a red circle in the same spatial location as the cue (one of two red circles presented). For all animals each testing session consisted of 75 trials (15 at each of the 5 delay intervals) randomly distributed in blocks of trials throughout a daily training session Data are mean ±SEM (N=5). + p<0.05, compared to MPTP vehicle (two way ANOVA, FSLD).

## CONCLUSIONS

- NYX-458 is orally bioavailable in non-human primates with no accumulation. NYX-458 is also highly tolerable, with no signs of adverse events in any assay.
- In the chronic low dose non-human primate MPTP model of Parkinson's cognitive impairment, NYX-458 significantly increased sustained attention, improved cognitive flexibility, and improved spatial working memory as early as 2 hours following a single dose, and those effects were maintained up to three weeks post dosing.
- NYX-458 is a unique NMDAR modulator with potential to be an effective therapeutic for treating cognitive deficits seen in people with Parkinson's disease.

## FINANCIAL DISCLOSURES

AG, AK, JM, and CC are employees of Aptinyx Inc.