ADS024 Attenuates Striatal Dopamine Loss and Restores Movement in Animal Models of Parkinson's Disease

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Objective

To evaluate the effect of ADS024, an oral single strain live biotherapeutic product (SS-LBP), on the pathophysiology of MPTP-induced Parkinson's Disease (PD) phenotypes in mice and zebrafish

Background

Gastrointestinal microbes have recently gained prominence in their ability to impact the brain via the gut-brain axis. PD is one of several diseases in which bacteria may play a role in disease progression or modification. ADS024, an oral single strain LBP of Bacillus velezensis, is being evaluated for the potential treatment of patients with PD.

Methods

Mice were dosed intraperitoneally with MPTP (Day 0 to 3; 20 mg/kg/day; n=30) or sham treated (saline; n=10). Mice were also orally gavaged (Days -3 to 7; bid) with saline (n=10), ADS024 (5x10^8 colony forming units (CFU); n=10), or bacterial formulation buffer containing Trehalose (n=10) and sacrificed on Day 7. Striatum was harvested, frozen, and homogenized in 0.3M perchloric acid. Dopamine and DOPAC were measured by reverse phase HPLC-EDC. Data were analyzed using two-way repeated measures ANOVA with post hoc Fisher's LSD multiple comparison test. Zebrafish larvae were dosed with MPTP (250 uM; 96 to 120 hours post fertilization) or sham treated (DMSO only; n =22) in water. ADS024 was dosed in water of MPTP exposed fish (4x10^6 CFU/ml; n=16). Movement was evaluated with an imaging system during 50 min of testing consisting of 10-min periods of alternating darkness/bright light. Data was analyzed by One-way ANOVA followed by a Dunnet test comparing against MPTP treatment.

Results

MPTP-treated mice had significant reduction of striatal dopamine and DOPAC content (54% and 45% of sham, respectively), while treatment with oral ADS024 significantly attenuated the loss resulting in levels of 68% of sham in both cases ($p<0.05$ for both). MPTP-treated Zebrafish larvae had significantly reduced total motor movement distance (24% of sham; $p<0.001$) which was attenuated by ADS024 (61% of sham; $p<0.001$).

Conclusion

Oral treatment with ADS024 improved dopamine and DOPAC striatal levels in an MPTP mouse model of PD and led to improved motor movement in an MPTP zebrafish model. Together, these results suggest that ADS024, an oral single strain live biotherapeutic product, has potential for positive impact on dopamine and associated motor movement for treatment in Parkinson's Disease.

MPTP Mouse Study

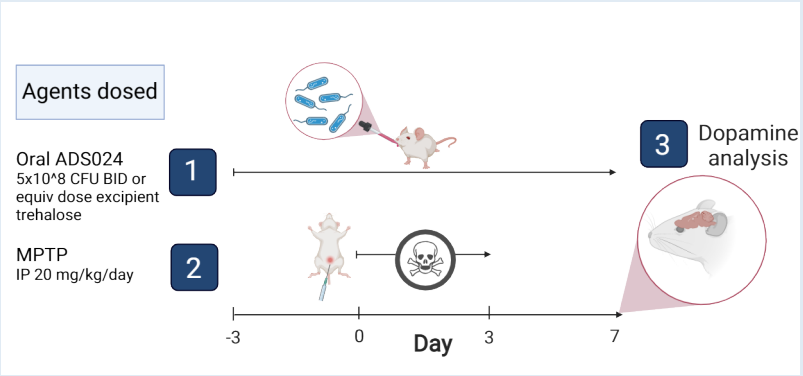


Table 1. Study design to test ADS024 in MPTP treated mice

Group	IP Treatment	IP Dosing	Oral Treatment	Group Size	Endpoints
Saline_Saline	Saline	PBS, QD Day 0-3 (4 doses)	Saline, BID Day(-3) to 7	10	Dissection of striata (bilateral) Determination of Dopamine and DOPAC
Saline_MPTP	MPTP	20 mg/kg QD, Day 0-3 (4 doses)	Trehalose, BID Day(-3) to 7		
Trehalose_MPTP			ADS024, BID 5x10^8 CFU Day(-3) to 7		
ADS024_MPTP					

Fig 1. Attenuation of MPTP-induced dopamine loss in mouse striatum by ADS024

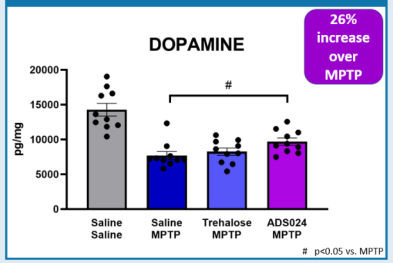
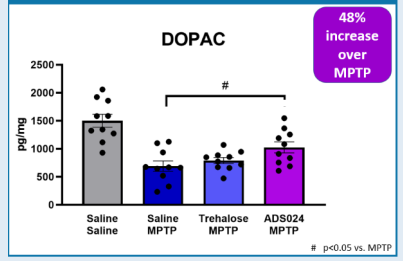


Fig 2. Attenuation of MPTP-induced DOPAC loss in mouse striatum by ADS024



MPTP Zebrafish Study

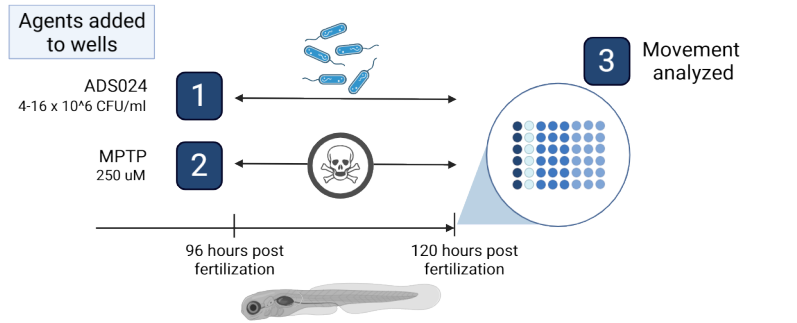


Table 2. Study design to test ADS024 in MPTP treated Zebrafish

Group	MPTP	MPTP dose	Bacteria	Bacterial dose	Group size	Endpoints
DMSO	-	-	-	-	22	Light/dark-stimulated distanced moved
MPTP	MPTP	250 uM 96-120 hpf	-	-	26	
MPTP_ADS024 low			ADS024	4 x 10^6 CFU/ml	16	
MPTP_ADSO24 med				8 x 10^6 CFU/ml		
MPTP_ADSO24 high				16 x 10^6 CFU/ml		

Fig 3. Restoration of Total Distance Moved in MPTP-treated zebrafish larvae by ADS024

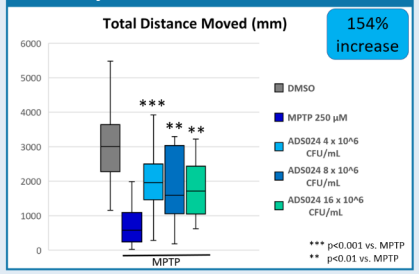


Fig 4. Restoration of Distance Moved per minute in MPTP-treated zebrafish larvae by ADS024