PRECLINICAL FINDINGS SUGGEST THAT EPM301 COULD OFFER MULTIPLE BENEFITS AS A NOVEL TREATMENT FOR SYMPTOMS OF PRADER-WILLI SYNDROME

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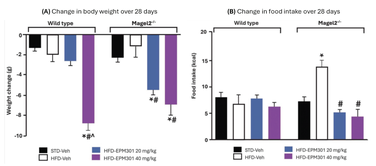
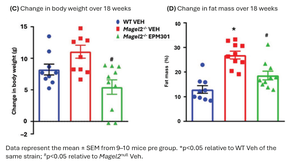
EPM301, a novel synthetic cannabidiol (CBD) analogue (cannabidiolic acid methyl ester) under development by EPM Group Inc. dba EPM Therapeutics, shows promise as a candidate for the treatment of Prader-Willi Syndrome (PWS). It has received Orphan Drug Designation (ODD) and Rare Pediatric Disease Designation (RPDD) from the FDA, as well as ODD from the EMA.

REDUCED BODY WEIGHT AND FOOD INTAKE IN HIGH-FAT DIET-FED MICE[1]

- The effect of EPM301 on body weight and hyperphagia was evaluated in a high-fat diet (HFD) fed Magel2null mouse model of PWS.
- Magel2null mice and their wild-type littermates control were fed ad libitum with HFD or standard diet (STD) or 14–16 weeks. Following which, mice were started on a daily treatment with EPM301(20 and 40 mg/kg/day, intraperitoneally) or vehicle (Veh) for 28 days.
- EPM301 promoted weight loss (A; $p<0.05$ vs STD-Veh and HFD-Veh) and decreased food intake (B; $p<0.05$ vs HFD-Veh) in Magel2null mice.
- Furthermore, EPM301 (20 mg/kg/day, intraperitoneally), when given to STD-fed Magel2null mice over18 weeks as a preventive treatment, completely inhibited weight gain (C; $p<0.05$ vs Magel2null Veh) and adiposity (D; $p<0.05$ vs Magel2null Veh).



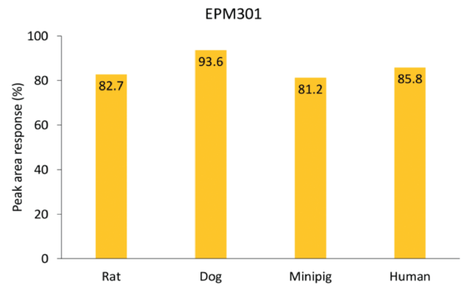
Data represent the mean + SEM from 4-13 mice pre group. *p<0.05 relative to STD-Veh of the same strain; #p<0.05 relative to HFD-Veh of the same strain; ^p<0.05 relative to HFD-EPM301 20 mg/kg of the same strain.



Data represent the mean + SEM from 9-10 mice pre group. *p<0.05 relative to WT Veh of the same strain; #p<0.05 relative to *Magel2*$^{-/-}$ Veh.

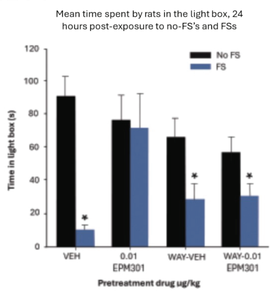
LIMITED METABOLISM ACROSS RAT, DOG, MINIPIG AND HUMAN HEPATOCYTES AFTER 4H INCUBATION, WITH NEARLY 100% PLASMA BINDING IN RAT, RABBIT, MINIPIG AND HUMAN PLASMA[4]

- The in vitro biotransformation of EPM301 was assessed using rat, dog, minipig and human hepatocytes.
- Cryopreserved hepatocytes in suspension were incubated with 10 M EPM301 for 4 hours and analysed using accurate mass LC-MS/MS.
- Limited metabolism of EPM 301 was observed across rat, dog, minipig and human hepatocytes.
- Additionally, plasma protein binding studies demonstrated nearly 100% binding in rat, rabbit, minipig and human plasma.

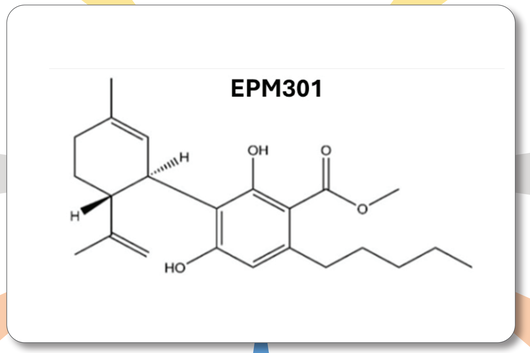


REDUCTION IN STRESS-INDUCED ANXIETY[2]

- The effect of EPM301 on anxiety-like responding was evaluated using the light-dark box emergence test following either foot shock (FS) or No FS stress.
- Rats received a single FS stress session or No FS stress session 24 hours before the light-dark emergence test. Rats in the FS group and the No FS group were then pretreated with vehicle (Veh) or 0.01 g/kg EPM301 (intraperitoneally). Forty-five minutes later, they were placed in the dark chamber of the light-dark box; their movement was tracked for 5 minutes.
- FS stress greatly enhanced the anxiety-like responding of decreased time spent in the light box.
- EPM301, at a low dose of 0.01 g/kg, reversed the effect of FS on the anxiety-like responding of decreased time spent in the light box.



Each bar represents the mean ± SEM; *p<0.05 and indicates a significant difference between FS and No FS stress groups.



HIGHER ORAL BIOAVAILABILITY COMPARED TO CBD[4]

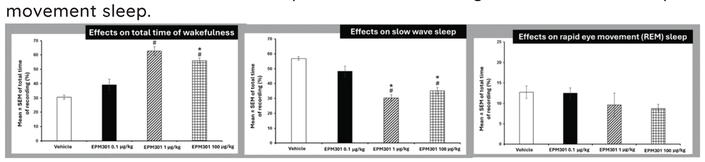
- The pharmacokinetics of EPM301 and CBD was evaluated following intravenous and oral administration to male Han Wistar rats.
- Each animal received a single intravenous or oral dose of EPM301 or CBD. Dose evaluated included: EPM301 intravenous (1 mg/kg), EPM301 oral (5, 25 and 50 mg/kg), CBD intravenous (1 mg/kg), CBD oral (5 mg/kg).
- Blood samples were collected from each animal at different timepoints. Concentration of EPM301 and CBD were determined using liquid chromatography with tandem mass spectrometric (LC-MS/MS) methods.
- The absolute bioavailability following 5 mg/kg oral administration was higher for EPM301 than CBD (37.4% vs 4.94%, respectively).

Analyte	%F					
	DN AUC_{0-t}			DN AUC_{0-inf}		
	5 mg/kg	25 mg/kg	50 mg/kg	5 mg/kg	25 mg/kg	50 mg/kg
CBD	4.94	NA	NA	6.81	NA	NA
EPM301	37.4	34.1	17.5	37.4	21.9	17.6

NA, not applicable
%F = [DN AUC (Oral)/DN AUC (Intravenous)*100

INCREASED WAKEFULNESS AND DECREASED SLOW-WAVE SLEEP DURATION, WITHOUT SIGNIFICANT EFFECTS ON REM SLEEP[3]

- The impact of EPM301 on the sleep-wake cycle was assessed in male Wistar rats.
- Rats were placed randomly into the following experimental groups: vehicle (n=8), EPM301 (0.1, 1.0 or 100 g/kg, intraperitoneal; n=8 for each dose). The sleep-wake cycle data were sampled in periods of 12s (epochs).
- EPM301 (0.1, 1.0 or 100 g/kg) demonstrated a dose-dependent increase in wakefulness and a decrease in slow-wave sleep duration, without significant effects on rapid eye movement sleep.



Each bar represents mean ± SEM; * vs Vehicle; # vs EPM301 0.1 µg/kg; p<0.0001.

WELL TOLERATED DOSE UP TO 100 MG/KG/DAY[4]

- The toxicity of EPM301 was evaluated in male and female Han Wistar rats, via intravenous (bolus) injection in the tail vein by a single dose in the Maximum Tolerated Dose (MTD) phase followed by 7 consecutive days of repeat dosing in the Dose Range Finding (DRF) phase.
- EPM301 dose evaluated in MTD phase: 10, 20, 50 and 100 mg/kg. EPM301 dose evaluated in DRF phase: 0, 25, 50 and 100 mg/kg/day. The following parameters were evaluated: clinical observations, body weights (DRF phase only), food consumption (DRF phase only), bioanalysis and toxicokinetic parameters, and gross necropsy findings and organ weights (DRF phase only).
- Administration of EPM301 by once daily intravenous bolus injection for 7 days was tolerated in rats up to 100 mg/kg/day (71–76 mg/kg/day) and was associated with transient clinical signs (abnormal respiratory rate, abnormal gait, decreased activity, subdued behavior salivation, ploughing and low carriage).
- A decrease in body weight gain was seen only in male rats at 100 mg/kg/day. The MTD was considered to be 100 mg/kg/day.

NON-MUTAGENIC AND NON-PHOTOTOXIC[4]

- The safety of EPM301 was evaluated in several mutation assays and was found to be non-mutagenic based on these assays.

Assay	Outcomes
Salmonella typhimurium reverse mutation assay	Not mutagenic
Escherichia coli reverse mutation assay	Not mutagenic
Thymidine kinase mutation assay in mouse lymphoma cells	Not mutagenic

- A phototoxicity study showed a reduction in viability in both the presence and absence of irradiation following treatment with EPM301. The photo-irritation factor (PIF) value was 1.191 which indicates a non-phototoxic response.

These promising preclinical findings suggest the EPM301 could offer multiple therapeutic benefits for individuals with PWS. A pre-IND meeting with the FDA is planned for Q2 2025, and a first-in-human study is planned for early 2026.

References: 1. Ben-Cnaan E., et al. Int. J. Mol. Sci. 2022;23(10):5610-5626; **2.** Pertwee R.G., et al. Br J Pharmacol. 2018;175(1):100-112; **3.** Murillo-Rodriguez E., et al. Brain Res Bull. 2020;155:166-173; **4.** Data on File.

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