Enhanced Bioavailability and Therapeutic Potential of EPM301, a Novel Cannabidiol Analogue, in the treatment of Prader-Willi Syndrome

Peter J. Welburn[1], Joseph Tam[2], Qasim Ahmed[3], Jana Lancova[3]

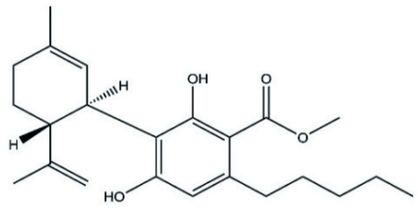
[1]EPM Therapeutics, 7310 Turfway Road, Suite 550, Florence, KY 41042; [2]Obesity and Metabolism Laboratory, Faculty of Medicine, School of Pharmacy, The Institute for Drug Research, The Hebrew University of Jerusalem, Jerusalem, Israel; [3]Labcorp Drug Development Laboratories Limited, Otley Road, Harrogate, North Yorkshire, UK

Background

- The therapeutic benefit of cannabidiol (CBD; the principal non-psychotropic compound derived from *Cannabis Sativa*) has been demonstrated in the treatment of various health conditions, including epilepsy, pain, nausea and anxiety.[1]
- The anti-inflammatory, immunomodulatory, antioxidant and neuroprotective properties of CBD renders it a potential therapeutic compound for patients with Prader-Willi Syndrome (PWS).
- However, CBD has high lipophilicity and low oral bioavailability in humans due to incomplete absorption and extensive first-pass metabolism – approximately 75% of an oral dose is metabolized hepatically before it reaches systemic circulation[2], and therefore presents challenges for its clinical use.
- EPM301, a novel CBD analogue in pre-clinical evaluation, is a promising candidate for the treatment of PWS.

EPM301, a novel CBD synthetic analogue[3]

- A stable analogue of cannabidiolic acid developed by EPM Therapeutics.



- EPM301(20 and 40 mg/kg/day, intraperitoneally) effectively reduced body weight and hyperphagia in a high-fat diet-fed *Magel2*^{null} mouse model of PWS.[3]

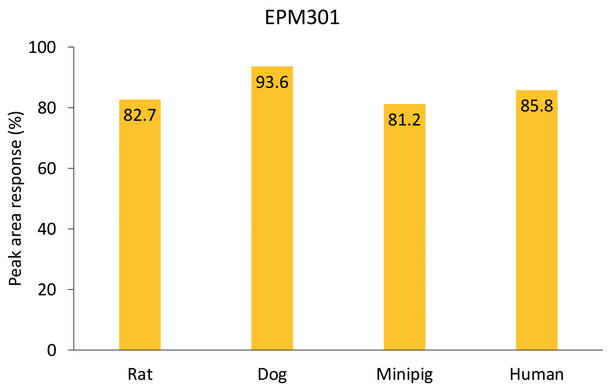
In vitro metabolism of EPM301[4]

Methods

- The *in vitro* biotransformation of EPM301 was assessed, using rat, dog, minipig and human hepatocytes, to characterize the metabolites.
- EPM301 was incubated at a nominal concentration of 10 µM with hepatocytes in suspension in Leibovitz L-15 medium.
- Samples were taken at 0 and 4 hours and analysed using accurate mass LC-MS/(MS) to determine relative proportions of EPM301 present at each timepoint and determine the profile of the metabolites formed.
- Positive control incubations with [^{14}C]7-ethoxycoumarin were performed to ensure suitable metabolic capacity of the hepatocytes used in the EPM301 incubations.

Results

- Following the incubation with EPM301, with cryopreserved hepatocytes in suspension for up to 4 hours, limited metabolism of EPM301 was observed in all species.
- The parent compound, EPM 301 and 14 further components were detected (above 1% of total response) across the samples analysed.
- The parent compound, EPM301, accounted for 82.7% of the total peak area response in rat, 93.6% in dog, 81.2% in minipig and 85.8% in human, following incubation for up to 4 hours.
- Based on the % total peak area response of EPM301 remaining after 4-hour incubation with hepatocytes, the extent of metabolism was minipig > rat > human > dog.



- The most abundant metabolite was M13 (EPM301 + O), which had a total peak area response of 4.0%, 0.2%, 5.0% and 4.0% in rat, dog, minipig and human hepatocytes, respectively, followed by M9 (EPM301 + $C_6H_8O_6$) which had a total peak area response of 0.2%, 4.0%, 3.3% and 2.6% in rat, dog, minipig and human hepatocytes, respectively.

- All the metabolites detected in human hepatocytes samples were also detected in one or more of the animal species – there were no unique *in vitro* human metabolites observed.
- Based on the qualitative data obtained, the minipig is the most comparable to human.

In comparison with CBD, where the major metabolites in rat, dog, and human liver microsomes and hepatocytes *in vitro* were 7-OH-CBD, 7-COOH-CBD, and 6-OH-CBD[5], the *in vitro* biotransformation of EPM301 is distinct and dramatically different.

Pharmacokinetics of EPM301 and CBD following intravenous and oral administration[6]

Methods

- The objective of this study was to measure the pharmacokinetics of EPM301 and CBD following intravenous and oral administration to male Han Wistar rats.
- Each animal received a single intravenous or oral dose of EPM301 or CBD.
- The intravenous formulation vehicle for EPM301 was 4% DMSO, 1% Tween 80, and 95% saline , and for CBD, 2% Ethanol in 5% Kolliphor EL in Phosphate Buffered Saline. The oral formulation vehicle for both EPM301 and CBD was 4% DMSO, 1% Tween 80, and 95% saline.

Test substance	Dose route	Dose level (mg/kg)
EPM301	Intravenous	1
EPM301	Oral	5
EPM301	Oral	25
EPM301	Oral	50
CBD	Intravenous	1
CBD	Oral	5

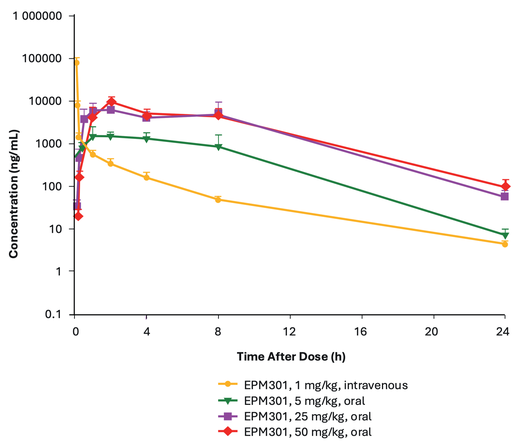
- Following dosing, blood samples were collected from each animal at the following timepoints: *Predose, 1 (Intravenous dosed animals only), 7, 15, 30 min, 1, 2, 4, 8 and 24 hours post dose.*
- Concentrations of EPM301 and CBD were determined using liquid chromatography with tandem mass spectrometric (LC-MS/MS) methods.
- Concentrations of both EPM301 and CBD were determined in the samples collected from the EPM301 dosed animals.

Results

- During the course of the study, no overt pharmacological or toxicological signs that could have been attributed to the administration of the test substance were observed in the test animals.
- EPM301 does not appear to metabolise to CBD following administration, as confirmed by no measurable concentrations of CBD being observed in any of the samples collected in the animals dosed with EPM301.
- The mean concentrations (ng/mL) of EPM301 following intravenous and oral administration are shown below:

Route	Dose (mg/kg)	Time after dose (h)									
		Pre-dose	0.0167	0.117	0.25	0.5	1	2	4	8	24
IV	1	0.00	75600	7480	1410	847	542	333	156	48.4	4.57
Oral	5	0.00	NA	20.8	193	931	1460	1530	1260	865	7.36
Oral	25	0.00	NA	33.6	449	3600	5540	6270	4030	4660	57.3
Oral	50	0.00	NA	20.9	171	634	4020	9330	4980	4320	93.3

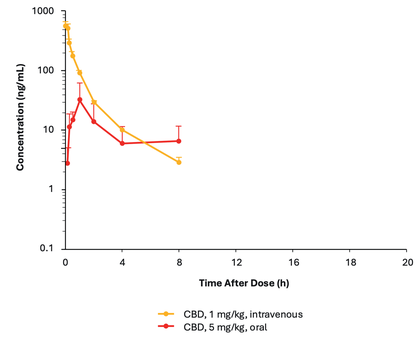
NA, not applicable



- The mean concentrations (ng/mL) of CBD following intravenous and oral administration are shown below:

Route	Dose (mg/kg)	Time after dose (h)									
		Pre-dose	0.0167	0.117	0.25	0.5	1	2	4	8	24
IV	1	0.00	577	545	301	180	92.3	29.6	9.92	2.90	0.00
Oral	5	0.00	NA	2.74	11.2	14.8	32.6	13.8	6.01	6.64	0.00

NA, not applicable



- The mean pharmacokinetic parameters for EPM301 and CBD following a single intravenous or oral administration are provided below:

Test substance	Route of administration	Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (h*ng/mL)	$t_{1/2}$ (h)
EPM301	IV	1	75600	8720	3.92
	Oral	5	1970	16300	2.61
	Oral	25	7660	47800	3.26
	Oral	50	9330	76700	3.33
CBD	IV	1	622	384	1.85
	Oral	5	35.2	131	1.68

- The absolute bioavailability following oral administration was higher for EPM301, with the value of 37.4% and 4.94% following dosing of EPM301 and CBD at 5 mg/kg, respectively.

Analyte	%F					
	DN $AUC_{0\text{-}t}$			DN $AUC_{0\text{-}inf}$		
	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

- Exposure was less than dose proportional for EPM301 which may suggest limited solubility of EPM301 in the oral formulation used in the study, with the increasing concentration.

In rat, EPM301 demonstrated higher C_{max} and AUC levels and superior oral bioavailability when compared to CBD.

Data from these studies confirm that EPM301 is a new, novel CBD analogue, with a different metabolic profile and superior oral bioavailability to CBD.

REFERENCES

1. Fraguas-Sánchez A. I., Torres-Suárez, A. I. *Drugs* 2018;78:1665-1703.
2. Perucca E, Bialer M. *CNS Drugs* 2020;34(8):795-800.
3. Ben-Cnaan E, et al. *Int J Mol Sci.* 2022;23(10):5610.
4. Data on File.
5. FDA Centre for Drug Evaluation, Non-Clinical Review, 2018.
6. Data on File.

SCAN ME

Presented at the FPWR Research Symposium and Family Conference 2024, 25–28 September 2024 , Atlanta, Georgia

epm Therapeutics