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Cognitive Performance and Psychedelic Effects Following Single and Multiple Ascending Doses of a New Cannabis Formulation (PPP001) Administered by Smoking/Inhalation in Male and Female Volunteers

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Abstract

Background: PPP001 is a dried cannabis product for smoked inhalation, being developed for the treatment of chronic pain. Advantages of intrapulmonary administration of cannabinoids (e.g., by smoking) include high systemic bioavailability and fast onset of action. (1) However, adverse events, including cognitive dysfunction, may be observed depending on exposure levels. The objectives of this study were to evaluate the safety, tolerability, and cognitive effects of PPP001 following administration via smoked inhalation over 1 or 7 consecutive days (including 5-day titration) in a repeat dose frequency fashion.

Methods: A randomized, double-blind, placebo-controlled, single (3 cohorts) and multiple (3 cohorts) staggered drug administration regimens (once [QD], twice [BID] or three [TID] times a day) design in 48 subjects (8 subjects/cohort; 2 placebo; 6 active). PPP001 (25 mg THC / 5.5 mg CBD) and placebo (0 mg THC / 0.8 mg CBD) were administered by smoking/inhalation with a titanium pipe at a dose of 9% (25 mg) THC / 2% (5.5 mg) CBD, QD (cohort A1), BID (cohort A2) or TID (cohort A3), 4 hours apart, for 1 day (Part A) and following a 5-day titration and 2 days of full assigned regimens (Part B, cohorts B1 to B3). Part A did not have specific fixed period for inhaling the whole pellet. Part B Day 7 had a fixed period of inhalation of 15 minutes. Number of inhalations required per administration(s) were taken as follows:
- Day 1: 2 inhalations within 15 minutes
- Day 2: 3 inhalations within 15 minutes
- Day 3: 4 inhalations within 15 minutes
- Day 4: 5 inhalations within 15 minutes
- Days 5 to 7: unlimited number of inhalations until the whole pellet(s) is/are smoked within 15 minutes.

Pharmacodynamic (PD) assessments included the Bowdle Visual Analog Scales (VAS), assessing subjective drug effects, as well as Choice Reaction Time (RTI), Paired Associate Learning (PAL), Spatial Working Memory (SWM) and the Rapid Visual Information test (RVP) assessing cognition/psychomotor processing. PD assessments were performed at baseline and 0.5, 1 and 2.5 hours following each drug administration. Descriptive analysis was performed using summary statistics. Pharmacokinetic, safety assessments, and cardiac safety monitoring were performed during the study.

Results: Subjects in Part A smoked the entire pellet using an average of 8 to 9 puffs, regardless of the dosing frequency (QD, BID, TID). Subjects in Part B used an average of 7 puffs to smoke the whole pellet, on Day 5, 6 and 7, across the different dosing frequency.

In Part A, a marked increase in Drug High was observed for PPP001 compared to placebo across each cohort for Part A (maximum peak effect ranged from 32.80 to 42.40 and 8.75 to 20.50, respectively). No cumulative effect was observed upon QD, BID or TID regimen (4 hours apart) administered on a single day. Similar trend (marked change from baseline) was observed for the psychomotor testing (e.g. processing speed, episodic learning/memory, working memory, executive function, sustained attention and psychomotor speed). Similar results were obtained for Part B. Overall AE incidence was 92% (22 / 24) in subjects who received either cannabis or placebo. Majority of the AEs were mild in intensity (80%). For THC and CBD T_{max} ranged from 0.05 - 0.17 h and 0.02 - 0.17 h, while AUC increased from 30 to 94 ng*h/mL and 7.8 to 21 ng*h/mL across cohorts, respectively. Both THC and CBD were eliminated in less than 1.6 hours (T1/2).

Discussion: Following controlled acute QD, BID or TID, administration(s) of cannabis by smoking/inhalation 4 hours apart, psychedelic effects and cognitive performance measures were different compared to placebo (increase or decrease) while no accumulation of the cognitive effect was observed. PK results also showed no evidence of accumulation and treatments were generally well tolerated.

1. Solowij N, Broyd SJ, Beale C, Prick J-A, Greenwood L-M, van Hell H, Suo C, Galettis P, Pai N, Fu S, Croft RJ, Martin JH, Yücel M. Therapeutic Effects of Prolonged Cannabidiol Treatment on Psychological Symptoms and Cognitive Function in Regular Cannabis Users: A Pragmatic Open-Label Clinical Trial. Cannabis Cannabinoid Res. 2018;3:21-34.

Objectives

The objectives of this study were to evaluate the safety, tolerability, and cognitive effects of PPP001 (25 mg THC / 5.5 mg CBD) following its administration via smoked inhalation over 1 or 7 consecutive days (including a 5-day titration). Only the cognitive performance and subjective effects of PPP001 are discussed in this presentation.

Methods

Figure 1. Study Design – Single and Multiple Ascending Dosing Frequency

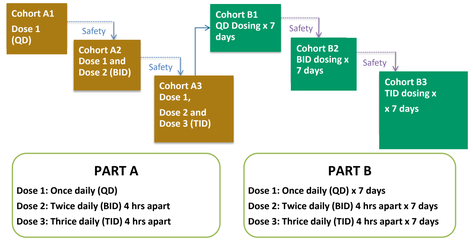


Table 1. Sample Size

Dose	Placebo	Cohort			Pool N (placebo: active)
		Cohort A1/B1	Cohort A2/B2	Cohort A3/B3	
Dose 1 (Cohorts A1 to A3)	6	6	6	6	6:18
Dose 2 (Cohorts A2 and A3)	4	0	6	6	4:12
Dose 3 (Cohort A3)	2	0	0	6	2:6

Pharmacodynamic Assessments:

Time points: Prior to 1st administration and 0.5, 1 and 2.5 hours after each study drug administration on Day 1 (Part A) and on Day 7 (Part B).

Cognitive Measures:

1. Spatial Working Memory (SWM) – Executive Functioning (Strategic Thinking) Alongside Working Memory
   - **Executive Function: Strategy**
   - **Working Memory: Between Errors**
2. Psychomotor Processing Speed: **Median 5-Choice Reaction Time (RTI)**
3. Paired Associate Learning (PAL) – **Episodic Learning/ Memory: Total Errors Adjusted**
4. Rapid Visual Information test (RVP) – Sustained Attention
   - **Psychomotor Speed: Median Latency**
   - **Sustained Attention: A' Prime**

Cognitive and psychomotor performance was assessed using computerized tasks validated to demonstrate accuracy in measuring cognitive impairment by Cambridge Neuropsychological Test Automated Battery (CANTAB).

Subjective Measures:

1. Feeling High
2. Feeling Drowsy

A 100-mm visual analog scale with the horizontal line anchored with 0 on the left and 100 on the right was used.

Statistical PD Analysis:

Only descriptive statistics were presented for change from baseline (CFBmax/min) and maximum effect (Emax). Statistical significance was not tested due to small sample size. Thus, inferential statistical comparison between placebo and active, as well as between the different dosing regimens, was not performed.

PK Assessments and Safety Results were presented at other meetings.

Results

Table 2. Summary Statistics of Cognitive Performance Tasks and Subjective Effects – PART A

PART A		DOSE					
		Dose 1 QD (Pool Cohorts A1 to A3)		Dose 2 – BID (Pool Cohorts A2 and A3)		Dose 3 -TID (Cohort A3)	
		Active	Placebo	Active	Placebo	Active	Placebo
Cognitive Measures	**Statistics**	**Maximum Change From Baseline (CFBmax)**					
Executive Function: Strategy (SWM)	n	15	6	10	4	5	2
	Mean (SE)	3.20 (0.81)	1.33 (0.92)	5.00 (0.88)	2.00 (1.78)	3.60 (2.01)	-1.50 (3.50)
Working Memory: Between Errors (SWMBE)	n	15	6	10	4	5	2
	Mean (SE)	27.60 (5.29)	6.83 (4.14)	24.20 (5.04)	11.25 (8.09)	16.40 (1.84)	0.00 (25.00)
Psychomotor Processing Speed: Median 5-Choice Reaction Time (RTI)	n	15	6	10	4	5	2
	Mean (SE)	16.00 (10.56)	8.42 (23.31)	21.25 (13.39)	-5.75 (29.09)	22.30 (18.51)	17.00 (1.50)
Episodic Learning/ Memory: Total Errors Adjusted (PAL)	n	15	6	10	4	5	2
	Mean (SE)	2.07 (1.98)	0.00 (1.48)	4.10 (1.64)	-0.50 (0.96)	6.80 (1.16)	0.00 (0.00)
Psychomotor Speed: Median Latency (RVP)	n	15	6	10	4	5	2
	Mean (SE)	39.10 (15.17)	31.25 (15.49)	1.30 (14.09)	4.00 (17.55)	-37.30 (17.49)	-14.25 (0.25)
		Minimum Change From Baseline (CFBmin)					
Sustained Attention: A' Prime (RVP)	n	15	6	10	4	5	2
	Mean (SE)	-0.017 (0.01)	0.003 (0.01)	-0.006 (0.01)	0.003 (0.01)	-0.010 (0.02)	0.000 (0.03)
Subjective Measures		**Maximum Effect (Emax)**					
Bowdle Bundle: Feeling High	n	15	6	10	4	5	2
	Mean (SE)	39.47 (7.58)	17.17 (9.29)	32.80 (9.25)	8.75 (8.75)	42.40 (16.42)	20.50 (20.50)
Bowdle Bundle: Feeling Drowsy	n	15	6	10	4	5	2
	Mean (SE)	52.33 (7.50)	2.00 (1.81)	40.50 (10.12)	0.00 (0.00)	44.80 (14.61)	0.00 (0.00)

Table 3. Summary Statistics of Cognitive Performance Tasks and Subjective Effects – PART B

PART B		DOSE					
		Dose 1 QD (Pool Cohorts B1 to B3)		Dose 2 BID (Pool Cohorts B2 and B3)		Dose 3TID (Cohort B3)	
		Active	Placebo	Active	Placebo	Active	Placebo
Cognitive Measures	**Statistics**	**Maximum Change From Baseline (CFBmax)**					
Executive Function: Strategy (SWM)	n	17	6	11	4	5	2
	Mean (SE)	1.647 (1.00)	0.167 (1.45)	3.182 (1.50)	-5.250 (2.84)	2.400 (1.12)	-8.50 (3.50)
Working Memory: Between Errors (SWMBE)	n	17	6	11	4	5	2
	Mean (SE)	14.35 (4.87)	6.33 (7.74)	10.36 (9.23)	-15.50 (6.90)	8.00 (14.04)	-14.50 (15.50)
Psychomotor Processing Speed: Median 5-Choice Reaction Time (RTI)	n	17	6	11	4	5	2
	Mean (SE)	18.12 (8.18)	8.58 (8.39)	24.46 (10.33)	3.75 (9.94)	28.20 (16.03)	-2.50 (19.00)
Episodic Learning/ Memory: Total Errors Adjusted (PAL)	n	17	6	11	4	5	2
	Mean (SE)	-1.29 (1.05)	2.33 (2.74)	-2.46 (1.32)	-2.75 (2.32)	0.80 (3.23)	-3.00 (1.00)
Psychomotor Speed: Median Latency (RVP)	n	17	6	11	4	5	2
	Mean (SE)	26.00 (18.69)	18.92 (17.35)	26.59 (26.28)	-19.63 (52.00)	17.00 (51.46)	-106.75 (73.75)
		Minimum Change From Baseline (CFBmin)					
Sustained Attention: A' Prime (RVP)	n	17	6	11	4	5	2
	Mean (SE)	-0.012 (0.01)	-0.007 (0.01)	0.000 (0.01)	-0.030 (0.02)	-0.021 (0.03)	-0.023 (0.05)
Subjective Measures		**Maximum Effect (Emax)**					
Bowdle Bundle: Feeling High	n	17	6	11	4	5	2
	Mean (SE)	50.24 (7.00)	15.17 (9.38)	49.45 (8.62)	11.50 (10.84)	54.20 (10.22)	1.50 (1.50)
Bowdle Bundle: Feeling Drowsy	n	17	6	11	4	5	2
	Mean (SE)	40.71 (8.05)	10.00 (5.12)	37.27 (8.42)	21.75 (7.36)	44.40 (10.80)	38.00 (16.00)

Figure 2. Pooled Change-From-Baseline Values Over Time By Treatment (Active vs Placebo) And Dosing Frequency (Doses 1, 2 and 3).

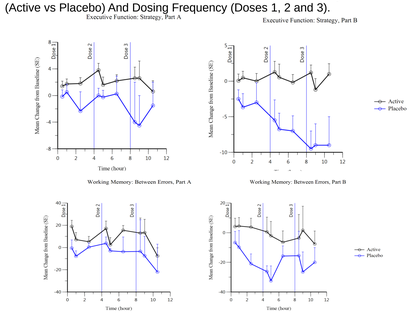
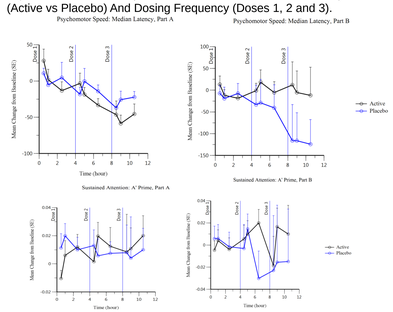


Figure 3. Pooled Change-From-Baseline Values Over Time By Treatment (Active vs Placebo) And Dosing Frequency (Doses 1, 2 and 3).



Spatial Working Memory (SWM) – Executive Functioning (Strategic Thinking) Strategic thinking was assessed by counting the number of times a subject began a new search pattern from the same box they started with previously. The subject had to search for tokens hidden in boxes on screen. If the subject always began a search from the same starting point, it was inferred that the subject was employing a planned strategy for finding tokens. A low score indicated high strategy use.

- A greater positive difference between baseline and post-dosing assessments (CFB) suggested a trend towards less effective strategic thinking (executive functioning) for subjects dosed with PPP001 when **compared to placebo**, particularly following repeated dosing with PPP001 (Part B). These effects were observed right after the 1st Dose.
- It is also observed that following **cumulative** dosing (Dose 2 and Dose 3), strategic thinking appears to improve more markedly and rapidly for placebo than active treatment indicative of a greater improvement in performance when not on active treatment while it did not appear to worsen when on active treatment.

Rapid Visual Information (RVP) Test – Sustained Attention: The median response latency on correct responses was assessed through the rapid visual information processing (RVP), evaluating sustained attention measured in milliseconds (ms). Mean change from baseline over time showed that the reaction time decreased across the testing day, suggestive of an improvement in performance, which appeared to be similar between placebo and the active treatment, with similar CFBmax for Part A. This same improvement was not observed for cohorts repeatedly dosed with PPP001 for 7 consecutive days (Part B). **A'prime** measured sustained attention by assessing ability to detect a target sequence (scores were expected to vary between 0 and 1, with higher score reflecting better performance). There was no clear trend in subject performance between placebo and active treatment, as the CFBmin remained generally similar between active and placebo treatments, and also following cumulative doses of PPP001 for both Parts.

Paired Associate Learning (PAL) – Episodic Memory
A low score indicated a low number of errors. Inspection of the time course of cumulative dosing (Doses 1 through 3) suggests a systematic increase in CFBmax after each dose of PPP001 (from 2.1 following Dose 1 to 6.8 following Dose 3) while consistent performance was observed following placebo as shown by a CFBmax near zero. The difference in CFBmax between active and placebo after Dose 1, Dose 2, and Dose 3 increases from 2.1 to 6.8 indicative of a sustained lower performance following active treatment. This same trend was not observed following repeated PPP001 administration for 7 consecutive days.

Choice Reaction Time (RTI) – Processing and Psychomotor Speed
Reaction Time Index (RTI) is a processing and psychomotor speed task. The median time for a subject to release the response button after presentation of a target stimulus was assessed in milliseconds. CFBmax was consistently higher than the placebo, although the gap with placebo appeared to be narrowing after the third dose (TID). The gap increased slightly following prolonged exposure to PPP011 for 7 days (Part B). However, the effect of cumulative doses in 1 day did not appear to accentuate the difference in processing and psychomotor speed as compared to placebo.

Conclusion:

In general, the differences between placebo and active treatment were lower for Part A, single day of exposure and while they tended to increased following repeated exposure of PPP001 (Part B, 7 consecutive days). In addition, cumulative frequency of dosing (Dose 2 and Dose 3) did not enhance subjective drug effects and cognitive and psychomotor effects observed after Dose 1, suggesting that repeated administration of the PPP001 formulation is not expected to accentuate the observed impairment on cognitive performance assessed using CANTAB.

Smoked PPP001 produced subjective drug effects, feeling high and drowsy, and some cognitive and psychomotor impairment as compared to placebo (mainly a decrease in executive functioning/strategic thinking) without being accentuated by cumulative dosing (BID, TID, 4 hour apart), or by chronic administration for 7 days. These data are valuable for clinical decisions surrounding the use of PPP001 (25 mg THC / 5.5 mg CBD) among adults with prior limited recreational cannabis use. No inferential statistics were performed due to low sample size, therefore it is suggested to interpret these results with great caution.

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