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A First-in-Human Trial Comparing Pharmacokinetics, Pharmacodynamics and Safety of Cannabis Following Multiple, Ascending Doses of Dried Pellets Delivered by Smoking Inhalation

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PURPOSE

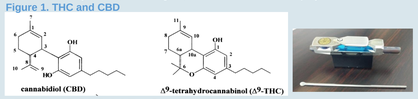
Cannabis is one of the oldest and most commonly abused drugs in the world. It is used in many areas as a medicinal product, but combustible cannabis has never received regulatory approval as a drug. Due to the promising data of the potential of using cannabis for pain and the very fast PK seen with inhaling combustible cannabis, Tetra Bio-Pharma developed cannabis pellets (PPP001) for combustion and are following the regulatory pathway for approval.

This study was designed as a first-in-human study to investigate the safety and tolerability, as well as the PK/PD profile, of this combination, when smoked/inhaled as intended in clinical therapeutic use (i.e. patients with neuropathic pain).

METHOD(S) - STUDY DESIGN

- This was a single-center, randomized, placebo-controlled, single and multiple ascending dose, parallel group study with the administration of 25 mg THC/5.5 mg CBD by smoking/inhalation in a subject population comprised of adult males and females who are social user of cannabis.
- SAD: Subjects received a single 25 mg inhaled dose of cannabis given once, twice or three times daily (4 hours apart).
- MAD: Subjects received a single 25 mg inhaled dose of cannabis given once, twice or three times daily (4 hours apart) over multiple days (7 consecutive days). Consecutive dosing should allow testing of the tolerability of chronic administration.
- To investigate the impact of the THC/CBD pharmacological activity on the cognition activity, cognitive tests were performed before and throughout the treatment and compared to the plasma levels of THC/CBD following single and multiple dosing.
- Blood samples for measurement of THC, OH-THC and CBD concentrations were collected pre-dose and over a 24-hour period post-dose.
- Safety endpoints included the occurrence of adverse events (AEs), clinical laboratory tests, vital signs, 12-lead ECGs and physical examination.

Figure 1. THC and CBD



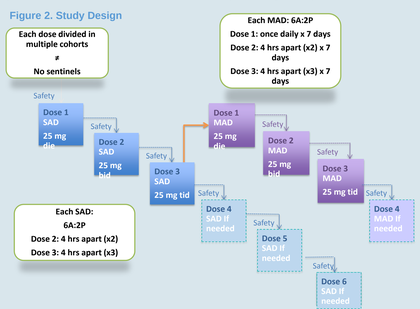
ETHICS AND SAFETY

- Ethics and Regulatory: The protocol was approved by the ethics committee and Health Canada with some modifications
- Safety: As cardiovascular and central nervous system events are reported with THC and CBD the I/E criteria were designed to exclude any subjects who might be at risk.
- The inclusion of volunteers who socially used cannabis was recommended

BIOANALYTICAL AND STATISTICAL ANALYSIS

- Samples were quantified for plasma THC, OH-THC, and CBD using validated LC-MS/MS methods
- Noncompartmental PK analysis was performed (Phoenix® WinNonlin® 6.3)
- Cognitive results were described and compared against placebo

Figure 2. Study Design



COMPLEXITIES

- A room with specialized ventilation was used to quickly exchange the air and not expose patients who received placebo to the active in dosed subsequently. Only 1 subject could be present in the room at a time
- Staff performed procedures during dosing, such as blood draws, had to required that they wear environmental protection suits with ventilators
- External groups experienced with use of medicinal cannabis (Santé Cannabis) came to train clinical staff on inhalation procedure with the titanium pipe
- Response to recruitment was very good, but the screen fail rate was ~ 4:1
- Subjects became anxious after dosing which required the investigator was always visible from the room where dosing occurred (see picture below)

SUBJECTS:

- It has to be verified that they were able to inhale the product using the pipe and following the cued puff procedures
- Training was required for PD cognitive testing

MAIN IE CRITERIA

- Male or female aged of at least 25 years but not older than 60 years and with a BMI within 21.0 to 32.0 kg/m^2, inclusively
- Volunteer who had history of cannabis recreational use (at least 10 times in their lifetime)
- No use of cannabis within the previous 3 months of dosing
- Volunteer able to use a pipe and follow instructions during the training smoking session
- Normal vital signs, ECG, and chest X-ray
- No psychiatric disorders revealed during medical history
- Other typical I/E criteria

DRUG ADMINISTRATION

- Each cohort received THC/CBD
- 280 mg dried cannabis pellet at the following doses: 9% THC and 2% CBD 25 mg THC / 5.5 mg CBD (PPP001)
- Placebo – 280 mg dried pellet: 0 mg THC / 0.8 mg CBD

STEPS TO FOLLOW:

- A cued-puff procedure standardized the administration of the THC/CBD
- Participants were verbally signaled to:
  - "light the pellet" (5-10 seconds);
  - "get ready" (5 seconds)
  - "inhale" (3 seconds);
  - "hold smoke in lungs" (3 seconds);
  - "exhale" and wait before repeating the puff cycle (30 seconds);
  - The volunteer repeatedly inhaled the smoke until the titanium pipe no longer generated smoke

PK AND PD ANALYSIS

- As per protocol, sampling schedule was mixed with cognitive tests as well as with vital signals assessment.
- Samples were quantified for TCH, 11-OH-delta-9-THC, and cannabidiol using validated LC-MS/MS method.
- Noncompartmental PK analysis was performed (Phoenix® WinNonlin® 6.3), a dose proportionality analysis and a steady state evaluation was used.
- The cognitive tests were to be assessed with computer based tests and Bowdle visual analogue scales (VAS).
- A training session was performed within the 3 weeks before the first occasion, in order to get acquainted with the pharmacodynamics tests and minimize learning effects
- As per Cantab Test (Cambridge Cognition), attention (processing and psychomotor speed, RVP and RTI), memory (visual episodic memory, PAL), working memory, and strategy (special working memory, SWM) were be evaluated.

RESULTS – SAFETY

Summary of Treatment-Emergent Adverse Events by System Organ Class Experienced by at Least Two Subjects in Any Treatment Group – Part A

System Organ Class MedDRA Preferred Term	Dose THC 25 mg (N=6)	25 mg – 2 doses (N=6)	25 mg – 3 doses (N=6)	Placebo (N=6)
Subjects with at least one TEAE	6 (100)	6 (100)	6 (100)	4 (67)
Nervous system disorders	4 (67)	6 (100)	6 (100)	3 (50)
Headache	3 (50)	3 (50)	3 (50)	2 (33)
Somnolence	3 (50)	5 (83)	2 (33)	0
Dizziness	2 (33)	3 (50)	2 (33)	0
General disorders and administration site conditions	4 (67)	5 (83)	5 (83)	2 (33)
Feeling abnormal	2 (33)	5 (83)	4 (67)	0
Fatigue	1 (17)	2 (33)	3 (50)	1 (17)
Feeling cold	1 (17)	2 (33)	1 (17)	1 (17)
Asthenia	0	0	2 (33)	0
Gastrointestinal disorders	2 (33)	2 (33)	3 (50)	0
Nausea	1 (17)	1 (17)	2 (33)	0
Dry mouth	2 (33)	1 (17)	1 (17)	0
Vascular disorders	1 (17)	3 (50)	2 (33)	0
Pallor	0	2 (33)	2 (33)	0
Psychiatric disorders	3 (50)	2 (33)	2 (33)	0
Euphoric mood	3 (50)	2 (33)	1 (17)	0
Metabolism and nutrition disorders	2 (33)	0	2 (33)	0
Decreased appetite	2 (33)	0	1 (17)	0

Summary of Treatment-Emergent Adverse Events by System Organ Class Experienced by at Least Two Subjects in Any Treatment Group – Part B

System Organ Class MedDRA Preferred Term	Dose THC 25 mg (N=6)	25 mg - 2 doses (N=6)	25 mg - 3 doses (N=6)	Placebo (N=6)
Subjects with at least one TEAE	6 (100)	6 (100)	6 (100)	6 (100)
Psychiatric disorders	4 (67)	5 (83)	6 (100)	3 (50)
Euphoric mood	3 (50)	5 (83)	6 (100)	3 (50)
General disorders and administration site conditions	6 (100)	5 (83)	5 (83)	4 (67)
Feeling abnormal	4 (67)	1 (17)	0	1 (17)
Fatigue	1 (17)	1 (17)	3 (50)	1 (17)
Feeling of relaxation	1 (17)	3 (50)	1 (17)	3 (50)
Feeling cold	1 (17)	0	2 (33)	0
Asthenia	0	0	2 (33)	0
Catheter site pain	2 (33)	0	0	1 (17)
Nervous system disorders	2 (33)	6 (100)	4 (67)	4 (67)
Headache	2 (33)	1 (17)	1 (17)	4 (67)
Somnolence	2 (33)	4 (67)	2 (33)	0
Dizziness	2 (33)	0	2 (33)	0
Disturbance in attention	1 (17)	0	3 (50)	0
Respiratory, thoracic and mediastinal disorders	5 (83)	4 (67)	3 (50)	1 (17)
Throat irritation	3 (50)	2 (33)	2 (33)	1 (17)
Oropharyngeal pain	2 (33)	2 (33)	1 (17)	0
Gastrointestinal disorders	4 (67)	3 (50)	1 (17)	1 (17)
Dry mouth	0	3 (50)	1 (17)	0
Nausea	3 (50)	0	0	0
Cardiac disorders	0	2 (33)	0	0
Palpitations	0	2 (33)	0	0

RESULTS- PHARMACOKINETICS

PART A

Figure 3. Linear Profile of Mean Plasma Concentrations versus Time for THC

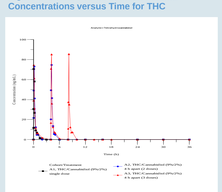
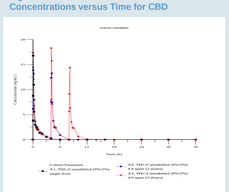


Figure 4. Linear Profile of Mean Plasma Concentrations versus Time for CBD



PART B

Figure 5. Linear Profile of Mean Plasma Concentrations versus Time for THC

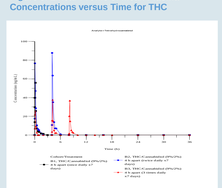
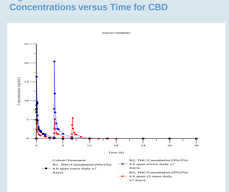
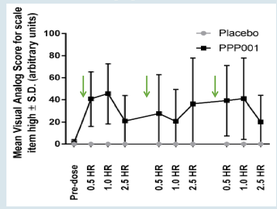


Figure 6. Linear Profile of Mean Plasma Concentrations versus Time for CBD



RESULTS – PSYCHOACTIVITY

Figure 7. Bowdle Results following 3 administrations – Feeling High



GENERAL OBSERVATIONS

- Rate of dropouts due to AEs was not higher than usual for other types of FIH trials
  - Cohort A2: Subject #208 did not receive her 2nd dose due to AEs (fainting)
  - Cohort A3: Subject #301 did not receive his 3rd dose due to AEs (vital signs too low)
  - Cohort B3: Subject #902 did not receive doses 16 to 21 due to AEs (paranoia)
- Logistics were the main challenge considering all the different steps and procedures required in the study, many of which needed to be performed wearing an environmental protection suit and ventilator
- After the training session, the subjects found the pellet and device easy to use
- Subjects followed the cued puff procedure, but large variation was still seen in PK of THC and CBD between subjects
- In general, 7 inhalations were required to consume the whole pellet (about 6-7 minutes)
- Presence of Investigator helped reduce the anxiety of the subjects
- Older volunteers seemed to have more difficulty tolerating the inhalation process and product was better tolerated if within 5 years of prior cannabis use, especially if at least once in the last year

CONCLUSIONS

- Overall, PPP001 was generally safe and well tolerated following its administration over 1 day or 7 consecutive days by smoking/inhalation using a titanium pipe in an escalating fashion to healthy male and female subjects.
- The conduct of the study went very well.
- As expected C_{max} was achieved very quickly, which supports the hypothesis that PPP001 should be able to achieve very fast symptom relief.
- Dosing 4 hours apart even up to 7 days did not result in accumulation, suggesting patients will be able to use PPP001 a number of times a day when their pain increases.
- The PK results of this study also demonstrated that following PPP001 administration as die, bid or tid, 4 hours apart over 1 day versus 7 consecutive days; PK profile of CBD, THC and 11-OH-9-delta-THC did not show meaningful trends over each 4-hour interval where C_{max} and partial AUC were characterized.
- On Day 7, T_{max} ranged from 0.05–0.17 hrs and AUC increased from 5.3 to 30.6 ng*h/mL across cohorts. For CBD, T_{max} ranged from 0.02–0.17 h and AUC increased from 3.0 to 9.5 ng*h/mL across cohorts. Half-life was short with both THC and CBD eliminated from plasma in less than 0.81 and 1.25 hrs postdose, respectively.
- Most AEs were related to CNS: Interesting to see that AEs seemed to decrease over time (Day 7 vs. Day 1).
- The results suggest that this preparation and dosing regimen of PPP001 impairs cognition on the first day of administration at the highest cumulated dose. It is possible that there is tolerance to some of these effects within 7 days of administration.

TETRA BIO-PHARMA

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