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A First-in-Human (FIH) Cannabis Trial: Overview of the Complexity to Conduct a Clinical Trial to Assess Pharmacokinetics and Pharmacodynamics from Single-Ascending Doses of Dried Cannabis Delivered by Smoking - Inhalation

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Abstract

BACKGROUND: Cannabis, is a well-known and widely used product, but dried cannabis has never been taken through the regulatory process for approval as a drug. Tetra Bio-Pharma has decided to develop a cannabis pellet (PPP001) delivered through combustion for regulatory approval for indications that require very fast onset of action, such as breakthrough pain. The objectives of this study were to evaluate the safety, PK and PD of Tetra Bio-Pharma's cannabis product in a first-in-human study SAD and MAD in healthy volunteers.
METHODS: The SAD part included 24 healthy subjects (who had history using cannabis > 10 times in their lifetime). Subjects participating in the first three cohorts were to inhale the combusted cannabis using a titanium pipe. The cannabis pellets contained either 25 mg of tetrahydrocannabidiol (THC) and 5.5 mg of cannabidiol (CBD) (PPP001) or a placebo pellet which contained no THC but small amounts of CBD. The subjects we dosed die, bid or tid (each dose separated by 4 hours). Cohorts included 8 subjects (6A:2P). THC and CBD were assayed by LC/MS/MS.
RESULTS: Only SAD results will be discussed. Recruitment was challenging as previous cannabis users must not have consumed the drug within 3 months of study start. Additionally, many cannabis users are cigarette smokers which was prohibited 3 months before dosing. Overall adverse events (AE) incidence was 92% (22 / 24) in subjects who received either cannabis or placebo (study still blinded). The % of AEs for the 25 mg die, bid or tid cohorts was 30 %, 27 % and 43 %. Majority of the AEs were mild in intensity (80%). For THC and CBD Tmax ranged from 0.05 - 0.17 h and 0.02 - 0.17 h, while AUC ranged 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 1.1 and 2.5 hours (T1/2), respectively. Cognitive test were be performed before and throughout the treatment.
CONCLUSION: Cannabis administered as a single 25 mg die, bid or tid regimen was generally safe and fairly well tolerated. PK of THC and CBD were similar across cohorts as the dosing interval (4 hours) allowed baseline return between each administration reflecting high clearance and no accumulation

Purpose

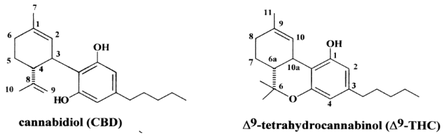
Cannabis is one of the oldest and most commonly abused drugs in the world. It is used in many areas as a medicinal product but combustible cannabis has never received regulatory approval as a drug. Due to the promising data of the potential of using cannabis for pain and the very fast PK seen with inhaling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

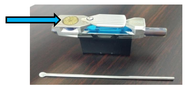
This study was designed as a first-in-human study to investigate the safety and tolerability as well as the PK/PD (cognitive) profile of this combination when smoked/inhaled as intended in clinical therapeutic use (i.e. patients with neuropathic pain).

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. The dose was given once, twice or three times on the same day (4 hours apart) (Figure 2).
- MAD: Subjects received single 25 mg inhaled dose of cannabis given once, twice or three times daily (4 hours apart) over 7 consecutive days. Consecutive dosing should allow to test the tolerability of chronic administration (Figure 2).
- 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 test, vital signs, 12-lead ECG and physical examination.

Figure 1. THC and CBD





* Proprietary device constructed for combusting and inhalation of the product

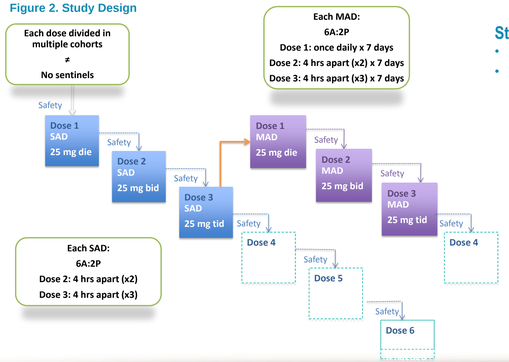
Ethical and Safety

- 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 method
- Noncompartmental PK analysis was performed (Phoenix® WinNonlin® 6.3)
- Cognitive results were to be described and compared against placebo

Figure 2. Study Design



Complexities

- A room with specialized ventilation had to be 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 had to perform procedures during dosing, such as blood draws, requiring that they wear environmental protection suits with ventilators
- External group 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 could inhale the product using the pipe and following the cued puff procedure
  - Training was required for PD cognitive testing

Main IE Criteria

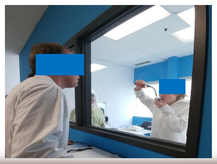
- Male of female aged of at least 25 years but not older than 60 years and with a BMI within 21.0 to 32.0 kg/m2, inclusively
- Volunteer who had history of cannabis recreational use (at least 10 times in their lifetime)
  - No use of cannabis within the previous 3 months of dosing
- Volunteer able to use a pipe & follow instructions at 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 was to smoke/inhale:
  - 280 mg dried cannabis pellet containing 9% THC and 2% CBD (PPP001); or
  - 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 patient repeatedly inhaled the smoke until the titanium pipe no longer generated smoke.



PK Procedure

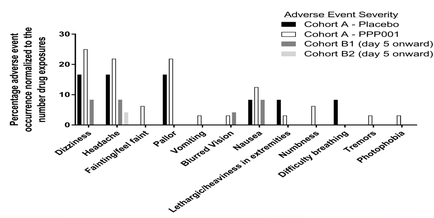
- As per protocol, sampling schedule was mixed with Cognitive tests as well as with vital signals assessment
- Part A1: prior to and 0.02, 0.03, 0.07, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30 and 36 h post-dose
- Part A2 : prior to and 0.02, 0.05, 0.17, 0.25, 0.5, 0.75, 1, 2, 4, 4.02, 4.05, 4.17, 4.25, 4.5, 4.75, 5, 6, 8, 10, 12, 16, 24, 30 and 36 h post-dose
- Part A3: prior to and 0.02, 0.05, 0.17, 0.25, 0.5, 0.75, 1, 2, 4, 4.02, 4.05, 4.17, 4.25, 4.5, 4.75, 5, 6, 8, 8.02, 8.05, 8.17, 8.25, 8.5, 8.75, 9, 10, 12, 14, 16, 18, 24, 30 and 36 h post-dose

PD Procedure

- 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) would be evaluated
- Bowdle scales were based on a list of 13 questions
- Cognitive tests were performed prior to the first drug administration and approximately 0.5, 1 and 2.5 hours after each study drug administration

Safety

Adverse Events	Number of Symptoms in Cohort A	
	Placebo	PPP001
Dizziness	2/12 (~17%)	8/32 (25%)
Headache	2/12 (~17%)	7/32 (~22%)
Fainting	0/12	2/32 (~6%)
Pallor	2/12 (~17%)	7/32 (~22%)
Vomiting	0/12	1/32 (~3%)
Blurred Vision	0/12	1/32 (~3%)
Nausea	1/12 (~8%)	4/32 (~12%)
Lethargic/heaviness in extremities	1/12 (~8%)	1/32 (~3%)
Numbness	0/12	2/32 (~6%)
Difficulty breathing	1/12 (~8%)	0/32
Tremors	0/12	1/32 (~3%)
Photophobia	0/12	1/32 (~3%)

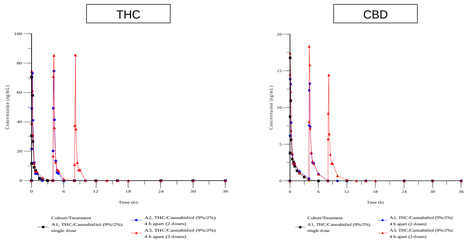


General Observations

- 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 2dn dose due to AEs (fainting)
  - Cohort A3: Subject #301: did not receive his 3rd dose due to AEs (vital signs too low)
- Logistics was 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 (then, about 6-7 minutes)
- Presence of Investigator helped reduce the anxiety of the subjects
- Older volunteers seemed to have more difficulties 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

PK Profiles

- THC
  - Mean C_{max} and AUC_T were similar between each cohort and between each dose but were variable between subjects
  - T_{max} was reached between 0.05 h and 0.17 h after dosing for each cohort
  - $T_{1/2el}$ ranged between 0.15 h and 1.1 h for all doses
- CBD
  - Mean C_{max} and AUC_T were similar between each cohort and between each dose
  - T_{max} was reached between 0.02 h and 0.17h after dosing for each cohort
  - $T_{1/2el}$ ranged between 0.2 h and 2.5 h for all doses



Conclusion

- 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 did not result in accumulation as it allowed baseline return between each administration reflecting high clearance. Although not shown, no accumulation was seen after 7 days as well in comparison do Day 1
- Most AEs were related to CNS : Interesting to see that AEs seemed to decrease over time (Day 7 vs. Day 1)
- Cognitive results remain to be analyzed and compared