ALTASCIENCES

CASE STUDY

Safety and Tolerability Study on the World's First Cannabis Extract Being Developed as a Drug for Regulatory Submission

STUDY OVERVIEW

A first-in-human safety and tolerability study on a cannabis extract (PPP001) smoked using a specialized delivery device, on behalf of Tetra Bio-Pharma. PPP001 is being developed as a drug for regulatory approval in Canada and the United States.

This was a single-center, double-blind, placebo-controlled, randomized within dose study to assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple ascending doses of cannabis (Delta-9-tetrahydrocannabinol/ Cannabidiol) by smoking/inhalation in healthy male and female participants. The investigational drug was a pellet made by compression of cannabis and designed to control the amount of THC and CBD delivered to the participant to allow consistent dosing and ease of use.

STUDY DETAILS

- **Drug Development Phase:** FIH
- **Class of Drug:** CNS
- **Indication:** Breakthrough Pain
- **Population Type:** Healthy Normal
- **# of Participants:** 48
- **Study Design:** single-center, double-blind, placebo-controlled, randomized within dose study to assess safety, tolerability, PK and PD of single and multiple ascending doses (SAD/MAD) of cannabis by smoking/inhalation in healthy male and female participants.
- **Services Provided:** Clinical conduct, Bioanalytics

STUDY PURPOSE

The primary objective of the study was to determine the safety and tolerability of PPP001 following its administration over one day and seven consecutive days when smoked/inhaled as intended for therapeutic use. The secondary objective was to evaluate the PK and PD of THC and CBD.

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METHODS

The study included 48 participants, between 25 and 60 years old, with a BMI between 21.0 and 32.0 kg/m2, inclusively. They were light or ex-smokers of tobacco, and had consumed cannabis recreationally at least 10 times in their lives, but not within the last three months. Participants had normal vital signs, ECG, chest X-rays and clinical labs. Furthermore, they needed to demonstrate that they could follow the instructions for smoking with the device to ensure they could inhale sufficiently.

The PK measurements were done over 24 hours, and the blood samples were analyzed at our bioanalytical laboratory by LC-MS/MS for THC, its active metabolite 11-OH-THC, and CBD. The PD measurements were psychoactivity using the Bowdle Visual Analog Scale (VAS), as well as spatial working memory, visual information processing, paired associative learning and mean reaction time.

The participants were evaluated in two parts:

Part A: SAD. Participants were dosed for one day

Part B: MAD. Participants were dosed daily for seven days.

In each cohort, six participants received 280 mg of dried cannabis (pellet) containing 9% THC and 2% CBD (25 mg THC / 5.5 mg CBD), and two participants received 280 mg of dried comparator, which contained a small about of CBD (0.8 mg), but no THC. The usual ascending dose technique (one morning dose that becomes higher between cohorts) was not followed. Instead, the first cohort received one morning dose, the second cohort received the same morning dose with an additional dose four hours later, and the third cohort received three doses spread out over eight hours. The MAD cohorts followed the same pattern, with the administration continuing for seven days. Following completion of each cohort in both parts A and B, the safety data of the previous cohort was reviewed prior to initiating dosing of the subsequent group.

The protocol was written as an adaptive design to allow for additional cohorts both in the SAD and MAD arms. The SAD could go up to four doses per day with the 25 mg dose, and then continue to 50 mg and 75 mg doses if needed. The MAD could go up to four doses per day for seven days. However, based on the results of the first three cohorts, it was decided that both the SAD and MAD would stop at three cohorts.

The clinical staff and participants received rigorous training on the specifics of the study before it began. The staff was familiarized with the purpose and protocol of the study. They were trained on the dosing procedure (cued-puff, below) and an external group (Santé Cannabis) was brought in to train them on the adequate inhalation procedure with the titanium pipe. They were informed of the possibility that participants may experience anxiety as an AE.

The participants were screened for their ability to inhale properly, and were trained on use of the titanium pipe and cued-puff procedure for dosing, as well as use of the iPad for cognitive tests and VAS.

Cued-Puff Drug Administration

Participants were verbally signaled to perform the following actions:

- Light the pellet (5-10 seconds)
- Get ready (5 seconds)
- Inhale (3 seconds)
- Hold smoke in lungs (3 seconds)
- Exhale
- Wait before repeating the puff cycle (30 seconds)
  - Participants had to complete a deep inhale with a hand on their chest.
  - Once the pellet was completely burned, we checked the grey ashes for remaining green plant material. Any remaining material was used for one final inhalation.

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RESULTS

The results from the SAD demonstrated that some participants did not tolerate the full dose and reported feeling nauseous and dizzy, with one participant fainting. After careful review, the Safety Committee amended the protocol for the MAD cohorts for dose titration over the first four days. The participants would start with one puff on day one, two puffs on day two, and so on, and were instructed to take the entire dose on days five through seven (a full dose is approximately seven puffs). The titration virtually eliminated reports of dizziness and nausea.

The PK results showed a very fast Cmax of 81.2 ng/mL for THC (less than 10 minutes), which was eliminated quickly and showed no accumulation even when dosing every four hours over seven days.

The PD results showed the participants experienced psychoactive effects of cannabis by the first measurement, 30 minutes after dosing (THC was below 10 ng/mL by 30 minutes).

A review of the AEs showed that PD effects started around the Tmax, but because of dosing and PK measurements, we were not able to perform the Bowdle VAS at that time. Even though the PK levels in plasma declined rapidly for a number of the measures such as 'feeling high', the peak effect was observed at 1 hour. By 2.5 hours, the PD effects were still present, at lower levels, even though THC levels were often below 2 ng/mL. Therefore, PPP001 might produce a sustained therapeutic effect after diminishing breakthrough pain.

The conduct of the study went smoothly and the amendment for titration succeeded in greatly reducing the AEs experienced on the first day of dosing. The PK and PD profiles seen were very promising for PPP001 to potentially be effective for the treatment of pain, and definitely warrant the continuation of PPP001's clinical development.

CONCLUSION/WHAT SETS US APART

Altasciences used well-ventilated specialized smoking rooms to quickly replace the smoke-filled air with fresh air and prevent cross-contamination between active and placebo participants. Our experts were able to observe the participants through large windows, such as when guiding the cued-puff procedure. Those inside the room wore decontamination suits so they could take blood samples while the participants were smoking without being exposed to the THC and CBD in the air. Since there was THC and CBD present, we used techniques previously employed in testing nicotine from tobacco smoke to ensure the outside of the test tubes were not contaminated, which could produce anomalous results from blood sample analysis. These techniques were successful in standardizing dosing between participants and in ensuring there was no contamination of samples.

ABOUT ALTASCIENCES

Altasciences is a forward-thinking, mid-size contract research organization offering pharmaceutical and biotechnology companies of all sizes a proven, flexible approach to preclinical and early phase clinical studies, from lead candidate selection to proof of concept. For over 25 years, Altasciences has been integrating into clients' projects to help support educated, faster, and more complete early drug development decisions. Altasciences' full-service solutions include preclinical safety testing, clinical pharmacology, bioanalysis, program management, medical writing, biostatistics, data management and more, all of which can be tailored to specific sponsor requirements.

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