ALTASCIENCES

The Altascientist

FEBRUARY 2018
ISSUE NO. 2

"Innovation is at the core of how we design and conduct clinical studies at Altasciences. When Tetra Bio-Pharma, the sponsor, approached us with the desire to conduct a first-in-human test on their product, a cannabis extract that is formed into a pellet and smoked in a specialized titanium pipe, we were happy to work with them to come up with the ideal design for what would be the first whole plant cannabis extract following the drug pathway for approval."

Dr. Graham Wood, PhD
Executive Vice President, Phase I Clinical Development

Revolutionizing traditional medicine with cannabis-based medicinal products

Cannabis, one of the oldest and most commonly used drugs in the world, is derived from the cannabis sativa plant and contains hundreds of active ingredients. These include the most abundant active constituents, tetrahydrocannabinol (THC), which is the primary psychoactive component of cannabis, and cannabidiol (CBD) which has therapeutic effects but less psychoactivity. They both act on the cannabinoid receptors that are part of the endogenous cannabinoid system. Beyond the well-known psychoactive effects of cannabinoids, new research has shown that these constituents also interact with a number of systems in the body where the cannabinoid receptors are located, leading to the potential therapeutic effects within the central nervous system and its periphery.

This discovery has led researchers to investigate the potential for cannabis-based medicines, from isolated components of cannabis to synthetic cannabinoids or whole plant extracts with a mix of cannabinoids, to treat conditions such as pain, epilepsy, nausea, insomnia, multiple sclerosis, spinal cord injuries, cancer and autoimmune diseases. Other topical applications can target localized pain, such as arthritis and burns, as well as neuropathic pain, for which there are few effective treatments. Finally, cannabinoids are being investigated for a number of dermatological conditions due to their potential effects on epithelial tissues.

It is well-known that aside from medicinal purposes, cannabis has been the drug of choice amongst recreational users, which resulted in it being scheduled as a controlled substance. Consequently, it has become difficult to conduct clinical research involving cannabis. Canada will soon be the first country in the G20 to introduce a legal framework regulating the use of cannabis by adults for non-medical purposes, which will create a countrywide natural experiment for the world to observe. Legalizing cannabis will break down traditional barriers to understanding the clinical and public health impacts of the drug and facilitate medical research.

There is hope that this drug policy change will come at a crucial time, as the opioid crisis spreads through North America, and cannabinoids show potential to treat pain by themselves or in combination with lower doses of opioids. By increasing access to the drug for therapeutic purposes, we will have the opportunity to investigate substitution effects within different populations of people who use opioids which, if successful, can play a dramatic role that will impact pain treatments worldwide. However, the key to implementing the use of cannabinoids to treat pain or other conditions is in continued research to identify the ideal cannabinoid components and doses for different indications. Finally, the product must be available in a dosage form that is safe, easy to use and results in the same dose, day after day.

Supporting Clinical Facts and Research

There are three unique pathways to introduce cannabis-based therapies to the market:

Recreational
Allowed in 8 U.S. states. Canada to follow in 2018.

Medicinal
Allowed in 28 U.S. states. Canada currently allows it.

Regulated Botanical or Drugs
U.S. and Canada are open to submission through NDA or NDS pathways.

The regulated pathway is what is being followed by many sponsors, and the classification of the product as a botanical or a drug is determined by how the finished product is manufactured. If a single or a few cannabinoid constituents are isolated, or it is a synthetic cannabinoid, then the product will be deemed a drug. However, the development pathway does not differ significantly between botanicals or drugs, and either pathway allows sponsors to rely on previously published data on the safety or efficacy of the product. In many cases, the preclinical and parts of the clinical development programs can rely on existing data rather than repeating studies, since many cannabis components have been studied over the years and, more recently, used under the medicinal programs in Canada and across many states.

It is important to note that although many of the studies do not need to be repeated when developing cannabinoids as drugs, the clinical development will almost always need to include initial studies on safety, tolerability and pharmacokinetics. Furthermore, depending on the molecules in question, drug-drug interaction studies may be required since many of the cannabinoids have been shown to be substrates of, and inhibit, products metabolized by Cytochrome P450 enzymes.

Sponsors will also need to consider conducting studies on the abuse potential of any new cannabinoid, since many that have been previously studied are known to have such potential. This has been shown for Dronabinol (synthetic THC) and Nabiximols (a botanical drug in which THC and CBD are the major active components). Compounds such as isolated CBD, which does not produce the same euphoria as THC, might not have the same abuse potential, but regulators may still require clinical studies to establish the facts.

The growing use of cannabis products and its legalization as a social drug are likely to increase the number of individuals going about their activities of daily living, including driving, operating machinery, engaging in work-related activities and social interactions after having consumed cannabis legally. The effect of cannabis use on an individual's cognitive abilities is a serious concern for sponsors looking to develop cannabis-based therapies as drugs. In fact, the FDA just finalized their guidance titled *Evaluating Drug Effects on the Ability to Operate a Motor Vehicle* concerning cognitive effects of drugs. They have made it clear that sponsors should start looking at the cognitive impairments produced by centrally-acting drugs in the early phases of clinical development, and that the measures need to go beyond collecting adverse events (AEs), with the use of targeted cognitive tests. If impairment is detected, which has been the case for many cannabis-based compounds, the FDA recommends conducting a driving study to examine how the cognitive impairments may affect the ability to drive.

Our experience and innovative approach to cannabinoid studies

Altasciences has been conducting studies on cannabinoid-based products for over 10 years and has run over 14 studies on different cannabinoids. We are at the forefront of testing vaping devices and comparing them to combustible products, as we conduct studies to meet the new FDA regulations for tobacco products. We have extensive experience with products delivered by inhalation and, over the years, have tested a large number of steroids and beta agonists delivered in metered-dose and dry-powder inhalers. Our skills also include buccal or sublingual administration, giving us the expertise in all the different delivery methods of cannabinoid therapies.

In addition to the above, we have been conducting CNS-related clinical trials with special populations for over 25 years, including human abuse liability, generalized anxiety disorder, ADHD, depression, sleep and pain — among many others.

Furthermore, Altasciences and Cognitive Research Corporation have partnered to provide sponsors with a leading-edge driving simulator study solution to test the impairing or performance-enhancing effects of a wide variety of drugs on driving abilities in both normal and patient populations. The simulator provides accurate driving performance data comparable in sensitivity to over-the-road testing, but in less time, for less cost, and with no risk of property damage or injuries. Moreover, we are working together to develop a driving scenario that will specifically test the cognitive impairments seen with cannabis use.

Altasciences' Ground-Breaking Case Study

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

In 2017, we conducted 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 by smoking/inhalation in healthy male and female participants. The investigational drug, PPP001, 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 (Figure 1).

Figure 1

The study included 48 participants, between 25 and 60 years old, with a BMI between 21.0 and 32.0 kg/m^2, 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 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 and inhaled as intended for therapeutic use. The secondary objective was to evaluate the PK and PD of THC and CBD. 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 consisted of a single ascending dose (SAD) where the participants were dosed for one day, and Part B consisted of multiple ascending doses (MAD) where the 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 amount 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, but 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 (Figure 2) 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 could stop at three cohorts.

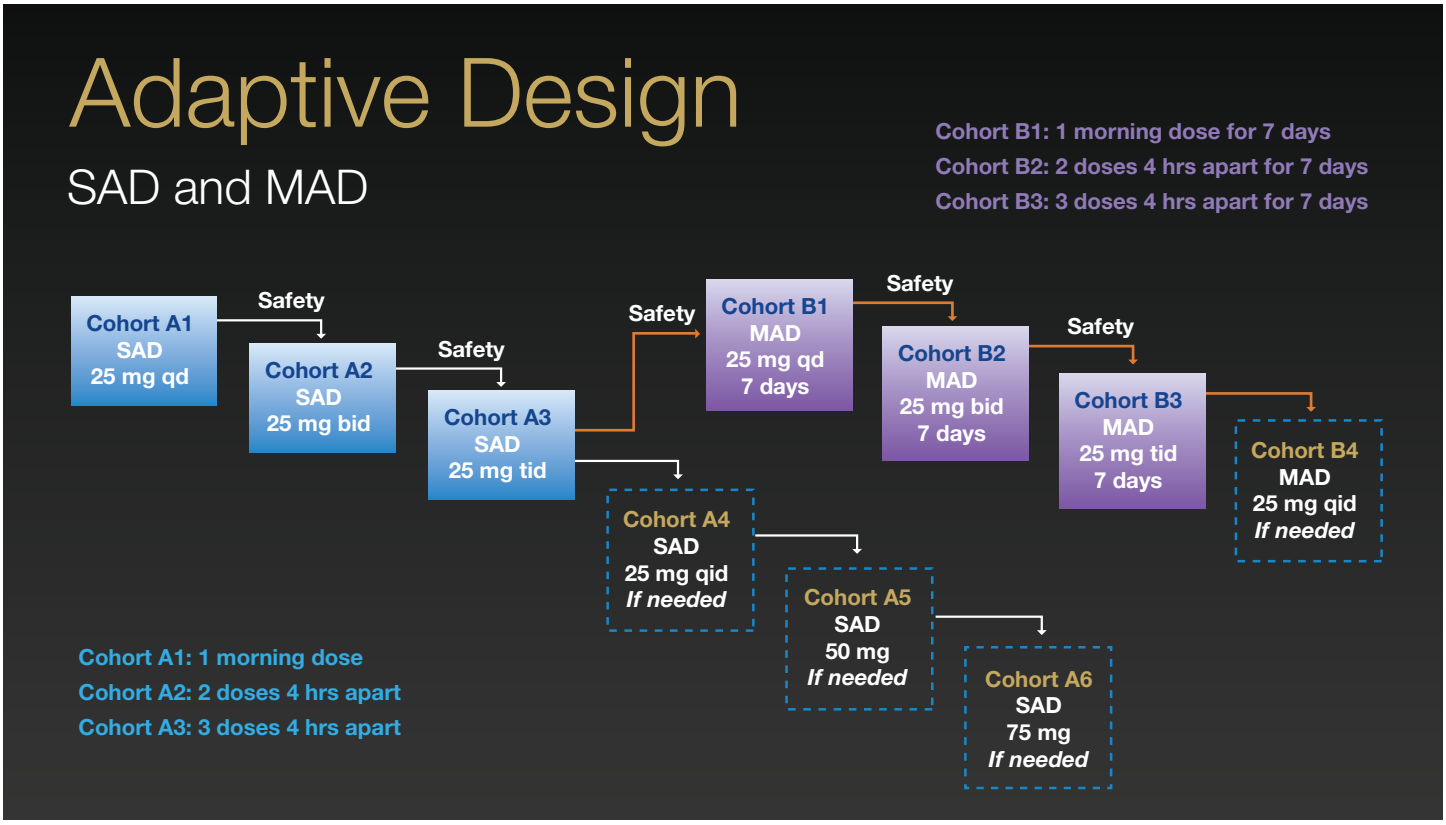


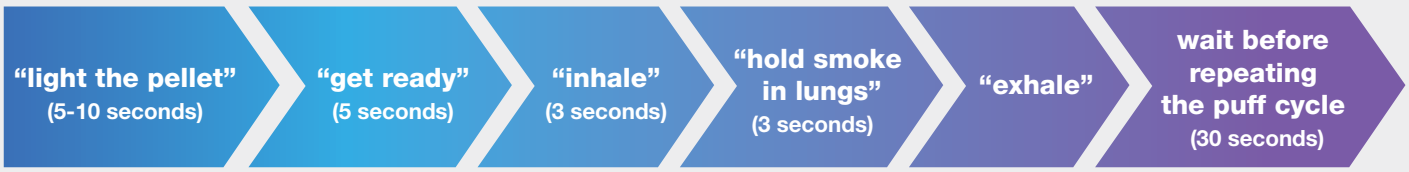
Figure 2

Altasciences' clinical staff and study participants received rigorous training on the specifics of the study before it began. Our staff was familiarized with the purpose and protocol of the study. They were trained on the dosing procedure (cued-puff, Figure 3) and an external group (*Santé Cannabis*) was brought in to train them on the appropriate inhalation procedure with the titanium pipe. They were also made aware that the participants may become anxious.

The participants were screened for their ability to inhale properly and then were trained on how to use the titanium pipe and follow the cued-puff procedure for dosing. Finally, they were trained on how to use an iPad for the cognitive tests and the VAS.

Cued-Puff Drug Administration

Participants were verbally signaled to perform the following actions:



- Participants had to complete a deep inhale with a hand on their chest.
- Once the pellet was completely burned, the grey ashes were checked for remaining green plant material. Any remaining material was used for one final inhalation.

Figure 3

Altasciences used their 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 them through the cued-puff procedure (Figure 4). Staff inside the room wore decontamination suits so they could take blood samples while the participants were smoking, but avoid exposure to the THC and CBD in the air. Also, since there was THC and CBD present, we used techniques previously employed when testing nicotine from tobacco smoke, to make sure the outside of the test tubes that were used did not get contaminated and result in anomalous results when the blood samples were analyzed for THC and CBD. These techniques were successful in standardizing the dosing between participants and in ensuring there was no contamination of samples.

Figure 4

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. Therefore, after careful review, the Safety Committee decided to amend the protocol for the MAD cohorts so that the dose would be titrated over the first four days. The participants would start with one puff on day one, two puffs on day two, and so forth, but were instructed to take the entire dose on days five through seven (a full dose is approximately seven puffs). The titration virtually eliminated the reports of dizziness and nausea.

The PK results showed a very fast Cmax of 81.2 ng/mL for THC (less than 10 minutes), and the latter was eliminated quickly and showed no accumulation even when dosing every four hours over seven days. The hope is that the very fast onset of action will make PPP001 suitable for breakthrough pain.

The PD results showed that participants experienced the psychoactive effects of the 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 the PD effects also 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 went down very quickly for a number of the measures, such as 'feeling high', the peak effect was around 1 hour. By 2.5 hours, the PD effects were still present, but at lower levels, even though THC levels were often below 2 ng/mL. Therefore, PPP001 might produce a sustained therapeutic effect after hopefully diminishing the breakthrough pain.

The conduct of the study went very well and the amendment to add in the titration was successful 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.

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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.

Altasciences… helping sponsors get better drugs to the people who need them, faster.