Listen to a recording of this issue

The Altascientist
SCIENTIFIC JOURNAL

ISSUE NO. 2
Original release 2018
Updated 2022

REVOLUTIONIZING TRADITIONAL MEDICINE WITH CANNABIS-BASED MEDICINAL PRODUCTS

Innovation is the cornerstone of the work we do at Altasciences. When sponsor Tetra Bio-Pharma approached us to conduct a first-in-human test on their product, a cannabis extract being studied for use in breakthrough cancer pain, we collaborated with them on the ideal development plan, including clinical study design and bioanalysis, for the first whole plant cannabis extract following the drug pathway for approval.

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 is widely used as a recreational drug, which resulted in it being scheduled as a controlled substance. Consequently, it has become difficult to conduct clinical research involving cannabis. Canada is the first country in the G20 to introduce a legal framework regulating the use of cannabis by adults for non-medical purposes, which created 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 open new therapeutic options, 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 have the opportunity to investigate substitution effects within different populations of people who use opioids which, if successful, can play a dramatic role in impacting pain treatments worldwide. 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. The product must be available in a dosage form that is safe, easy to use and delivers consistent therapeutic levels.

SUPPORTING CLINICAL FACTS AND RESEARCH

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

Recreational
Legal in 18 (and counting) U.S. states, and all Canadian provinces and territories.

Medicinal
Legal in 37 U.S. states, and all Canadian provinces and territories.

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

The regulated pathway is being followed by many sponsors, and the classification of the product as a botanical or a drug is determined by the manufacturing method of the finished product. If a single or several cannabinoid constituents are isolated, or it is a synthetic cannabinoid, then the product will be deemed a drug. 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. Often, the preclinical, and part 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 used under the medicinal programs in Canada and certain U.S. states.

It is important to note that although some studies can be waived when developing cannabinoids as drugs, the clinical development typically must include initial studies on safety, tolerability and pharmacokinetics. Depending on the molecules in question, drug-drug interaction studies may be required since many cannabinoids have been shown to be substrates and inhibitors of products, products metabolized by cytochrome P450 enzymes.

Sponsors will also need to consider conducting human abuse potential (HAP) studies for any new cannabinoid, as previous research indicates they 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 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, after having legally consumed cannabis. The effect of cannabis on an individual's cognitive abilities is a serious concern. In fact, in 2017 the FDA finalized their guidance titled Evaluating Drug Effects on the Ability to Operate a Motor Vehicle concerning cognitive effects of drugs. They have stated a clear position that sponsors should consider 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, the FDA recommends conducting a driving study to examine how the cognitive impairments may affect the ability to drive.

ALTASCIENCES' EXPERIENCE AND INNOVATIVE APPROACH TO CANNABINOID STUDIES

Altasciences has been conducting studies on cannabinoid-based products for over 10 years and has run over 25 studies on different cannabinoids. We are at the forefront of testing all the different delivery methods of cannabinoid therapies.

We have vast experience 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.

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' 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) 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 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.

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.

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 taken 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 amended; 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 (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.

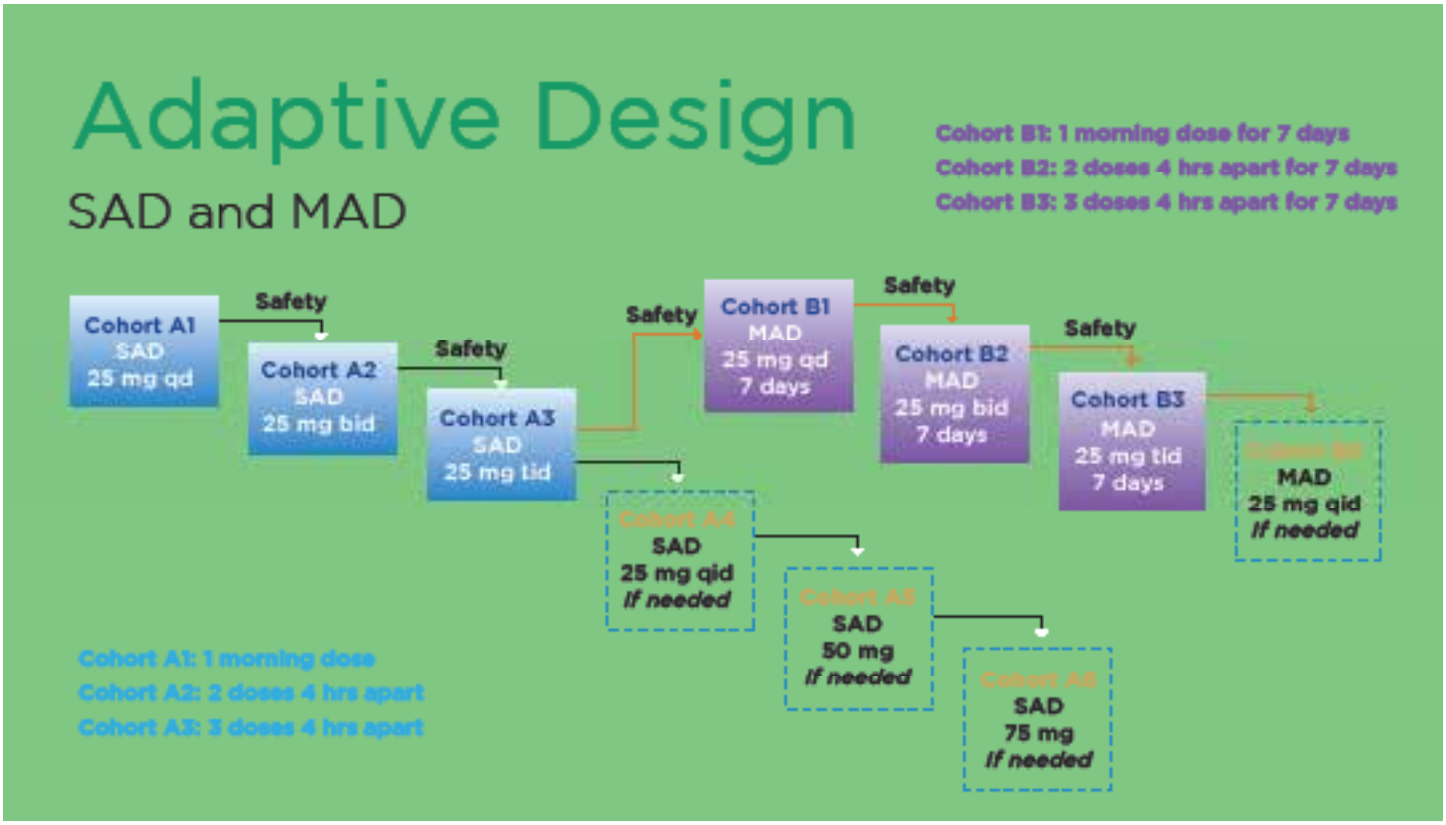

Figure 2

Altasciences' clinical staff and study participants received rigorous training on the specifics of the study prior to startup. Our staff was familiarized with the purpose and protocol of the study. They were trained on the dosing procedure and an external group (Santé Cannabis) was brought in to train them on the appropriate dosing procedure. They were also sensitized to the possibility that the participants may become anxious.

The participants were screened for their ability to follow the dosing procedure and use a tablet for cognitive testing and VAS.

Altasciences used their purpose-built, testing facilities to closely observe and ensure that participants followed the protocol procedures to the letter and were dosing correctly. We developed and followed stringent protocols to ensure that we standardized dosing between participants, that clinic staff were not exposed to THC or CBD, and that there was no contamination of samples.

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 to titrate the dose over the first four days. The participants started with one dose on day one, two doses on day two, and so forth, and were instructed to take the entire dose on days five through seven. The titration virtually eliminated reports of dizziness and nausea.

The PK results showed a rapid C^{max} 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 speed of onset demonstrated that PPP001 may be 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 T^{max}, 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 rapidly for a number of the measures, such as 'feeling high', the peak effect was observed at approximately 1 hour. By 2.5 hours, the PD effects were present at lower levels even though THC levels were often below 2 ng/mL. The duration of effect demonstrated that PPP001 may offer sustained relief after treating breakthrough pain.

The study conduct was smooth, and the additional titration greatly reduced the AEs experienced on the first day of dosing. The PK and PD profiles indicated promise for PPP001 to be effective for the treatment of pain, and definitely warrant the continuation of PPP001's clinical development.

REFERENCE

Legal weed: An accidental solution to the opioid crisis? (Online).
Available: https://theconversation.com/legal-weed-an-accidental-solution-to-the-opioid-crisis-81603

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.