6th May 2019 | CannPal Animal Therapeutics Limited ACN: 612 791 518 | ASX:CP1

CannPal CPAT-01 Results Presentation and Research Abstract

Key Highlights

- CannPal presented at the 2019 AVA (Australian Veterinary Association) Innovation, Research and Development Symposium on Sunday, the 5th of May;
- Dr Margaret Curtis Presented on the Company's Phase 1 research results for CPAT-01, in development for pain and inflammation control in dogs;
- Attached is a copy of the research abstract to be published in the AVJ (Australian Veterinary Journal), Australia's premier veterinary scientific journal;
- The Company has strengthened its IP for CPAT-01 with the filing of a further provisional patent application incorporating the results of CannPal's ongoing research.

6th May 2019: Animal health company **CannPal Animal Therapeutics Limited (ASX:CP1)** ("CannPal" or "the Company") is pleased to enclose a copy of the presentation that was delivered by Dr Margaret Curtis at the 2019 AVA (Australian Veterinary Association) Innovation, Research and Development Symposium on Sunday the 5th of May.

Also enclosed is a copy of the research abstract that will be published in the AVJ (Australian Veterinary Journal). The AVJ is Australia's premier veterinary scientific journal, reaching an audience of over 5000 AVA members.

Dr Margaret Curtis presented on the pharmacokinetic, safety, gene expression and inflammatory biomarker results from the Company's robust randomised three group parallel pharmacokinetic study that was completed in 2018 for CPAT-01, the Company's lead drug candidate in development for pain and inflammation control in dogs.

Strengthening IP

The Company would also like to confirm it has filed a further provisional patent application relating to the CPAT-01 program incorporating the results of CannPal's ongoing research.

This further provisional application builds on an earlier filed provisional patent application for the CPAT-01 formulation [ASX Announcement: June 18, 2018].

The invention relates to a composition comprising a combination of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The invention also relates to methods using the composition.

CannPal's Head of Research and Development, Dr Margaret Curtis:

"The Innovation Symposium was a fantastic opportunity to showcase the breadth and depth of CannPal's research to the veterinary fraternity in Australia. It was a pleasure to share some of the exciting data that CannPal is generating with the wider scientific community, which we believe can help contribute to the advancement of cannabinoid-derived therapeutic research across all species."

About CannPal Animal Therapeutics

CannPal Animal Therapeutics Limited (ASX: CP1) is a pharmaceutical-focused animal health Company researching the benefits of medical cannabis for companion animals. CannPal is researching and developing medicines derived from cannabinoids to provide veterinarians with clinically validated and standardised therapeutics to treat animals in a safe and ethical way.

CannPal has identified a significant opportunity to benefit from the rapidly growing medical cannabis and health markets by developing innovate therapeutics derived from the cannabis plant. The Company is working closely with regulatory authorities and veterinary research organisations conducting clinical trials to commercialise therapeutic products that will meet regulatory approval and support the health and well-being of companion animals. To learn more please visit: www.cannpal.com

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Research Abstract

Title: Safety and availability of tetrahydrocannabinol (THC) and cannabidiol (CBD) after oral dosage in the dog: Influence on pain and inflammatory pathways associated with the endocannabinoid system (ECS).

Authors: Dr Margaret Curtis, Dr Ted Whittem, Dr Rayson Tan, Dr Natalie Castrechini, Dr Christie Budd, Dr Ahmad Rabiee, Mr Layton Mills.

Abstract

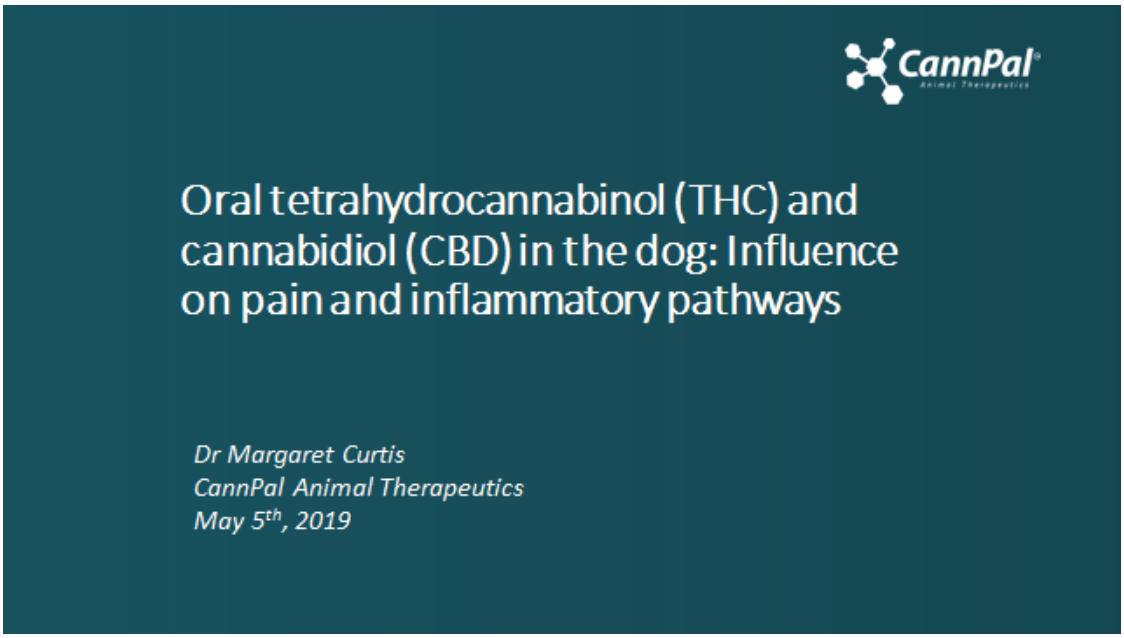
Introduction: The most prevalent cannabinoid (CB) in cannabis is THC, a partial agonist of CB receptors. The next most abundant is CBD, an indirect antagonist of CB receptors which interacts with several other receptors systems. These receptors and endogenous CBs form the endocannabinoid system (ECS), which influences cognitive, physiological and metabolic functions in animals, including pain and inflammation control. The ECS is targeted therapeutically by medical cannabis.

Materials and Methods: A randomised three group parallel dose-evaluation study was conducted using 11 healthy male Beagle dogs. Single oral doses were administered to each dog 2.5 hours after feeding. Group 1 (n=4) received THC (0.24 mg/kg) and CBD (0.12 mg/kg), Group 2 (n=4) received THC (0.12 mg/kg) and CBD (0.24 mg/kg), Group 3 (n=3) received a placebo containing no CBs. Dogs were monitored for clinical effects for 3 days. Samples for plasma and whole blood were drawn at 15 timepoints in 72 hours after dosing. Plasma samples were analysed for THC and CBD concentrations and a range of other biomarkers. The effect of treatment on pain and inflammatory pathway associated gene expression was evaluated using qPCR on whole blood.

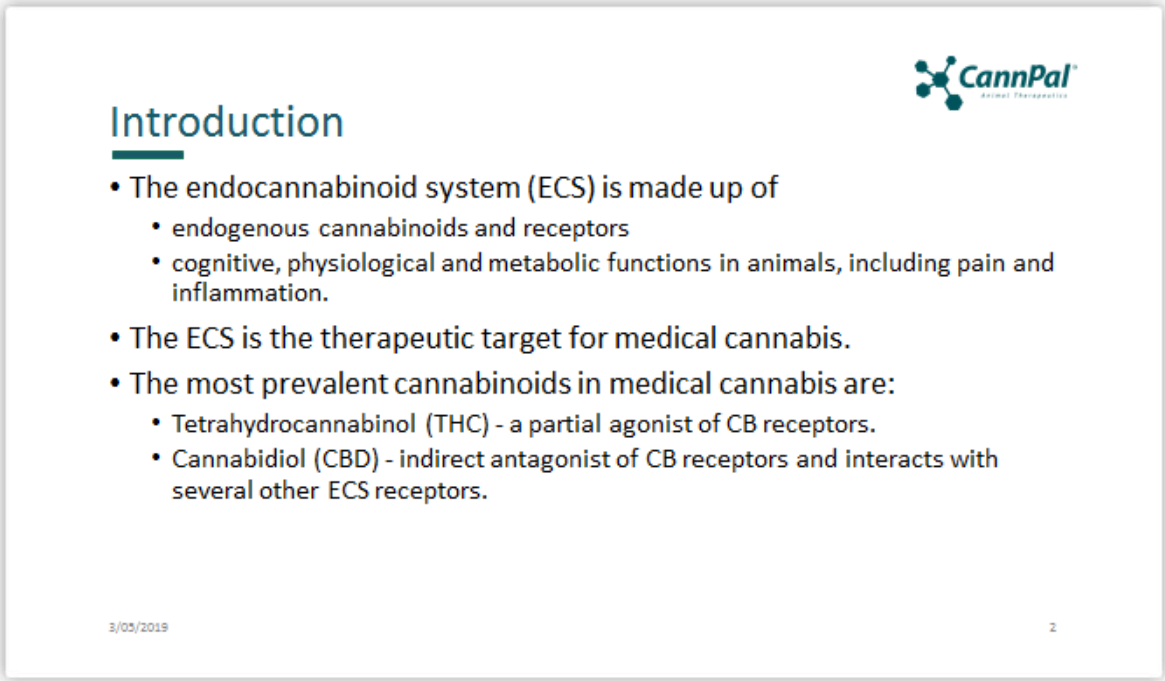
Results: No adverse events or psychotropic changes were observed in any dog. The time of peak concentration (Tmax) for both CBD and THC across treatment groups occurred from 40 to 90 min post treatment. Mean THC peak concentration (Cmax) in Groups 1 and 2 were 46.6 ng/mL and 38.8 ng/mL and mean CBD-Cmax were 13.1 ng/mL and 37.8 ng/mL, respectively. The terminal elimination half-lives were found to be slow for both CBD (12.6 h) and THC (18.5 h). Gene expression was compared at 1.5 hour and 72 hour time points for each group, accounting for pre-treatment values. A significant ($p<0.05$) change in fold regulation was seen in expression of Chemokine ligand 5, Cerebellar degeneration-related protein 2, CB2 and Interleukin 8 in Group 1 compared with placebo; and Chemokine ligand 5, CB2 and Interleukin 8 in Group 2 compared with placebo. The effects of THC and CBD on inflammatory cytokines and neurotransmitters were tested at 7 time points from 0-24 hours in all groups. Significant differences ($p<0.05$) accounting for time, pre-treatment values and group x time interaction were observed in some biomarkers known to be associated with modulation of anti-inflammatory processes in treatment groups compared to placebo.

Conclusion: THC and CBD are bioavailable, reaching plasma after oral administration. These data suggest that THC and CBD have the potential to control pain and inflammation in dogs and are slowly eliminated from blood circulation. These effects are likely to be a combination of direct effects and supporting the ECS allowing animals to maximise endogenous pain control processes.

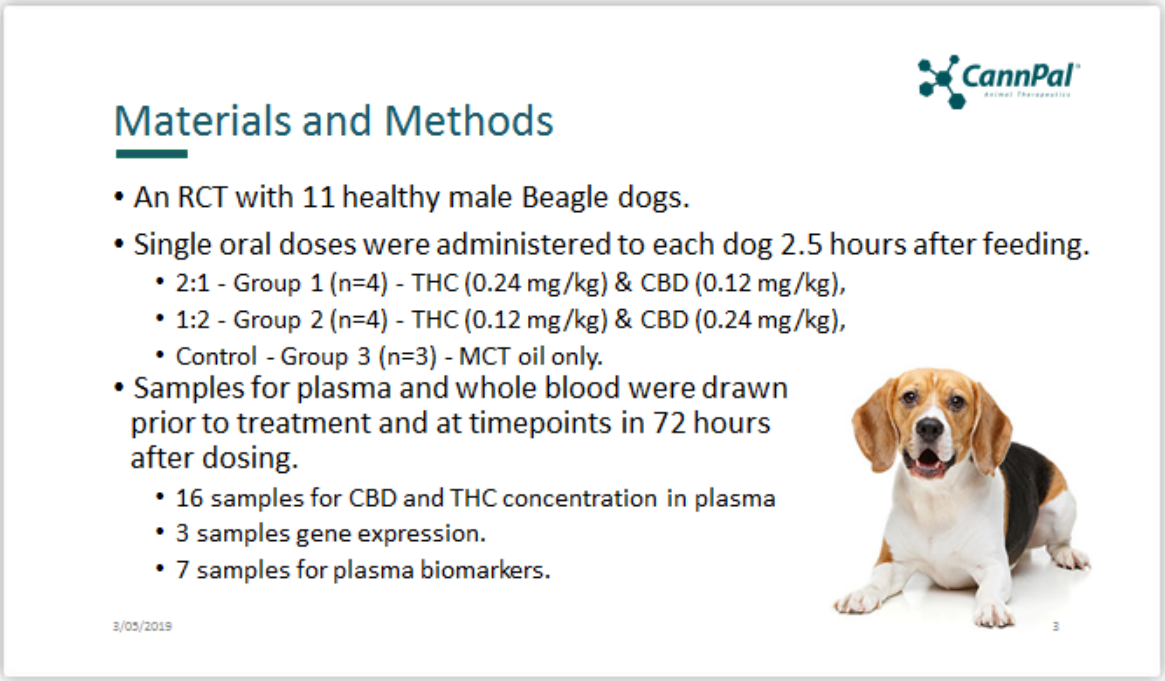
Innovation Symposium Presentation Slides and Speaker Notes



Thank you chairperson and good afternoon everybody. I'd like to talk to you today about work that we are doing in CannPal to develop plant-based therapeutics for pets that target the endocannabinoid system.

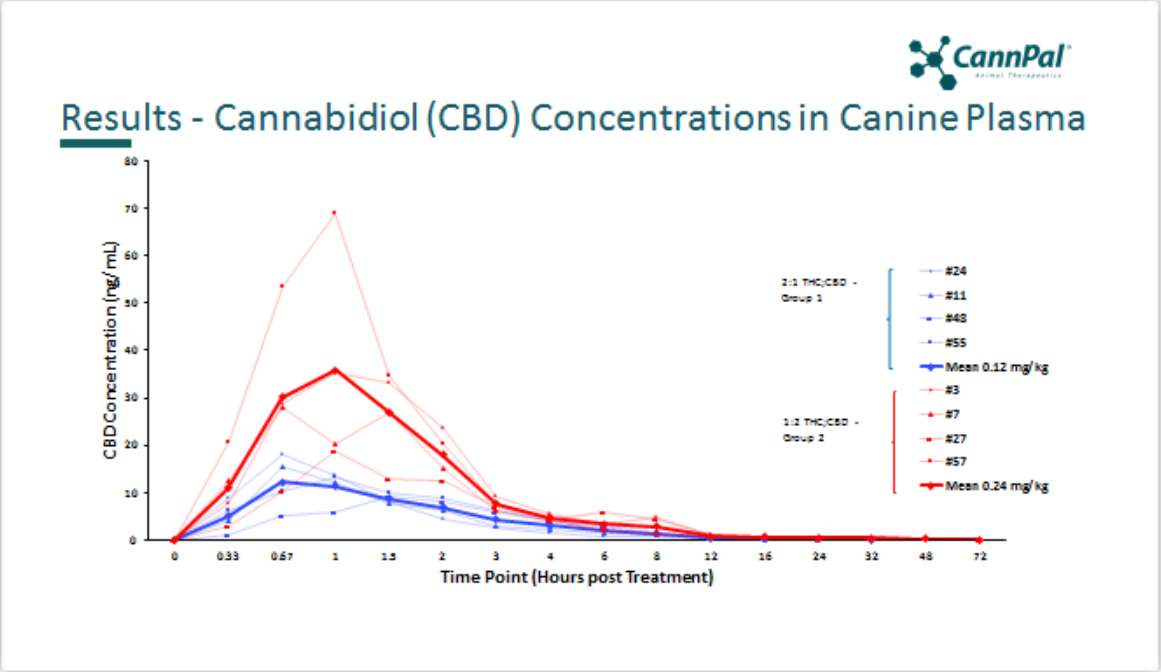


The Endocannabinoid system, relatively newly discovered in the 1990s, consists of a number of receptors and endogenous cannabinoids and enzymes that play key roles in cognitive, physiological and metabolic functions in animals including the control of pain and inflammation. The pet medicine we are talking about today contains tetrahydrocannabinol (or THC) and cannabidiol (or CBD). These are the two most abundantly found cannabinoids in Cannabis sativa which is grown in large greenhouses and extracted for us in Canada.



Today I want to share with you some of our early findings in our drug development journey for medical cannabis in pets. I will cover two areas of findings:

1. Pharmacokinetics of CBD and THC in Beagle
2. The impact of two different ratios of THC and CBD in these healthy dogs on genes and cytokines that modulate pain and inflammation in the dog
   a. 2:1 and 1:2 groups were compared with placebo (containing MCT oil, which is the carrier oil in the test treatments) in these 11 dogs

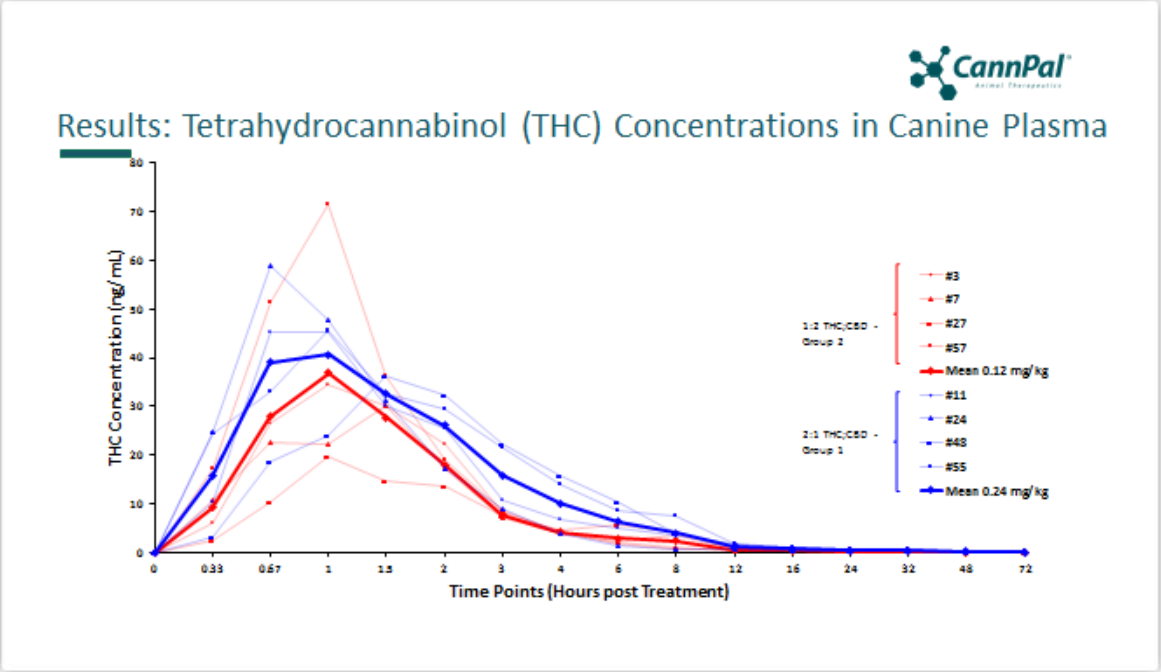


I'm going to show you 2 slides that relate to the pharmacokinetics of the cannabinoids in these dogs. This first one is CBD and the next will be THC. Just to orientate you, the vertical axis is the concentration of the cannabinoid in nanograms per mL and the horizontal axis is the sampling time from prior to treatment out to 72 hours post treatment. Sampling was more intensive in the first 8 hours after dosing.

The blue line represents dogs in the 2:1 THC:CBD group and the red line is the 1:2 group. The lighter lines are the actual dog curves and the thicker lines are the means for each group.

The time to maximum concentration (Tmax) of cannabinoids across both treatment groups was within the range of 40 to 90 minutes after treatment.

The mean maximum concentration of CBD in the 2:1 group was 13.1 nanograms per ml. The mean maximum concentration of CBD in the 1:2 group was 37.8 nanograms per ml. The cannabinoid concentrations were analysed using a compartmentalised model. The terminal elimination half-life of CBD was found to be slow at 12.6 hours.



Similarly in the analysis of plasma tetrahydrocannabinol, the blue lines represent dogs in the 2:1 THC:CBD ratio and the red line represents the group receiving the 1:2 THC:CBD ratio. As I mentioned in the previous slide, time to maximum concentration of THC was approximately 40 to 90 minutes after treatment. The mean maximum concentration of THC in the 2:1 group was 46.6 nanograms per ml and the mean maximum concentration of THC in the 1:2 group was 38.8 nanograms per ml. The terminal elimination half-life of THC was found to be slow at 18.5 hours.

You can see from these graphs that in the 1:2 group that the THC and the CBD curves are very similar within dogs and that the THC curve in the 1:2 group is close to that seen with THC in the 2:1 group despite the dogs only receiving ½ the amount of THC.

As a point of interest, when humans are given THC and CBD at doses like the doses used in these dogs, the peak plasma concentrations are less than 5 nanograms per ml even when using bioavailability enhanced preparations. An amount of THC that produced marked psychotropic effect in humans of 45 mg THC resulted in only 8.4 ng/ml. Dogs treated in this study had no psychotropic nor any other adverse effects.

Results – Whole blood qPCR - Pain and Inflammation pathway focused array

- The delta delta Ct method was used to calculate relative fold gene expression in treatment samples compared to pre-treatment samples
  - Up-regulated genes have a +ve fold regulation
  - Down-regulated genes have a -ve fold regulation
- Gene expression was compared with placebo at 1.5 hour and 72 hour time points for each treatment group.
- Differences between treatment groups (accounting for pre-treatment values and time) were assessed using REML.

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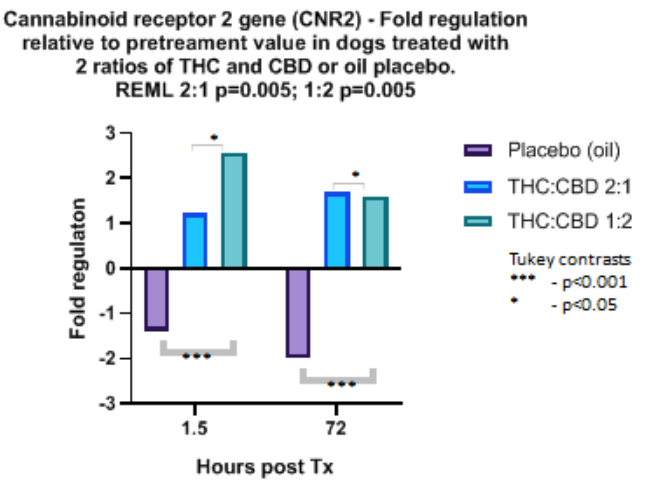
The next few graphs show some of the gene expression changes that we saw, associated with treatment. A pain and inflammation pathway array was customised for this study and the testing was done on whole blood. Many genes showed changes associated with treatment however today I will just focus on a few that showed significant differences of interest.



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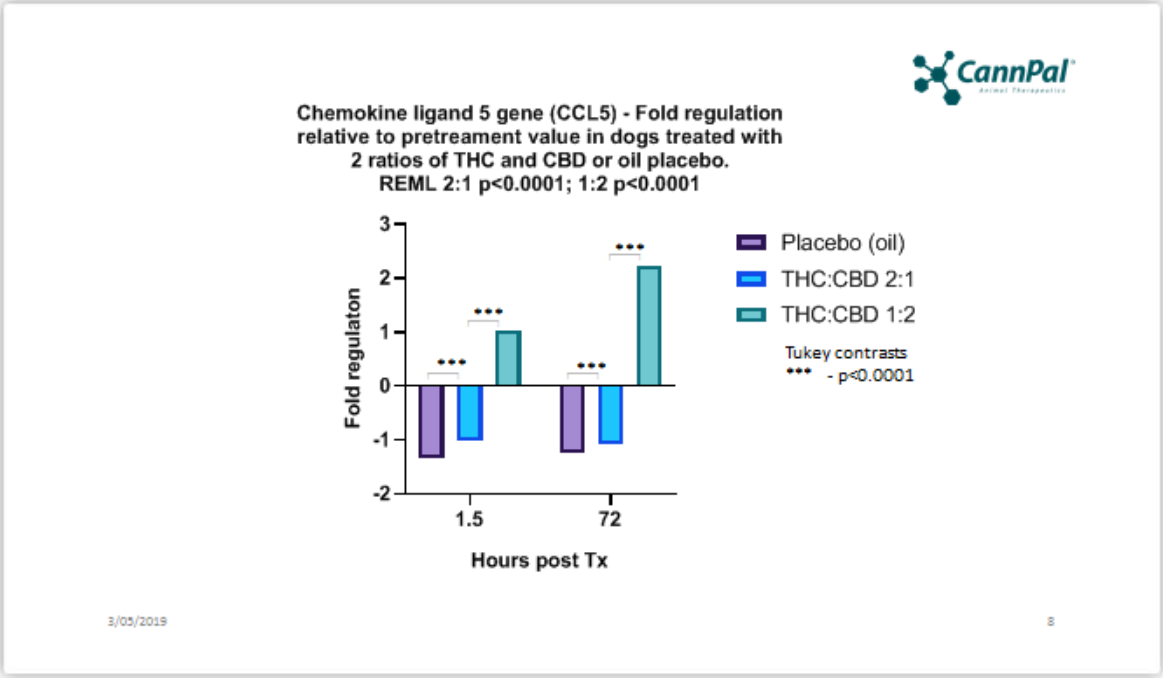
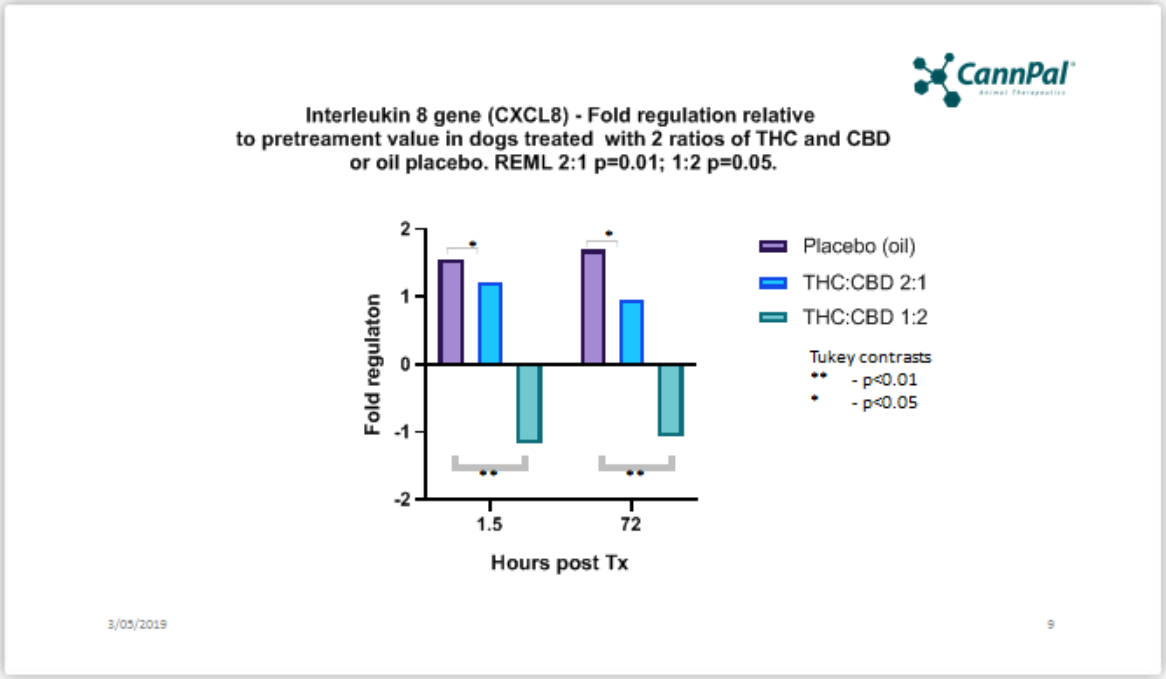
To orientate you on these graphs, the fold regulation on the vertical axis, determined using the delta delta CT takes the real-time polymerase chain reaction (qPCR) results and in this case compares them to the pretreatment value for each gene in each dog. Negative results are down-regulated genes and positive results reflect upregulated genes.

The horizontal axis shows the hours after treatment when the gene expression was assessed, as well as it being evaluated prior to treatment. Purple bars are the placebo group, blue bars are the 2:1 ratio of THC:CBD group and green bars are the 1:2 ratio of THC:CBD group. Difference between groups was evaluated using restricted maximum likelihood models that accounted for pretreatment and time effects.

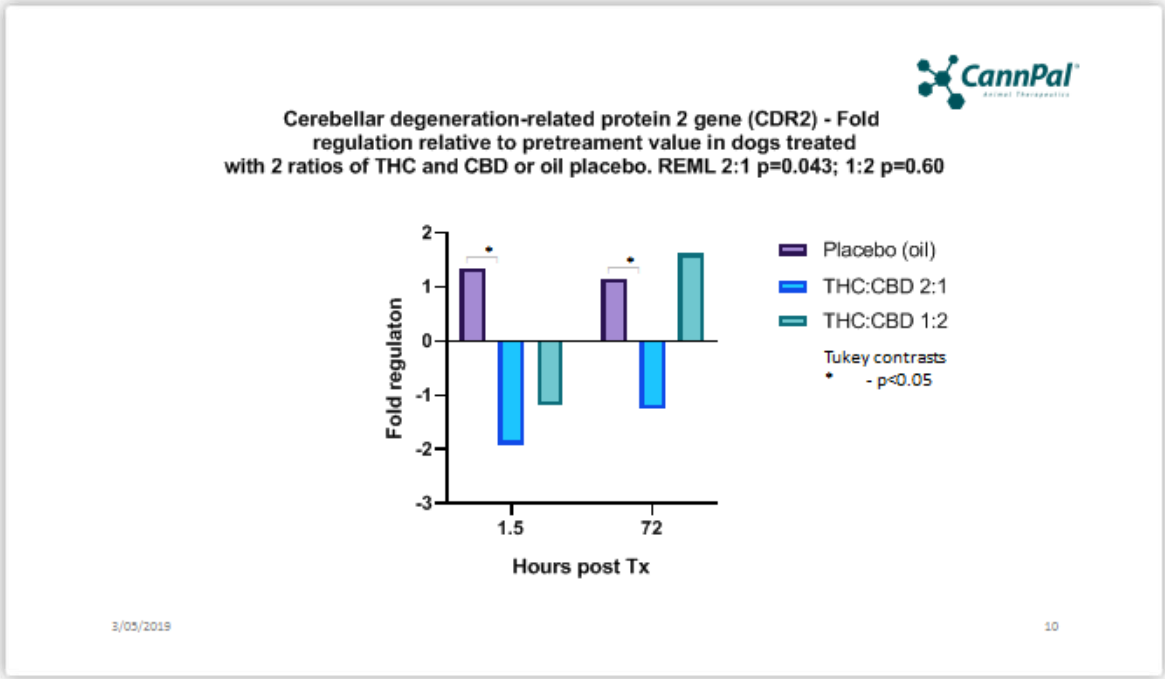
As expected the CB2 cannabinoid receptor 2 was impacted by treatment when the dogs were treated with cannabinoids. These receptors are very important players in the ECS and are found in a wide variety of tissues including the immune system, the central and peripheral nervous system, the gut and reproductive organs. They play an important role in pain and inflammatory signalling and responses. They are also prevalent in cells associated with bone remodelling, suggesting an involvement of upregulation of this gene in bone and joint integrity.



CCL5 (chemokine ligand 5) was upregulated by treatment and from a magnitude perspective this was more apparent in the 1:2 THC:CBD group. The chemokine that this gene codes for is important for recruiting white blood cells to inflammatory sites.



CXCL8 gene which codes for interleukin 8, is an important component of the inflammatory cascade. The down regulation of this gene, particularly in the 1:2 THC:CBD group is consistent with cannabinoids being potent inhibitors of the inflammatory cascade.



CDR2 (cerebellar degeneration related protein 2) gene while only significantly down regulated for the 2:1 THC:CBD group is associated with increased CBD activity at the mitochondrial level and its suppression is thought to be related to neuroprotective effects of cannabinoids.

Results – Inflammatory biomarkers modified by cannabinoid treatment

- The effects of THC and CBD on inflammatory cytokines were tested at 7 time points from 0-24 hours in all groups.
- Significant ($p<0.1$) changes in biomarkers known to modulate anti-inflammatory processes were seen in treatment groups compared to placebo.
- Significant differences ($p<0.1$), accounting for time, pre-treatment values and group x time interaction were determined using REML

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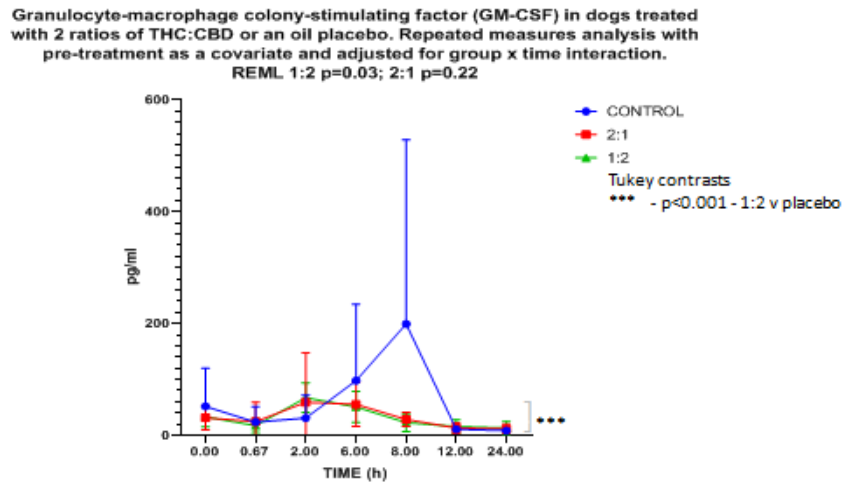
Some inflammatory biomarkers, that is the output of some of the genes we examined were assayed in dog plasma.



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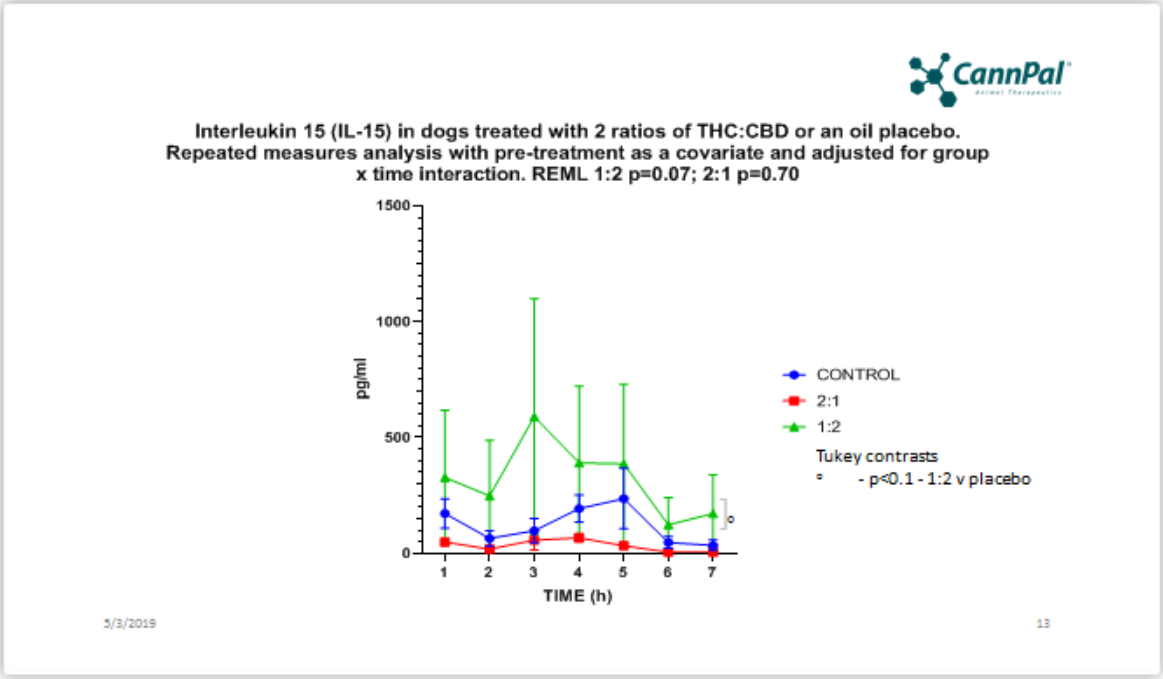
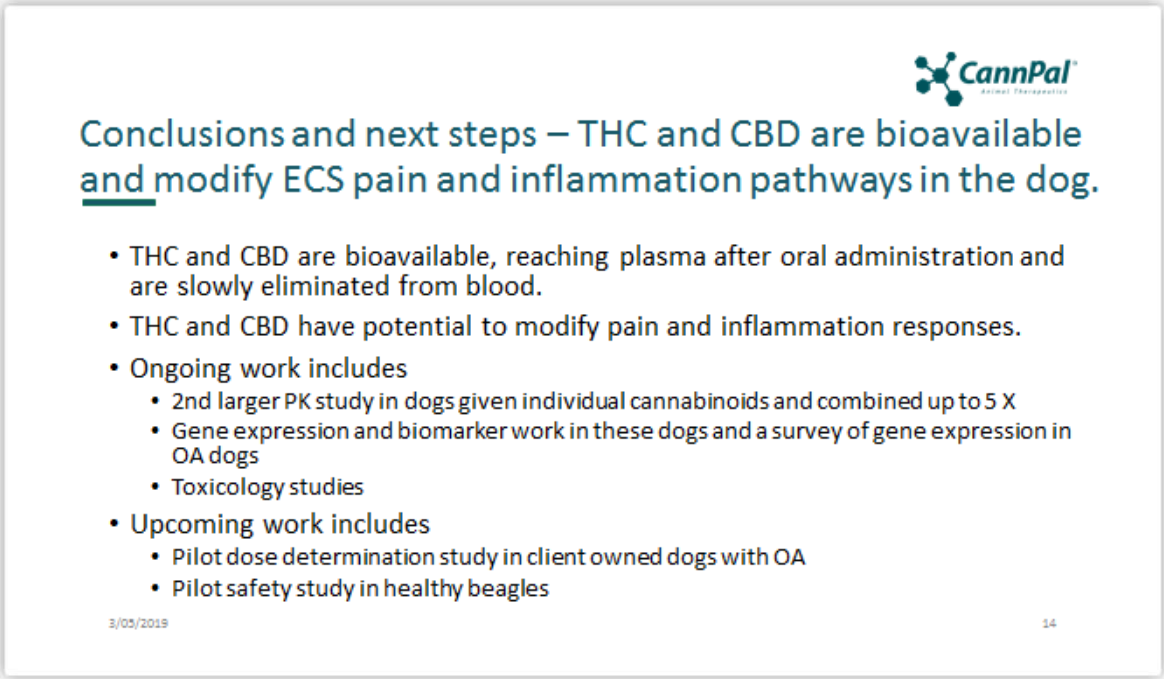
To orientate you on these graphs the vertical axis is the biomarker in picograms per ml. The horizontal axis shows the time points for plasma sampling in the first 24 hours after dosing. The release of these biomarkers are influenced by many factors and with the small number of dogs in the study the p value we used to evaluate significance was <0.1. REML was used accounting for pre-treatment, time and group/time interactions.

GM-CSF, a pro inflammatory cytokine was reduced by treatment. This is consistent with effects seen in humans treated with THC and CBD (Zgair et al. 2017),

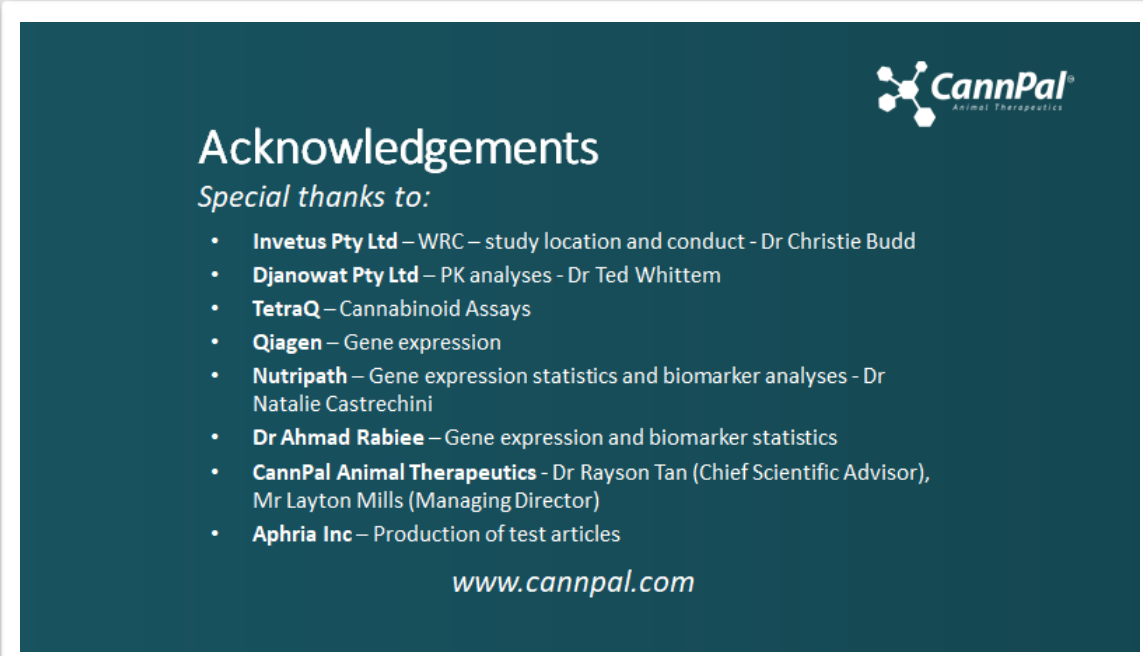


Interleukin 15 is another proinflammatory cytokine and it is interesting that it was increased in the 1:2 group. It may relate to actions that switch white cell function close to the site of action to anti-inflammatory activity. The result is consistent with an upregulation of IL-15 reported to modulate the immune response in humans. IL-15 is being evaluated as a drug candidate and also as a candidate for inclusion in vaccine adjuvants (Patidar et al. 2016).



The purpose of these assays is to start to get some data the blood profile associate with our proposed treatments and on plausibility of modes of action for THC and CBD as an anti inflammatory, and pain reliever in the dog.

We know that we are getting the cannabinoids absorbed into the blood with our oils and the concentrations are substantially higher than is seen in humans without the psychotropic effects. We have seen a number of pain and inflammatory genes and cytokines that were modified by treatment in healthy dogs.



This work would not have been possible without the hard work of many people. In particular I would like to call out the Invetus team especially Dr Christie Budd, Dr Ted Whittem, Qiagen, Dr Natalie Castrechini of Nutripath, Dr Ahmad Rabiee and our Chief Scientific Advisor, Dr Rayson Tan. We also thank Aphria Inc for the manufacture of the test materials.