Pilot Clinical and Pharmacokinetic Study of Δ9-Tetrahydrocannabinol and Cannabidiol Oro-Buccal Spray in Advanced Cancer with Uncontrolled Pain.

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Abstract

AIM: This study aimed to assess the pharmacokinetics, tolerability, safety and exploratory analgesic efficacy of a novel water-soluble oro-buccal nanoparticle spray of a cannabis-based medicine in advanced cancer patients with unrelieved pain. METHODS: The study was a non-blinded single arm, single escalating dose (n=5) [2.5 mg Δ9-THC and 2.5 mg CBD) and multiple escalating doses (up to 5.5 doses)] of a two-stage pilot study in patients diagnosed with advanced cancers and intractable pain (n=25). RESULTS: As the cannabis-based medicine dose increased, maximum plasma concentrations of all analytes were approximately proportional to dose. The bioavailability of ?9-THC and CBD in this water-soluble nanoparticle formulation was approximately twice the bioavailability reported for a ?9-THC/CBD formulation with ethanol. The water-soluble formulation in the current study resulted in a higher median (min, max) bioavailability of Δ9-THC than CBD (AUC from 2.5 mg each of Δ9-THC and CBD was 1.71 ng mL.h^{-1} (1.1, 6.6) and 0.65 ng mL.h^{-1} (0.49. 4.1), respectively). Analyte accumulation was not observed. In a subgroup of patients diagnosed with breast and prostate cancer with bone metastases, mean pain scores improvement from baseline was 40% (unadjusted) and 33% adjusted for rescue medication use. For all patients the most commonly reported adverse events were mild or moderate drowsiness affecting 11 (44%) and 4 (6%) patients, respectively and nausea and vomiting that affected 18 (72%) patients. CONCLUSIONS: The water-soluble cannabis-based medicine (NanaBisTM) provided acceptable bioavailability for Δ9-THC and CBD, appeared safe and tolerable in cancer with uncontrolled pain with preliminary evidence of analgesic efficacy.

ABSTRACT

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METHODS: The study was a non-blinded single arm, single escalating dose (n=5) [2.5 mg Δ9-THC and 2.5 mg CBD) and multiple escalating doses (up to 5.5 doses)] of a two-stage pilot study in patients diagnosed with advanced cancers and intractable pain (n=25).

RESULTS: As the cannabis-based medicine dose increased, maximum observed plasma concentrations of all analytes were approximately proportional to dose. The bioavailability of Δ9-THC and CBD in this water-soluble nanoparticle formulation was approximately twice the bioavailability reported for a Δ9-THC/CBD formulation with ethanol. The water-soluble formulation in the current study resulted in a higher median

(min, max) bioavailability of Δ9-THC than CBD (AUC from 2.5 mg each of Δ9-THC and CBD was 1.71 ng mL.h^{-1} (1.1, 6.6) and 0.65 ng mL.h^{-1} (0.49. 4.1), respectively). Analyte accumulation was not observed. In a subgroup of patients diagnosed with breast and prostate cancer with bone metastases, mean pain scores improvement from baseline was 40% (unadjusted) and 33% adjusted for rescue medication use. For all patients the most commonly reported adverse events were mild or moderate drowsiness affecting 11 (44%) and 4 (6%) patients, respectively and nausea and vomiting that affected 18 (72%) patients.

CONCLUSIONS: The water-soluble cannabis-based medicine (NanaBis^{TM}) provided acceptable bioavailability for Δ9-THC/CBD, appeared safe and tolerable in cancer with uncontrolled pain with preliminary evidence of analgesic efficacy.

| Introduction

The dried leaves of the *Cannabis sativa* L. plant have long been used for both medicinal and recreational purposes [1, 2].*Cannabis sativa* L. contains a number of chemical compounds, some of which are classified as cannabinoids. Phytochemistry studies of*Cannabis sativa* L. has identified several medically useful components including the psychoactive cannabinoid tetrahydrocannabinol (Δ9-THC), the non-psychoactive cannabinoids such as cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG), and many non-cannabinoid constituents that belong to diverse classes of natural products [3]. Two major types of cannabinoid receptors have been characterised, namely CB_1 and CB_2 [3, 4]; however, Δ9-THC and CBD exert therapeutic effects via several other targets[5]. Given these varied pharmacological targets, it is not surprising that Δ9-THC and CBD induce varying pharmacologic responses depending on the formulation, dose and patient characteristics [4].

Relief from chronic pain (cancer or non-cancer related) is a common condition cited by patients for the medical use of cannabis [6, 7]. A recent systematic review and meta-analysis of 43 randomized controlled trials (RCTs) suggested that cannabis-based-medicines could be effective for chronic pain treatment and primarily for neuropathic pain [8]. Others have reported that cannabinoid-based pharmacotherapies may serve as effective replacement/adjunctive analgesic options [9].

Most of the studies that have investigated cannabis for analgesia have concentrated on those with neuropathic pain. For example, low dose Δ9-THC (1.29%) as vaporized cannabis was better for relieving central or peripheral neuropathic pain that was resistant to standard treatments compared to placebo [10]. Studies with oral / oromucosal routes of administration of cannabis as herbal crude or dry leaf cannabis extracts or synthetics of THC (dronabinol, nabilone) and plant-derived extracts of Δ9-THC/CBD oromucosal spray (nabiximols) formulations have also shown efficacy in chronic neuropathic pain [11]. The number needed to benefit (NNTB) for patients taking medicinal cannabis for chronic neuropathic pain was calculated in a Cochrane review as 11 to 20 (95% CIs 7-100), although clinical study sample sizes were small and lacking high-level evidence [7]. All cannabis-based-medicines pooled together were also better than placebo in reducing sleep problems and improving psychological distress and health related quality of life [7]. Medicinal cannabis may also be effective for other types of pain. Studies of smoked cannabis in postsurgical or post-traumatic pain [12] and in painful human immunodeficiency virus (HIV)-associated neuropathy [13-15] have reported efficacy over placebo in relieving pain, as well as being well tolerated [13].

Although, the effectiveness of medicinal cannabis for chronic pain has been established [16], all five previous clinical trials of medicinal cannabis for cancer pain (as reviewed by Boland et al [17] have failed to reach the efficacy endpoint. Oral administration of cannabis-based medicines with gastrointestinal absorption leads to highly variable systemic concentrations of pharmacologically active constituents leading to slow and erratic an onset of action for analgesic use [18]. Inhaled cannabis requires too frequent dosing for a maintenance analgesic as its half-life is less than 20 minutes [18, 19]. Furthermore, the high THC blood concentration (20- to 30-fold higher C_{max}) after inhalation administration is associated with treatment limiting acute adverse effects and long-term damage from toxic chemicals associated with smoking or vaporizing [18] (high temperatures involved with vaporized cannabis can oxidize the medicine and excipients) [20].

The unsatisfactory nature of oral and inhaled administration routes for medicinal cannabis has led to addi-

tional proposed routes of administration such as transdermal and intranasal modes of delivery [21]. However, due to the lipophilic nature of cannabinoid molecules, drug delivery remains a challenge. Given that cannabinoids show promise, a feasible path toward highly regulated prescribed medicines is encouraged [21]. NanoCelle^{TM} is an innovative nanoparticle delivery method that is ideal for improving the mucous membrane absorption of small lipid soluble molecules, such as the cannabinoid molecules Δ9-THC and CBD. The aim of this study was to investigate the safety, tolerability and preliminary efficacy in a two-dose approach pharmacokinetic investigation of an oro-buccal water-soluble nanosized delivered cannabis-based medicine containing a mixture of

Δ9-THC/CBD in advanced cancer outpatients with uncontrolled pain who self-administered NanaBis^{TM}.

1. | Material and Methods
2. | Study Design

This study consisted of two stages, namely: Stage I was a two-day single ascending dose (SAD) pharmacokinetic / pharmacodynamic investigation of the nanoparticle Δ9-THC/CBD formulation in five participants diagnosed with advanced cancer. On day 1 all participants were administered 2.5 mg Δ9-THC and 2.5 mg of CBD in 300 μL (two actuations of the pump) to the oro-buccal mucosa. On day 2 all subjects administered 7.5 mg of Δ9-THC and 7.5 mg of CBD in 900 μL (six actuations of the pump). Blood samples were collected at 0, 30, 60, 90, 120, 150, 180, 240, 360 minutes and 24 hours after dose administration via indwelling cannula.

Stage II was a multiple ascending dose (MAD) pilot study of 25 eligible participants with advanced cancer and uncontrolled pain that participated over three phases in a 30-day period. The three phases in Stage II were divided into a dose escalation phase over days 1 to 9; a treatment phase over days 10 to 15; and a follow-up phase over days 16 to 30. Prospective participants for the dose escalation phase were patients with incurable cancer attending the Royal North Shore Hospital Medical Oncology unit (North Sydney Local Health District Human Research Ethics Approval number: RESP/16/341 on 16th June 2017). For the second phase, patients from the first cohort were included if they had pain uncontrolled by opioid analgesics. Screening visits occurred -2 to 0 days prior to commencing administration of the Δ9-THC/CBD water soluble nanoparticle oro-buccal spray (Supplement 1). All participants commenced dose escalation, treatment and follow-up phases of Stage II (Figure 1). However only n=22 of 25 patients completed all phases of Stage II. The Stage II dose escalation phase timeline is presented in Figure 1. In the treatment phase, patients administered to their oral cavity (to the inside of a cheek) one, two or three actuations (sprays) every four hours (unless asleep) for six days. The dose to be administered was dependent on the safe and tolerable dose administered in the previous dose escalation phase of the study, as directed by the Principal Investigator (oncologist). In the follow-up phase, all patients were observed for the next 15 days after treatment cessation. Subsequently, for patients who reported significant benefit, in the treatment phase compassionate access to ongoing medicinal cannabis was provided. Plasma samples were collected prior to the first morning administration on days 1, 4, 7, 10, 13, 16 and 30.

2.2 | Oro-buccal (inside of the cheek) Dosing

Medlab Clinical developed the formulation of the cannabis-based medicine (NanaBis^{TM}). Whereas the manufacturer of NanaBis^{TM} was PCI Pharma Services in Melbourne, Australia a GMP accredited facility. PCI Pharma also conducted the filling of the vials containing the drug substance, labelling and packaging and quality assurance release.

The Δ9-THC and CBD formulation of the cannabis-based medicine is a water-soluble submicron particle solution that also contains glycerol, peppermint oil flavor and a non-ionic oil-in-water solubilizer and emulsifying agent that is administered to the oro-buccal mucosa through a sealed pump action device that produced a fine mist spray. One actuation of the pump in this study administered 1.25 mg Δ9-THC and 1.25 mg CBD in a 150 μL volume.

2.3 | Sample Analysis

The cannabinoid concentrations were measured using a validated assay that was co-developed with Medlab Clinical and that was conducted by Agilex Biolabs (previously known as CPR pharma services), a National Association of Testing Authorities (NATA) accredited facility based in Adelaide, Australia. Agilex Biolabs co-developed and validated the assay method. Laboratory assessments included a two-dose levels approach analysis of pharmacokinetic data. Blood samples from all eligible participants were assayed for Δ9-THC, CBN, CBD, 11-hydroxy-THC (OH-THC) and 11-nor-9-carboxy-THC (COOH-THC). Determination of cannabinoids CBD, CBN, Δ9-THC, Δ9-THC metabolites 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (COOH-THC) and their respective deuterated Internal Standards from 100 μL aliquots of human plasma was carried out using protein precipitation followed by solid phase extraction (using acidified acetonitrile) followed by Solid Phase Extraction procedure (using micro-elution plates). The analytes were separated by high performance liquid chromatography (HPLC) on a Phenomenex Kinetex Biphenyl column, and the eluates monitored by a QTRAP5500 tandem mass spectrometry (MS/MS) detector in negative MRM mode. The extract was then assayed against a calibration curve. The data were acquired an Analyst® (Sciex) system linked directly to the QTRAP5500 MS/MS detector and then processed in Watson LIMS (Thermo Scientific), where applicable. The detection range was from 0.100 to 10.0 ng mL^{-1} for CBD, CBN, Δ9-THC and OH-THC and from 1.00 to 100 ng mL^{-1} for COOH-THC, using 100 μL of plasma and has a run time of approximately 8 minutes per duplicate samples. Laboratory assessments of the cannabinoids

There was no significant interference at the retention time of the internal standard (IS), or at the retention time of the other analytes for each individual analyte injected at PS8 concentration without IS added (except for analyte CBN where the percentage interference was approximately 29.0% of the mean CBN Lower Level of Quantification response when Δ9-THC was injected at Upper Level of Quantification level of 10.0 ng mL^{-1}). There were 5 repetitions performed on the same day. Coefficient of determination for curves run during validation had a linearity of >99%. Moreover, inter- and intra-assay precision had a mean % coefficient of variation of approximately 3% (n=18) and inter- and intra-assay accuracy had a mean % bias of approximately 3% (n=18). Furthermore, there were no significant effects observed for any of the analytes in six individual lots plus in lipemic and hemolysed sources.

2.4 | Inclusion and Exclusion Criteria

The inclusion criteria for Stage I and eligibility:

Patients were eligible for inclusion if they: **i)** were aged greater than 18 years; **ii)** gave informed consent and agreed to comply with the study procedures; **iii)** had been diagnosed with an incurable malignancy; **iv)** were willing to abstain from using other cannabis-based medicines/recreational cannabis; **v)**agreed, where applicable, to use an effective form of birth control;**vi)** consented to baseline test for pregnancy; **vii)**consented to baseline tests for recent cannabis use; **viii)**agreed not to drive a car or other motor vehicle or operate any type of heavy machinery for 72 hours after the last dose of study medication;

*Additional **inclusion** criteria for Stage II and eligibility:*

Patients were eligible to be included in Stage II if they: i**x)**reported experiencing moderate to severe pain; **x)** had used strong opioid analgesics for at least one week to relieve pain associated with incurable malignancy (one-week prior use of opioid treatment is sufficient duration because it would represent established opioid treatment and most patients would have developed tolerance after one week, especially with multiple daily doses totalling > 60 mg of oral morphine or equivalent) and/or patient is on a low dose opioid regimen and still experiencing pain and is unable to increase the opioid dose due to poor tolerance as confirmed by the treating principal investigator; **xi)** reported pain severity greater than four on a 0-10 Numerical Pain Rating Scale (NPRS) assessment tool.

*The **exclusion** criteria and ineligibility:*

Patients were excluded from participation if they met any of the following: **i)** demonstrated cognitive impairment or intellectual disability; **ii)** had a history of primary psychotic disorder, bipolar affective disorder, bipolar disorder with psychotic features, depressive disorder with psychotic features, borderline personal-

ity disorder, antisocial personality disorder, or a positive family history (first degree relative) of psychotic disorder or bipolar affective disorder; **iii)** had any history of allergic or hypersensitivity reaction to any herbal product, including cannabinoids; **iv)**reported a prior sensitivity reaction to an oro-mucosal administered medicine or supplement (e.g., liposomes); **v)** had undergone radiotherapy to the mouth or oral cavity; **vi)** had significant intercurrent medical illnesses that the PI assessed to make them unsafe to be enrolled; especially a history of epilepsy (or a previous history of seizures), or clinically significant hepatic or renal impairment;**vii)** uncontrolled brain metastases; **viii)** pregnant or breast feeding; **ix)** had received epidural analgesia within 48 hours of the baseline assessment; **x)** had received radiotherapy within two weeks of the initial baseline assessment; **xi)** were currently receiving levodopa, sildenafil (or any other PDE5s), anticonvulsants and/or cannabinoids, or ketamine.

| Clinical Study Endpoints

Primary Endpoints: consisted of a clinical assessment of safety and tolerability from recorded adverse events/serious adverse events; quality of life scores as measured with The European Organisation for Research and Treatment of Cancer Quality of Life for Cancer Patients Questionnaire (EORTC QLQ-C30-v3) [22]. The minimum threshold for clinical importance for **functioning scales scores** were: physical functioning, 83; role functioning, 58; social functioning, 71; emotional functioning, 71; cognitive functioning, 75. The minimum threshold for **symptom scales scores** were: fatigue, 39; pain, 25; nausea/vomiting, 8. The minimum threshold for **sleep disturbances scores** were: dyspnea, 17; appetite loss, 50; constipation, 50; diarrhea, 17; financial impact, 17. The sensitivities of these thresholds for clinical importance ranged from 0.71 to 0.91 [22].

Furthermore, pharmacokinetic parameters AUC, C_{max}, T_{max} and bioavailability would be determined.

Secondary endpoints: cannabis treatment analgesic efficacy as assessed by Mean Numerical Pain Rating Scale (NPRS) scores; Mean Brief Pain Inventory scores, Short Form (BPI-SF); Morphine Milligram equivalent (MMeq) doses; rescue analgesia (opioid) doses.

| Study Safety Endpoints

At each visit the incidence and severity of adverse events were recorded. Any clinically significant changes in vital signs or physical examination were reported as adverse events. Clinically relevant changes in concomitant medications, e.g., changes in morphine milligram equivalent doses were also recorded (Supplement 1).

1. **| Statistical Methods**
2. **| Sample size**

A sample size of n=5 was considered adequate for a limited assessment of the Stage I SAD PK study, which was similar in design to a phase I study that assessed the single and multiple dose PKs and safety and tolerability of an oro-mucosal administered Δ9-THC/CBD spray [23]. Pharmacokinetic parameters were presented as medians within the range of minimum and maximum values.

| Data Analysis:

Analysis of the primary outcome (safety and tolerability) was descriptive. Pharmacokinetic analysis was conducted using a one-compartment open pharmacokinetic model with first order absorption and elimination. The area under the curve (AUC) was calculated using linear extrapolation. The PK analysis included calculating C_{max} and T_{max} by observation of the concentration-time profile curve; the AUC was calculated from 0 hours to 6 hours using the linear trapezoidal rule; and the half-life ($t\frac{1}{2}$) was calculated from the elimination rate constant (kel) which was estimated from the slope of the terminal portion of the log-concentration-time profile.

The limit of detection for all metabolites was 0.1 ng mL^{-1}. For the two secondary efficacy variables (i.e., NPRS pain score and use of breakthrough medication), the Hochberg method [24] was used to test the global hypothesis for a treatment effect on pain [25]. The daily pain NPRS score was calculated as the

mean of all the daily assessments. The change in mean NPRS pain scores from baseline (all days in run-in period) to the end of treatment was analysed using analysis of covariance (ANCOVA), with baseline pain as a covariate and grouped study and treatment as factors [26]. The proportions of responders (patients with [?] 30% improvement from baseline to end of study NPRS and BPI-SF pain scores) was compared. Use of breakthrough medication (during treatment) was recorded. In addition, the change from baseline in mean number of doses of escape medication was analysed using ANCOVA. The EORTC-QLQ-30 was scored according to its scoring manual [27], and differences over time explored using ANOVA. All analyses were conducted in Stata MP V16 for Mac (StataCorp, Texas Station, US).

1. | Results
2. | **Patient Demographics**

Patient demographics and clinical characteristics for both phases of the trial are presented in Table 1. In Stage I there was a predominance of women. The mean age was 65 years, and patients had controlled pain. There was a range of tumor types. In Stage II there was a predominance of women and the median age was 56 years. Again, there was a wide range of tumor types and sites of metastases, however 8 patients (32%) had bone metastases causing pain. There was also a mixture of different types of pain, including patients with multiple types of pain. The most common types of pain, bone origin [8] and neuropathic (11) (Table 1).

3.2 | Pharmacokinetic Parameters

The PK assessment of a single dose of 2.5 mg each of Δ9-THC and CBD (2 sprays on Day 1) versus a single dose of 7.5 mg each of Δ9-THC and CBD (six sprays on Day 2) was investigated for all participants in Stage I. The PK parameters calculated for Δ9THC, CBD and Δ9-THC metabolites, 11-OH-THC and COOH-THC, are presented in Table 2. There was a rapid uptake of Δ9-THC and CBD, as indicated by detectable plasma levels at the first 30 minute time point following oro-mucosal administration (Figure 2) and cannabinoids having a mean t_{max} of 0.88 hours (Table 2). Single doses of Δ9-THC and CBD were rapidly eliminated, with 2.5 mg of Δ9-THC and CBD eliminated in just under 1 hour and 45 minute, respectively, and approximately twice that duration for the higher 7.5 mg dose (Table 2). The plasma concentration of the main active metabolite of Δ9-THC, OH-THC, peaked soon after Δ9-THC (0.12 and 0.4 hours after Δ9-THCfor the low and high dose, respectively) and persisted for approximately three-fold longer (OH-THC $t_{1/2}$ was 3.4 and 5 hours for the low and high dose, respectively). Mean plasma concentrations of Δ9-THC, CBD, OH-THC and COOH-THC were approximately proportional to dose, with a six-fold high dose providing a 2.8-, 3.2- 3.0- and 3.6-fold higher area under the curve (AUC) and a 1.4-, 1.5-, 1.8- and 2.6-fold high C_{max}, respectively (Table 2). The single ascending dose PK analysis of this study showed that C_{max} and bioavailability was always higher for Δ9-THC than for CBD. For the 2.5 mg Δ9-THC/2.5 mg CBD dose, the C_{max} of Δ9-THC was 1.58 ng mL^{-1} 1.5-fold higher than the 1.02 ng mL^{-1} for CBD; and the $AUC_{(0\text{-}t)}$ of

Δ9-THC was 2.79 ng $mL.hr^{-1}$, 1.9-fold higher than the 1.46 ng $mL.h^{-1}$ for CBD (Table 2). Furthermore, as the concentration of the drug was increased from 2 sprays on day 1 to 6 sprays on day 2, there was an increased change in the plasma con cen trations of Δ9-THC and CBD that demonstrated a n.on-linear PK behaviour.

3.3 | Adverse Events (AEs) and Serious Adverse Events (SAEs)

All causally related AE that occurred during treatment (treatment-emergent adverse events) and their frequency are presented in Table 3 [28]. Some patients experienced multiple AEs. The most common treatment emergent AE was drowsiness (mild, moderate and severe in 68%, 44% and 16%, respectively). Fatigue was also common experienced as mild in 4%, moderate in 20% and severe in 12% of patients. Vomiting was also reported as mild in 20%, moderate in 4% and severe in 12% of patients respectively.

In 6 (24%) patients, vomiting was associated with nausea. In one patient nausea and vomiting were reported as persistent that subsided on interrupting the administration of the cannabis-based medicine. The last administered dose in this patient occurred on day 9 (first dose of the day) of the dose escalation phase of

Stage II. In this patient the cannabis-based medicine was not tolerated at a dose frequency of 8 doses per day unless asleep. The patient discontinued administering the cannabis-based medicine for the rest of the dose escalation period and the treatment phase.

3.4 | Pain Medications Administered

The cohort in this study consisted of patients diagnosed with advanced cancers with uncontrolled pain and were therefore prescribed opioids for the management of pain. Figure 3 shows the oral morphine milligram equivalent (MMeq) dose recorded as the study progressed from day 1 to day 30 by groups.

During study progression from day 1 to day 30 all patients (n=25 of Stage II) as a group recorded an increase in MMeq with a mean (SD) on day 1 (baseline) of 152 (70.6) mg, on day 16 (end of intervention) of 153.6 (71.1) mg and on day 30 (end of follow-up) of 224.3 (124.2) mg, respectively (Figure 4). Whereas MMeq administered in participants diagnosed with breast or prostate cancers (n=8) with bone metastases recorded significantly less changes as the study progressed. Mean (SD) values of 61 (13.8) mg on day 1, 57.1 (12.9) mg on day 16 and 64.5 (18.1) mg on day 30 respectively.

The most frequently prescribed rescue opioids were oxycodone, hydromorphone and morphine. As a group, patients diagnosed with bone metastatic breast and prostate cancer reported less prescribed rescue medications for the management of pain.

During the escalation phase of Stage II (Days 1 to 9) patients administered a mean of 1.5 to 5.5 doses of NanaBis^{TM}every four hours unless asleep and was generally well tolerated. A step-down dose-approach was adopted as per the treating clinician's discretion. During the treatment phase of Stage II (days 10 to 15) patients administered a mean of 3 to 3.5 doses of NanaBis^{TM} every 4 hours unless asleep and again this was generally reported as well tolerated. As per the protocol further administration of the test cannabis-based medicine was discontinued from day 16. However, 15 patients (60%) received compassionate use of NanaBis^{TM} on day 16 for an additional 24 hours.

The mean daily doses of NanaBis^{TM} administered from day 1 to day 15 is presented in

Figure 4.

3.5 | Pain intensity

There was recorded a significant reduction in pain overall for the study cohort of 12% (p=0.02) by the end of the treatment phase (Figure 5). In addition, all patients diagnosed with bone metastasis reported a significant reduction in pain scores at the end of the treatment phase. A significantly decreased pain score on the NPRS scale was recorded for participants diagnosed with breast or prostate cancer with bone metastatic disease. In the group of patients with breast and prostate cancers with bone metastasis the median score from baseline to 15 days was 7.5 to 3.5, an unadjusted pain improvement from baseline of approximately 40%. The adjusted improvement (re rescue medications) in pain from baseline to day 15 was 33% (p<0.01). From the end of the treatment phase (day 15) following discontinuation of NanaBis^{TM} to the end of the monitoring phase on day 30, there was a change in mean pain scores which corresponded to an overall worsening of pain scores of approximately 13% from baseline values (Figure 5).

3.6 | Quality of life

Given the complex presentation of the cohort of patients under investigation, we report the EORTC-QLQ-30 scores (Figure 6) for those patients diagnosed with breast and prostate cancer with metastasis to the bone versus those of the whole cohort.

There was an overall improvement from baseline for global health status; physical functioning; emotional functioning; cognitive functioning; fatigue; pain; dyspnoea and insomnia (Figure 6). Participants diagnosed with cancer metastatic to bone reported similar trends to the whole cohort

(Figure 6). The threshold for clinical significance was only achieved for emotional functioning, fatigue, dyspnoea, insomnia and appetite loss.

| Discussion

Quality of life measures in this SAD MAD study met the primary endpoint of safety and tolerability. The study demonstrated that the administration of the investigative medicine (NanaBis^{TM}) was generally safe in a cohort of chronically ill patients diagnosed with advanced cancers with intractable pain despite opioid treatment. Moreover, results from patient-reported outcome questionnaires suggest that patient functioning (e.g., physical, social, emotional and cognitive) improved clinically for emotional functioning, fatigue, dyspnea, insomnia and appetite loss.

The water-soluble nanoparticle cannabis formulation has appropriate pharmacokinetics of cannabinoids for a maintenance analgesic, with peak plasma concentration in less than an hour and efficacy durable enough to support dosing every four hours (with multiple dosing). Oromucosal delivery using 50% ethanol (and propylene glycol) [23] does not seem to be as effective as the nanoparticle water-soluble spray. For example, comparing the PK data with that reported for an ethanol-based Δ9-THC/CBD spray, NanaBis^{TM} achieved an approximate equivalent $AUC_{(0\text{-}t)}$ and C_{max} with half the Δ9-THC/CBD administered dose. The ethanol-based spray (5.4 mg Δ9-THC/5.4 mg CBD) reported mean $AUC_{(0\text{-}t)}$ and C_{max} of 2.99/0.82 ng mL.h^{-1} and 1.48/0.39 ng mL^{-1} respectively [23]. A comparison with half the dose from NanaBis^{TM} 2.5 mg Δ9-THC/2.5 mg CBD), the calculated means for $AUC_{(0\text{-}t)}$ and C_{max} were 2.79/1.46 ng mL.h^{-1} and 1.58/1.02 ng mL^{-1} respectively. Furthermore, the nanoparticle water-soluble delivery technology provided one peak consistent with mostly mucosal delivery, whereas 50% ethanol provided two peaks and inconsistent serum levels [23], indicating inefficient mucosal absorption with substantial swallowing of the medicine and less effective gastrointestinal absorption. The NanoCelle^{TM}delivery platform also avoids the local and systemic adverse effects of ethanol and propylene glycol [29].

There is significant interest in the use of cannabis for the management of chronic cancer pain or non-cancer pain [30, 31] irrespective of any adverse outcomes that have been reported. As yet, there is minimal evidence on the prevalence or predictors for adverse events in people administered cannabis [32]. In recreational users of cannabis, coughing fits, anxiety and paranoia were the most common adverse reactions [32]. In the clinical trial setting, oral, gastrointestinal or sublingual administered cannabis, was associated with nausea, fatigue, vertigo/hallucinations, diarrhoea, constipation and dry mouth [11, 33-36]. In our study, the administration of a nanoparticle water soluble cannabis-based medicine resulted in mild drowsiness, fatigue, nausea and vomiting. Drug tolerability was established at 2-8 sprays, namely 2.5 mg to 10 mg each of Δ9-THC and CBD every 4 hours, which reported no evidence that the cannabis formulation increased the risk of serious adverse events. An independent safety monitoring panel concluded at the end of Stage I of this study, that there were no safety issues that would impede continued development of the study's cannabis-based medicine. The oro-buccal delivered cannabis-based medicine administered as a water-soluble nanoparticle is of significant clinical interest given that this formulation was a self-titrated medicine, that showed preliminary analgesic efficacy in a subgroup of patients.

There are clearly however, limitations to this study. The sample was small with an open label pilot design with no comparator that included only patients with advanced cancer, with intractable pain unrelieved by opioids. There was a substantial variation in eligible patient cancer diagnoses that produced a largely heterogenous study group. Furthermore, patients presented with multiple and overlapping types of pain.

In this cohort of patients with complex advanced cancers the adverse events encountered were similar to those commonly reported from other studies that have administered a cannabis-based medicine [37]; with the most common being drowsiness, fogginess, fatigue, nausea and vomiting. The level of emetogenicity in cancer varies based on different factors and the incidence in this study was 36%. In 8 (32%) patients that developed nausea, the causal attribution was probably / possible associated with the administered cannabis-based medicine. In 6 (24%) patients though, vomiting was concomitantly reported with nausea, with one patient reporting persistent nausea and vomiting that interrupted the further administration of the cannabis-based medicine. Notwithstanding this study of single and multiple cannabis doses that were oro-buccal administered, demonstrated an overall safety and tolerance profile.

Various clinical investigations with administered cannabis-based medicines via the gastrointestinal tract have reported limited tolerability and efficacy in a variety of indications [38]. Furthermore, the frequency of delivery and the magnitude of exposure to a drug can also influence the abuse potential and safety profile.

Numerous animal [39-41] and human studies [42-44] have reported the synergistic analgesic effects of concomitant administration of opioids and cannabinoids. In our study, patients reported significant improvement in pain scores over the course of the intervention phase of the study of approximately 12% (p=0.02). Notwithstanding, all patients diagnosed with bone metastasis reported a significant reduction in pain scores at the end of the treatment phase. In participants with a diagnosis of metastatic breast and prostate cancers (only to bone) had a highly significant reduction in pain scores (adjusted for rescue medications) of 33% (unadjusted of 40%) during the escalation and treatment phases ($p<0.01$) with minimal mean increases in MMeq and rescue medications as compared to the cohort overall.

Although this SAD MAD study was not placebo controlled, the improvement in pain was consistent with a recent systematic and meta-analysis that concluded that cannabis-based medicines probably increase the number of people achieving pain relief of 30% or greater compared with placebo. The pain relief was reversed on cessation of administration of the investigated medicine. In the metastatic breast and prostate cancer group cessation of NanaBis^{TM} use resulted in a decrease in pain relief efficacy of 13%.

5 | Conclusions

This report described a single ascending dose / multiple ascending dose of a water-soluble

Δ9-THC/CBD nanoparticle formulation administered to advanced cancer patients with intractable pain as a co-analgesic. The oro-mucosal administration of this formulation at doses from 2.5 mg to 10 mg per 4 hours of Δ9-THC and CBD (unless asleep) was found to be safe and tolerable.

There was an overall significant improvement in average NPRS pain scores over the study treatment period from baseline. There was however a significant improvement in pain recorded over the treatment period for all patients diagnosed with bone metastasis. The significant improvement in average adjusted NPRS pain scores of 33% as recorded for an eligible subgroup of participants with a diagnosis of breast and prostate cancers with metastatic disease (only to bone). This may partly be due to the superior delivery method that the NanoCelle^{TM} platform of the cannabis-based medicine provides, as well as the cancer pain subgroup of metastatic bone pain.

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Conflicts of Interest: JDH DR SH and LV are employed by Medlab Clinical Australia and participate in its cannabis-based medicines research program. BB is an independent statistician who was funded by Medlab Clinical Ltd Australia to conduct the statistical analysis.

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Table 1: Patient baseline demographic and clinical characteristics for Stage I and Stage II.

Demographics Stage I	**Demographics Stage I**
Sex	**Number (%)**
Males	2 (40%)
Females	3 (60%)
Age	**Mean (SD)**
Years old	64.8 (12.1)
Ethnicity	**Ethnicity**
European	5 (100%)
Cancer Diagnosis	**Number (%)**
Glioblastoma	1 (20%)
Lung	1 (20%)
Myeloma	1 (20%)
Thyroid	1 (20%)
Prostate	1 (20%)

Demographics Stage II	**Demogra**
Sex	**Number**
Males Females	10 (40%) 1
Age	**Mean (SI**
Years old	55.9 (11.9)
Ethnicity	**Number**

Demographics Stage II	**Demogra**
European Hispanic/Latino East Asian	20 (80%) 1
Cancer diagnosis	**Number**
Breast Lung GI cancers Haematological Pancreatic Ovarian Melanoma Central nervous system Prostate Other	5 (20%) 5
Stage	**Number**
Metastatic	20 (80%)
Type of pain*	**Number**
Bone Chronic Neuropathic Nociceptive Somatic Visceral	8 2 11 5 2

*Note, some patients had more than one form of pain.

Table 2: Summary of two dose-approach (one dose escalating to three doses) pharmacokinetic parameters for Δ9THC, CBD, 11-OH-THC and COOH-THC.

Parameter	**Day 1 (n=4) 2.5 μγ Δ9-THˆ+ 2.5 μγ ˆBΔ Median (Min, Max)**	**Day 2 (n=5) 7.5 μγ Δ9-THˆ+ 7.5 μγ ˆBΔ Median (Min, Max)**
Δ9THˆ	**Δ9THˆ**	**Δ9THˆ**
$AUC_{(0\text{-}t)}$ ng $mL.h^{-1}$	1.71 (1.11, 6.61)*	8.26 (2.67, 11.72)
C_{max} ng mL^{-1}	1.31 (0.76, 2.94)*	2.35 (1.09, 3.19)
t_{max} hours	0.75 (0.5, 1.5)*	1.00 (0.5, 2.0)
$t_{1/2}$ hours	0.94 (0.75, 1.14)*	1.39 (1.30, 2.88)
CBD	**CBD**	**CBD**
$AUC_{(0\text{-}t)}$ ng $mL.h^{-1}$	0.65 (0.49, 4.06)*	5.96 (1.51, 12.15)*
C_{max} ng mL^{-1}	0.58 (0.48, 2.45)*	1.55 (0.62, 2.25)
t_{max} hours	0.75 (0.5, 1.5)*	1.00 (0.5, 2.0)
$t_{1/2}$ hours	0.72 (0.57, 0.86)*	1.53 (1.16, 7.06)
11-OH-THC	**11-OH-THC**	**11-OH-THC**
$AUC_{(0\text{-}t)}$ ng $mL.h^{-1}$	3.10 (2.17, 49.37)	17.2 (7.91, 99.13)
C_{max} ng mL^{-1}	2.06 (0.29, 13.8)	3.74 (1.06, 20.4)
t_{max} hours	1.00 (0.5, 1.5)	1.50 (0.5, 2.0)
$t_{1/2}$ hours	4.05 (1.19, 5.23)	5.31 (1.60, 8.02)
COOH-THC	**COOH-THC**	**COOH-THC**
$AUC_{(0\text{-}t)}$ ng $mL.h^{-1}$	126.32 (34.29, 251.29)*	223.39 (162.57, 1172.98)
C_{max} ng mL^{-1}	13.70 (6.62, 25.40)*	26.80 (13.1, 96.0)
t_{max} hours	1.25 (0.5, 2.0)*	2.5 (1.5, 3.0)
$t_{1/2}$ hours	10.94 (2.34, 12.33)*	10.09 (7.41, 19.23)

AUC = area under the plasma concentration versus time curve, from time zero to the last measurable concentration at t = 6 hr; C_{max} = maximum measured plasma concentration over the time span specified; T_{max} = time of maximum measured plasma concentration; t1/2 = time required for the concentration of the drug to halve * for n=4 patients only

Table 3: Treatment emergent adverse events affecting one or more participants (n=25) during the MAD Stage II of the pilot trial.

Adverse Event Description	**Mild**	**Moderate**	**Severe**
Auditory hallucination	1 (4%)	-	-
Burning throat	1 (4%)	-	-

Adverse Event Description	Mild	Moderate	Severe
Constipation	2 (8%)	1 (4%)	-
Dizziness	10 (40%)	1 (4%)	-
Drowsiness	17 (68%)	11 (44%)	4 (16%)
Dry mouth	1 (4%)	3 (12%)	2 (8%)
Fatigue	1 (4%)	5 (20%)	3 (12%)
Fogginess	5 (20%)	2 (8%)	1(4%)
Hallucinations	-	2 (8%)	-
Impaired Concentration	1 (4%)	-	-
Lethargy	-	1 (4%)	1 (4%)
Nausea	9* (36%)	5 (20%)	1 (4%)
Nightmare	1 (4%)	-	-
Numbness bottom lip	1 (4%)	-	
Pain crisis post coming off IP*	-	-	1 (4%)
Restless at night	-	1 (4%)	-
Vivid dreams	1 (4%)	-	-
Vomiting	5 (20%)	1 (4%)	3 (12%)

*Post administration of spray (1) as a standardized AE [28].

FIGURE LEGENDS:

Figure 1: Multiple Ascending Dose (MAD) schema for Stage II. After baseline assessments, patients started with one spray of cannabis-based medicine (1.25 mg each of Δ9-THC and CBD in 0.15 mL) every 4 h while awake for 3 days, then dose escalated to two sprays every 4 hours while awake for 3 days, and finally dose escalated to three sprays every 4 hours while awake for 3 days.

Figure 2: PK of Stage I SAD. Mean (SEM) plasma concentration over time for Δ9-THC and CBD on Day 1 (single dose of 2.5 mg Δ9-THC/2.5 mg CBD) and Day 2 (three doses of 7.5 mg Δ9-THC/7.5 mg CBD).

Figure 3: Morphine Milligram equivalent doses administered between the two groups.

Figure 4: Mean daily Δ9-THC + CBD doses administered every 4 hours unless asleep from day 1 to day 15. [Day 1-3, Day 4-6, Day 7-9 = dose escalation phase; Day 10-15 = treatment phase].

Figure 5: NPRS scores for all patients.

** denotes significant difference from baseline with $p<0.01$, one-way ANOVA.

Figure 6: EORTC-QLQ-30 scores relevant to improvement or deterioration of global functioning and symptoms.

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