ASX : MDC

NanoCelle®

International Cannabinoid-Derived Pharmaceuticals Summit | Boston – September 2022

Presented by Dr Sean Hall | CEO

Conflict of Interest Statement

Dr Sean Hall
Chief Executive Officer

I am the Chief Executive Officer of Medlab Clinical Limited and co-author on a number of patents and publications.

Welcome To Medlab

Medlab Clinical Ltd is a globally recognised Australian publicly listed (dual listing on Nasdaq) Biotech company, built on a proprietary drug processing and bio-delivery technology – **NanoCelle®** - that enhances the effectiveness, safety and reaction speed of new and existing medicines. Our initial therapeutic focus includes pain and mental health.

NanoCelle®: Our validated delivery platform is patented and protected in all western regions until 2036

Scientifically optimized portfolio of cannabinoid therapeutics

What We Do

Our **NanoCelle®** R&D portfolio consists of:

Cannabinoid Development

- Cancer Bone Pain
- Non-cancer pain
- Stress

Generics Plus

- Depressive disorders
- Cholesterol lowering
- Pain
- Allergy
- Large bowel cancer

Large molecule program

- Insulin
- Covid-19 Vaccine

Textile program

- Antibiotics

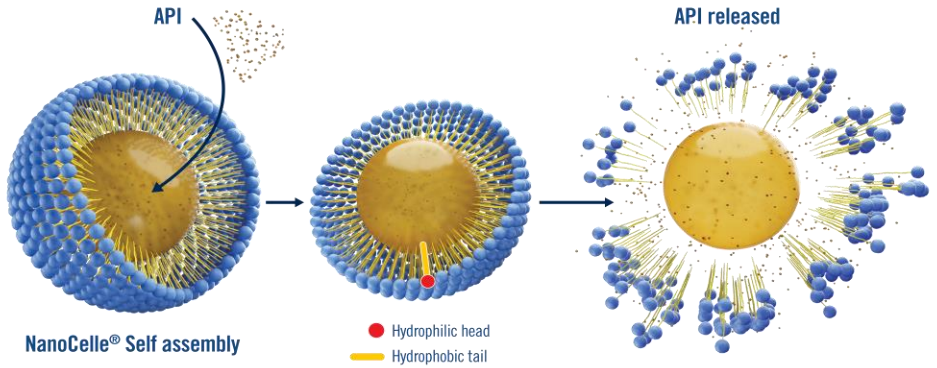
About NanoCelle®

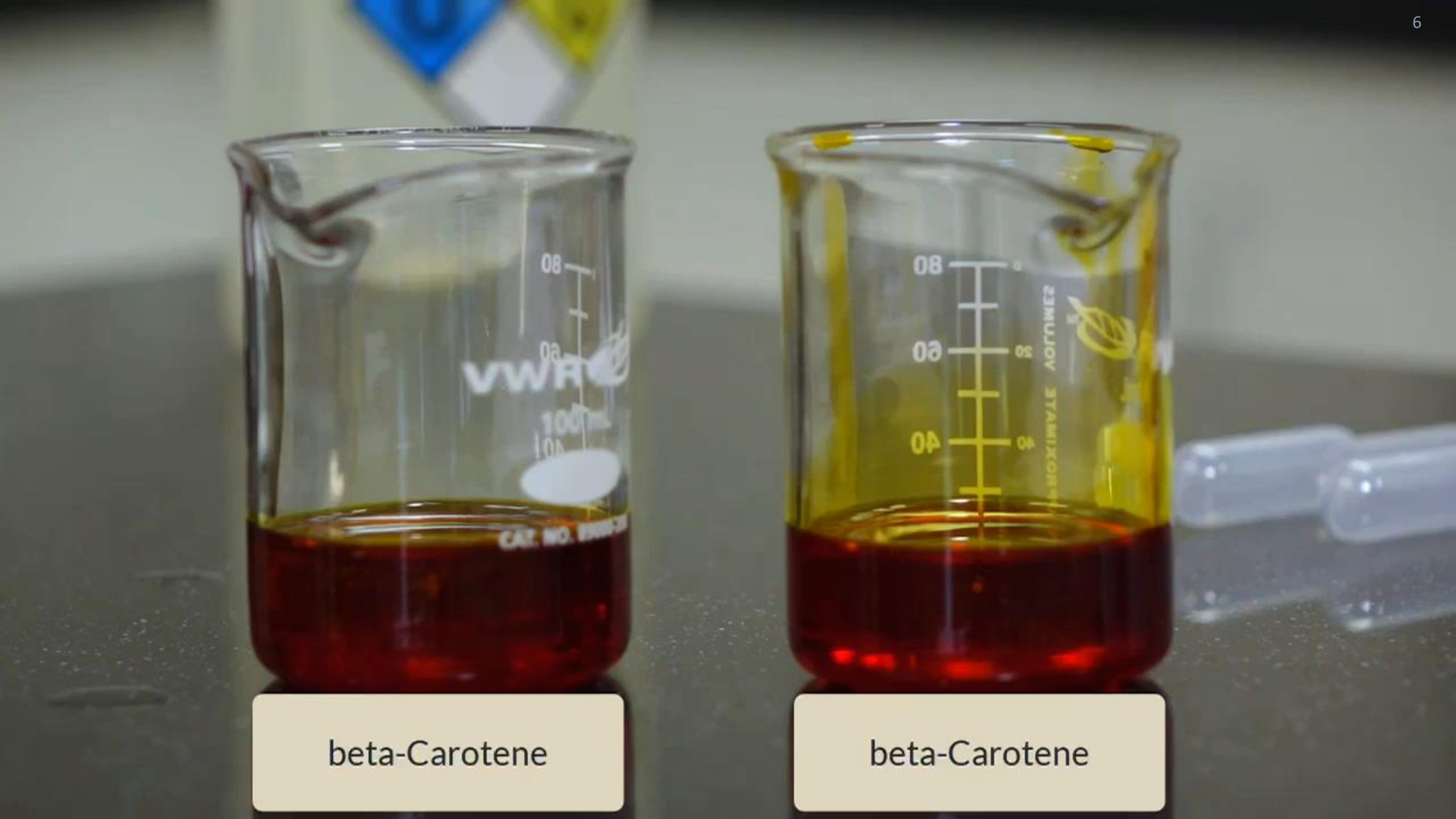
NanoCelle® has a diverse use - principally it is designed to improve a medicines bioavailability and improve patient compliance, this includes a reduced risk profile effectively making the medicine safer and more tolerable.

- NanoCelle® is the registered name of our clinically validated, patent protected delivery platform, that uses nanoparticles to significantly enhance medicines
- NanoCelle® bypasses the gastrointestinal tract, known as 1st pass metabolism, this means we can administer a lot less of a medicine, improve the patient's exposure to harmful side effects, whilst conferring the intended therapeutic benefits
- NanoCelle® is a key differentiator to our programmes, such as the cannabinoid cancer pain program - NanaBis™
- The NanoCelle® technology optimises the bioavailability of medicines, making compounds more easily and rapidly absorbed by the body
- The NanoCelle® process can additionally improve the stability of medicines [Patent Pending].

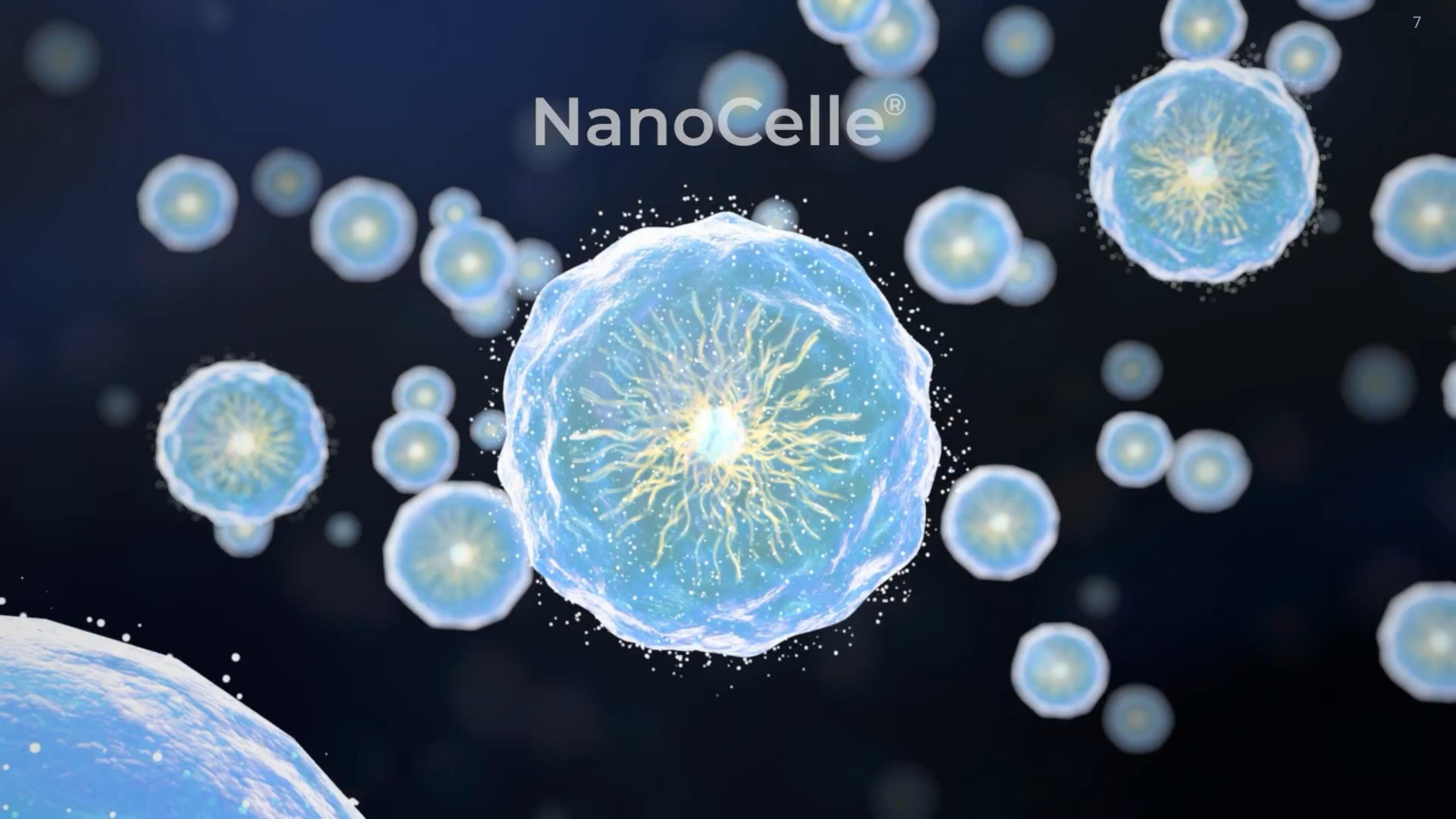
How NanoCelle® Works

- Creates an average particle size of 5 nm to approximately 90 nm (depending on payload)
- Consists of an inner hydrophobic core (active agents combined with lipid carrier or itself lipid-soluble) and outer hydrophilic shell (various surfactants)
- Utilizes a variety of administration routes (oro-buccal, oral, topical, nasal) for a more optimized delivery of a medicine




beta-Carotene
beta-Carotene

NanoCelle®



Cannabidiol oil has purported health benefits, including helping to relieve chronic pain.

DRUG REGULATION

From menace to medicine

NATURE | VOL 572 | 29 AUGUST 2019

In 2019 CANNABIS
Classified by
US Drug Enforcement Administration
with heroin and LSD as a schedule 1 substance.

NanoCelle® in Cannabinoid-based Medicine

Medlab has two investigative offerings:

- **NanaBis™** as a 1.25mg CBD and 1.25mg THC actuated at 140uL
- **NanoCBD™** as a 2.5mg CBD actuated at 150uL

Efficacy and Safety of a water-soluble Nanoparticle Cannabis-Based Medicine

Smoking

- Acute cannabis smoking associated ↑ risk myocardial infarction / ischemic stroke in health[1]
- Respiratory / Cataract health issues
- Dangerous in over consumption of tars and toxins[234]

Vaporizers

- Plant material not heated enough to cause combustion… ↓ harmful by-products inhaled[56]
- Both vaporizing and smoking are associated with high peak plasma THC levels that cause dose-limiting side effects

Edibles

- Cannabis infused products…may have high THC/dose
- Onset of effects is longer…intestinal dysbiosis…[78]

Tinctures

- These can be liquid/emulsions in a liquid/food
- Offer versatility in delivery
  - liver processing with foods and reduce time to onset
  - fatty meal consumption will ↑ concentration of cannabinoid metabolites released by liver metabolism[78]

Topicals

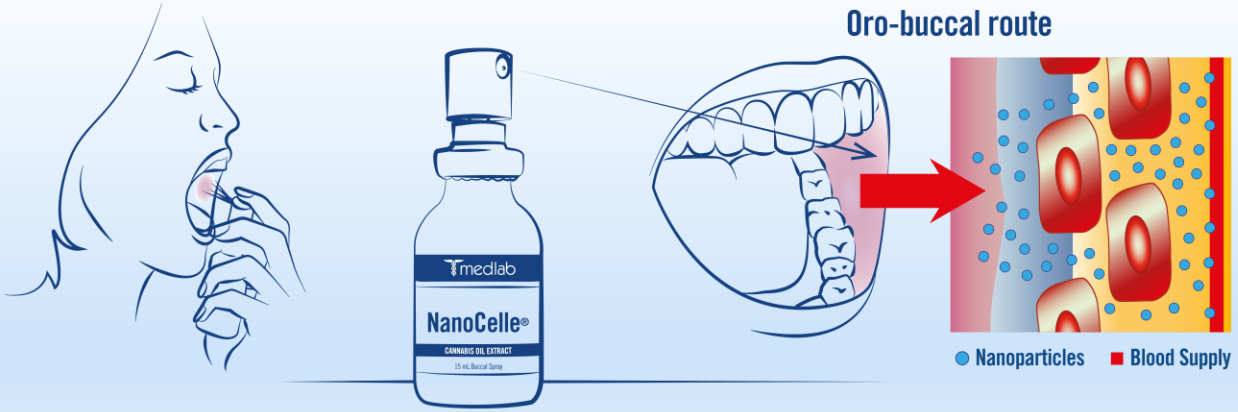
- Lotions, balms, sprays, ointments
- Usually made from:
  - Cannabis extracts and oils chemically processed to active cannabinoids[9]

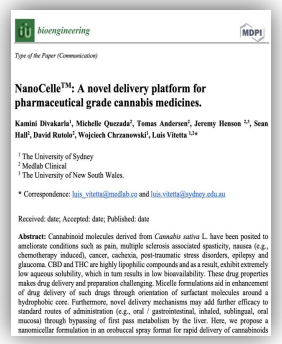
[1]Can J Cardiol 2022:S0828-282X(22)00261-6.
[2]J Fr Ophtalmol 2022;45(3):267-271
[3]Chem Res Toxicol 2021;34(10):2169-2179
[4]Food Chem Toxicol 2021;156:112447
[5]Food Chem Toxicol 2021;156:112447
[6]Pharmacol Ther 2021;224:107838
[7]Journal of Cannabis Research 2020;2:3
[8]Int J Mol Sci 2017; 18(5): 1070
[9]Molecules 2018; 23(10): 2478

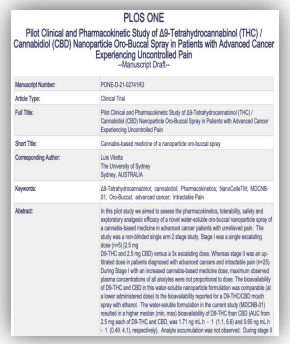
Route of Administration

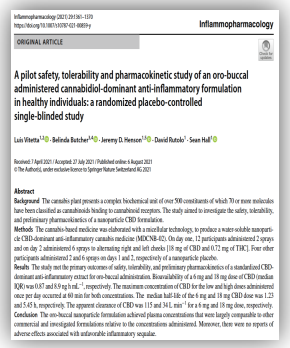
THC / CBD formulation is an easy and convenient oro-buccal spray for improved bioavailability and absorption.

- Direct access to the systemic circulation bypassing the portal system
- Passive diffusion of NanoCelle® facilitates / enhances drug delivery and absorption to achieve a therapeutic effect
- Convenient oral spray that bypasses the gastrointestinal tract




bioengineering
MDPI
Type of the Paper (Communication)
NanoCelle™: A novel delivery platform for pharmaceutical grade cannabis medicines.
Kamini Divakarla[1], Michelle Quezada[2], Tomas Andersen[3], Jeremy Henson [1,2], Sean Hall[2], David Rutolo[2], Wojciech Chrzanowski[1], Luis Vitetta [1,2]*
[1] The University of Sydney
[2] Medlab Clinical
[3] The University of New South Wales.
* Correspondence: luis_vitetta@medlab.co and luis.vitetta@sydney.edu.au
Received: date; Accepted: date; Published: date
Abstract: Cannabinoid molecules derived from Cannabis sativa L. have been posited to ameliorate conditions such as pain, multiple sclerosis associated spasticity, nausea (e.g., chemotherapy induced), cancer, cachexia, post-traumatic stress disorders, epilepsy and glaucoma. CBD and THC are highly lipophilic compounds and as a result, exhibit extremely low aqueous solubility, which in turn results in low bioavailability. These drug properties makes drug delivery and preparation challenging. Micelle formulations aid in enhancement of drug delivery of such drugs through orientation of surfactant molecules around a hydrophobic core. Furthermore, novel delivery mechanisms may add further efficacy to standard routes of administration (e.g., oral / gastrointestinal, inhaled, sublingual, oral mucosa) through bypassing of first pass metabolism by the liver. Here, we propose a nanomicellar formulation in an orobuccal spray format for rapid delivery of cannabinoids

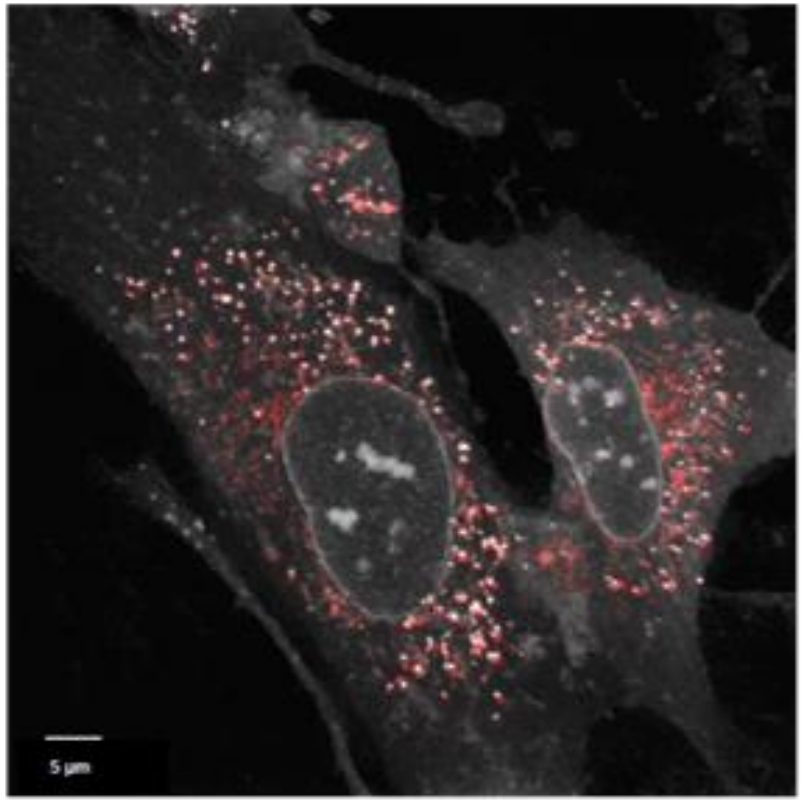

PLOS ONE
Pilot Clinical and Pharmacokinetic Study of Δ9-Tetrahydrocannabinol (THC) / Cannabidiol (CBD) Nanoparticle Oro-Buccal Spray in Patients with Advanced Cancer Experiencing Uncontrolled Pain
--Manuscript Draft--
Manuscript Number: PONE-D-21-02741R3
Article Type: Clinical Trial
Full Title: Pilot Clinical and Pharmacokinetic Study of Δ9-Tetrahydrocannabinol (THC) / Cannabidiol (CBD) Nanoparticle Oro-Buccal Spray in Patients with Advanced Cancer Experiencing Uncontrolled Pain
Short Title: Cannabis-based medicine of a nanoparticle oro-buccal spray
Corresponding Author: Luis Vitetta
The University of Sydney
Sydney, AUSTRALIA
Keywords: Δ9-Tetrahydrocannabinol; cannabidiol; Pharmacokinetics; NanoCelleTM; MDCNB-01; Oro-Buccal; advanced cancer; Intractable Pain
Abstract:

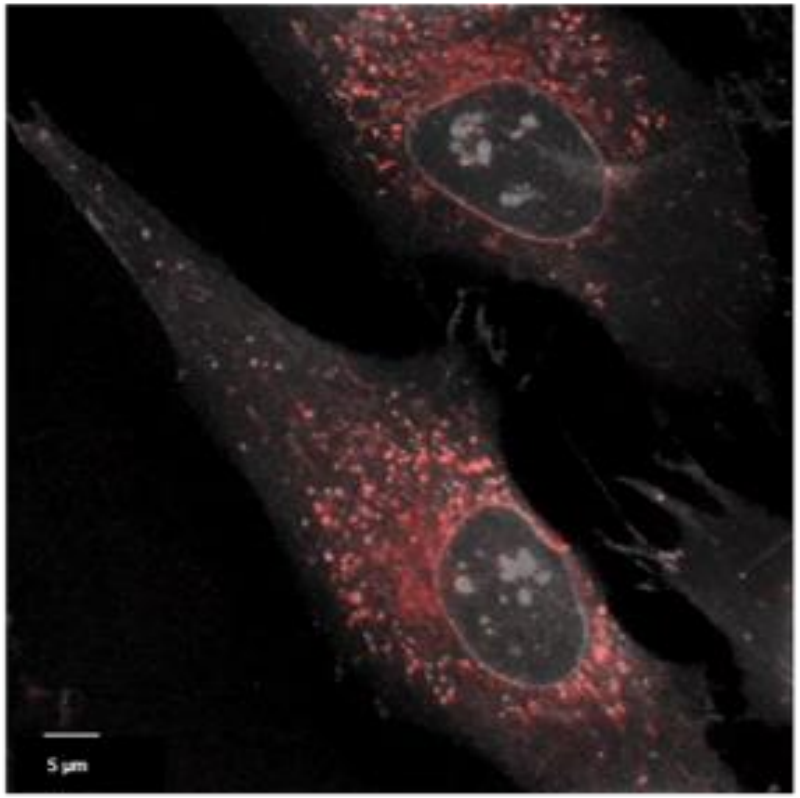

Inflammopharmacology
ORIGINAL ARTICLE
A pilot safety, tolerability and pharmacokinetic study of an oro-buccal administered cannabidiol-dominant anti-inflammatory formulation in healthy individuals: a randomized placebo-controlled single-blinded study
Luis Vitetta[1,2] · Belinda Butcher[1,2] · Jeremy D. Henson[1,2] · David Rutolo[1] · Sean Hall[1]
Abstract
Background The cannabis plant presents a complex biochemical unit of over 500 constituents of which 70 or more molecules have been classified as cannabinoids binding to cannabinoid receptors. The study aimed to investigate the safety, tolerability, and preliminary pharmacokinetics of a nanoparticle CBD formulation.
Methods The cannabis-based medicine was elaborated with a micellar technology, to produce a water-soluble nanoparticle CBD-dominant anti-inflammatory cannabis medicine (MDCNB-02). On day one, 12 participants administered 2 sprays and on day 2 administered 6 sprays in alternating right and left cheeks [18 mg of CBD and 0.72 mg of THC]. Four other participants administered 2 and 6 sprays on days 1 and 2, respectively of a nanoparticle placebo.
Results The study met the primary outcomes of safety, tolerability, and preliminary pharmacokinetics of a standardized CBD-dominant anti-inflammatory extract for oro-buccal administration. Bioavailability of a 6 mg and 18 mg dose of CBD (median IQR) was 0.87 and 0.9 ng·h/mL[-1], respectively. The maximum concentration of CBD for the low and high doses administered once per day occurred at 60 min for both concentrations. The median half-life of the 6 mg and 18 mg CBD dose was 1.23 and 5.45 h, respectively. The apparent clearance of CBD was 115 and 341 mL·min[-1] for a 6 mg and 18 mg dose, respectively.
Conclusion The oro-buccal nanoparticle formulation achieved plasma concentrations that were largely comparable to other commercial and investigated formulations relative to the concentrations administered. Moreover, there were no reports of adverse effects associated with unfavorable inflammatory sequelae.


Australasian Journal of Clinical Oncology
ABSTRACT
219. Pilot clinical and pharmacokinetic study of a water soluble nanoparticle cannabis-based medicine in advanced cancer with intractable pain
The volume 16, Issue 5B supplement is an educational resource available online via https://onlinelibrary.wiley.com/doi/10.1111/ajco.13448 and is free to access.

Fast and Effective Entry into Tissue

NanoCelle® has been shown to effectively enter target tissue and release API.





Holotomography imaging overlayed with fluorescence showing Nile Red uptake into fibroblasts. Scale bar represents 5 µm

Developmental Studies

Morphological Analysis with two formulations:

NB = CBD / THC

NBD = 20:1 ratio CBD to THC

- Dynamic light scattering
- Nano flow cytometry
- Atomic force microscopy

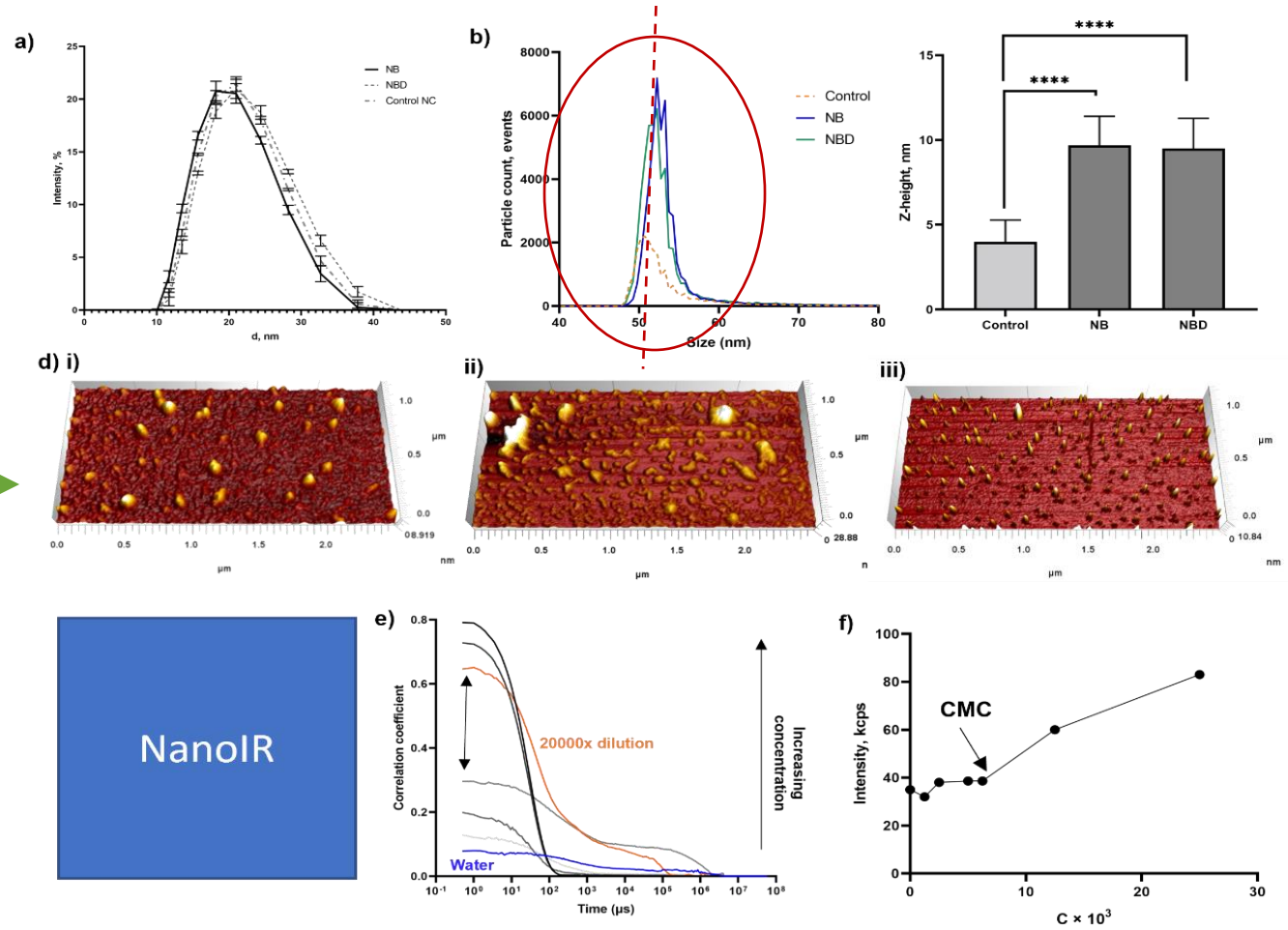


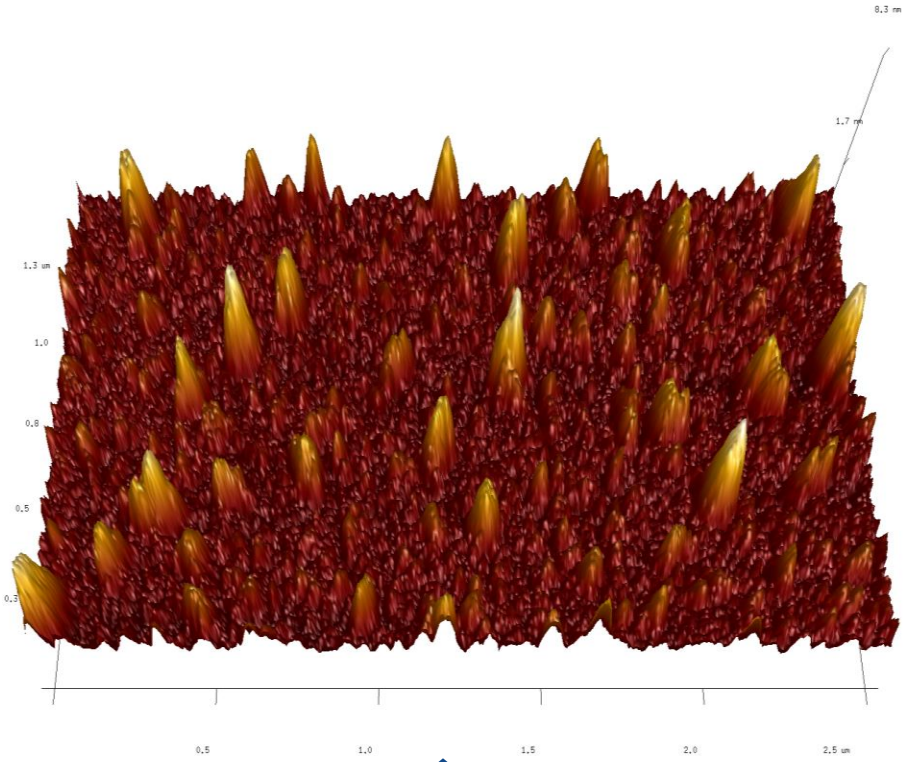
Figure 3: CAPTION

~ 52 nm for NB and NBD

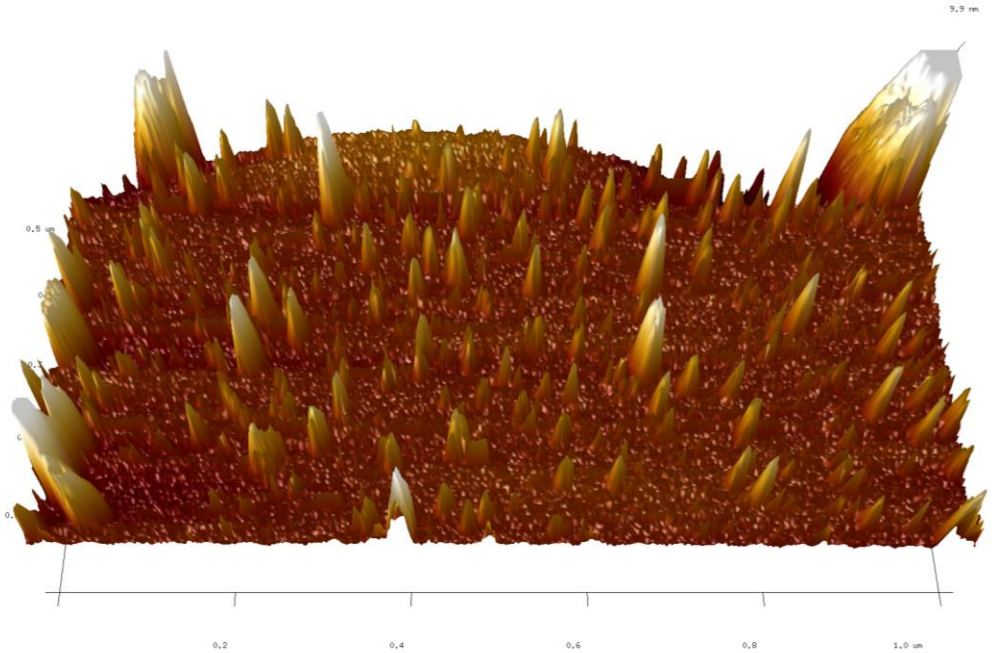
Nanoparticles

Medlab's *in vitro* Studies in Collaboration with University of Sydney's Nanoparticle Group

THC / CBD particle height size determinations via Atomic Force Microscopy in **3-Dimensions**



CONTROL NANOPARTICLE

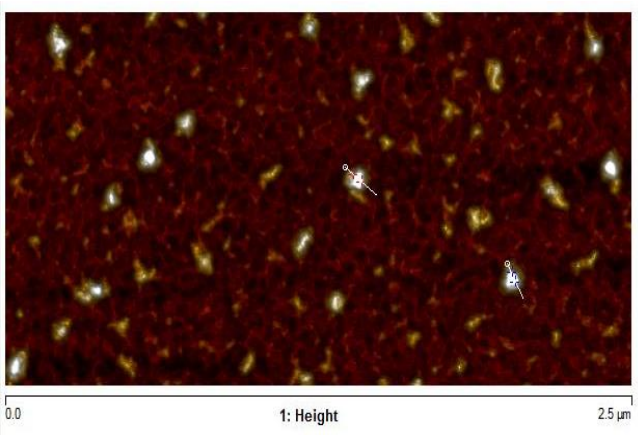


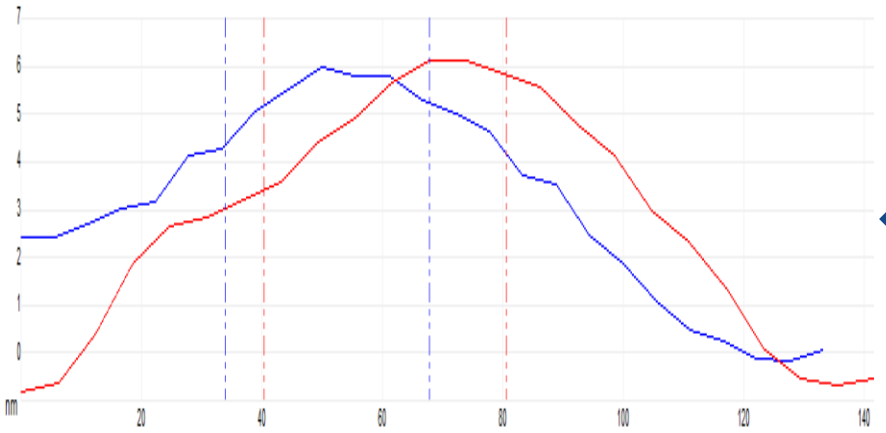
THC/CBD NANOPARTICLE

Nanoparticles

Our in Virto Studies in Collaboration with University of Sydney's Nanoparticle Group

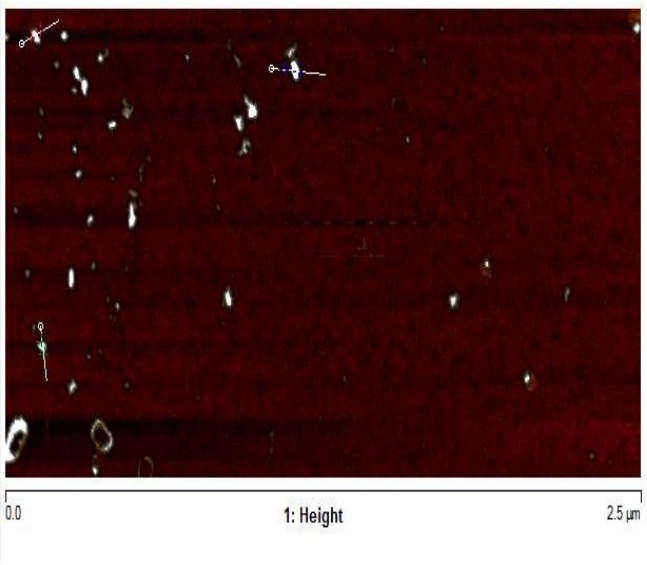
THC CBD particle height size determinations
via Atomic Force Microscopy in **2-Dimensions**

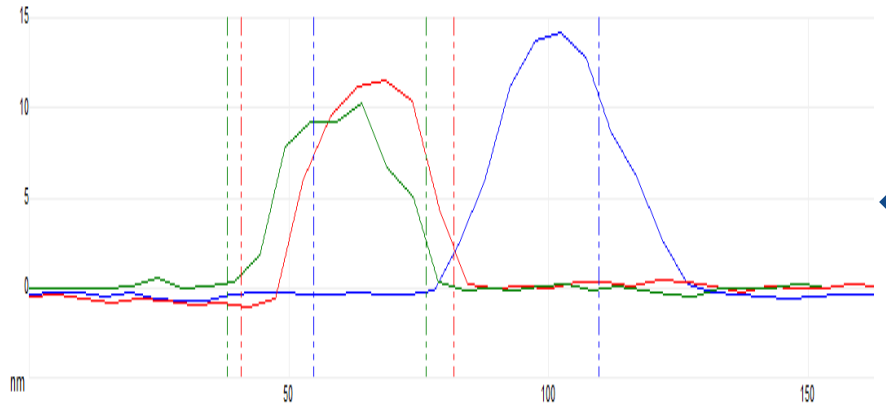




CONTROL PARTICLE

Diameter at the minor axis
~7 nm in height and flat/wide





THC / CBD PARTICLE

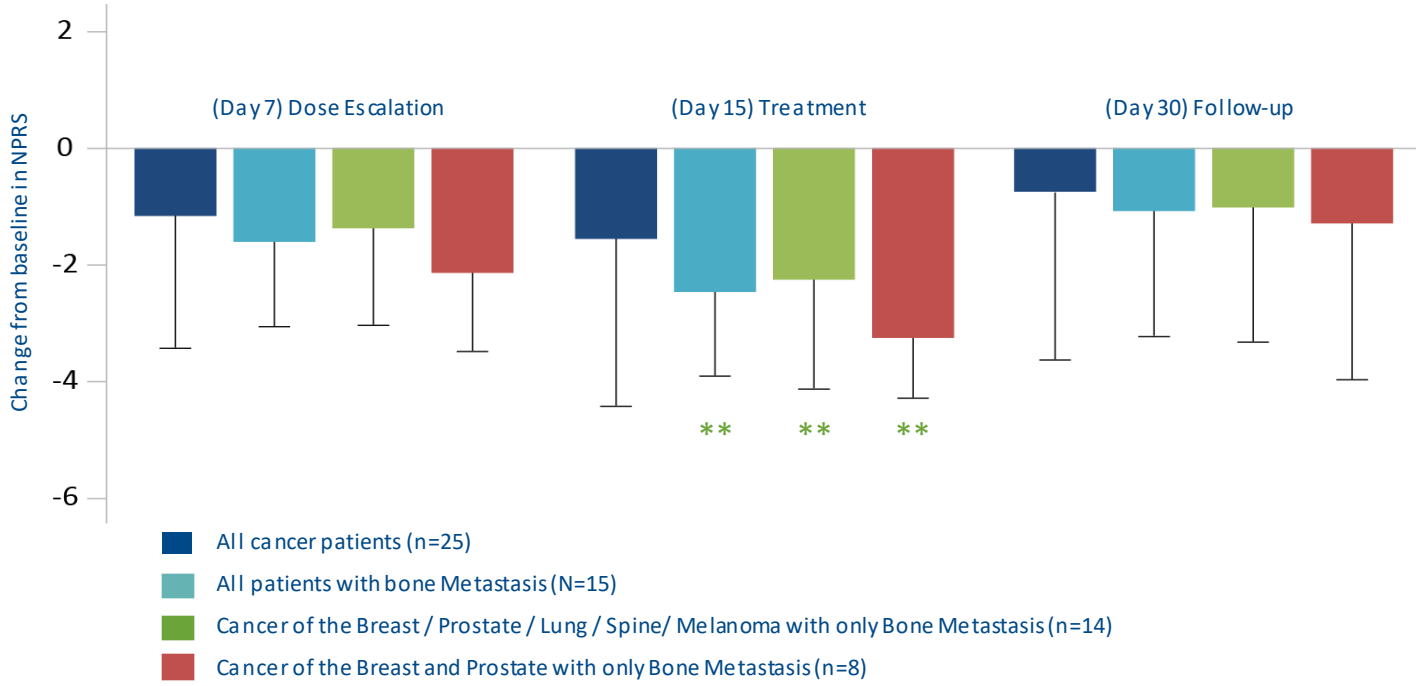
Diameter at the minor axis
~10-15 nm in height
the profile shows a morphologically flat and wide particle, whereas the combination nanoparticle (THC+CBD 1:1) profile is less flat and largely uniform in morphology.

NanaBis™ - Robust Clinical Experience

Primary and secondary endpoints met in Phase I/II study

- 30 advanced cancer pain patients, single ascending dose / multiple ascending dose
- Patient subset of breast or prostate cancers with bone metastasis had **40% improvement in pain scores** from baseline (to be confirmed in Phase III trial)
- Improvements in Quality of Life measures (emotional functioning and insomnia)
- MMEQ (morphine in milligrams equivalent) **significantly reduced**
  – quantifiable measure of efficacy

NanaBis™ significantly decreased MMEQ



Real world data replicates clinical data

12-month observational (OBS) study underway, data released every quarter

Real-world data

could expedite path to market

Strong body of RWE could reduce the total number of patients required to be observed in clinical trials

1151 of 2000

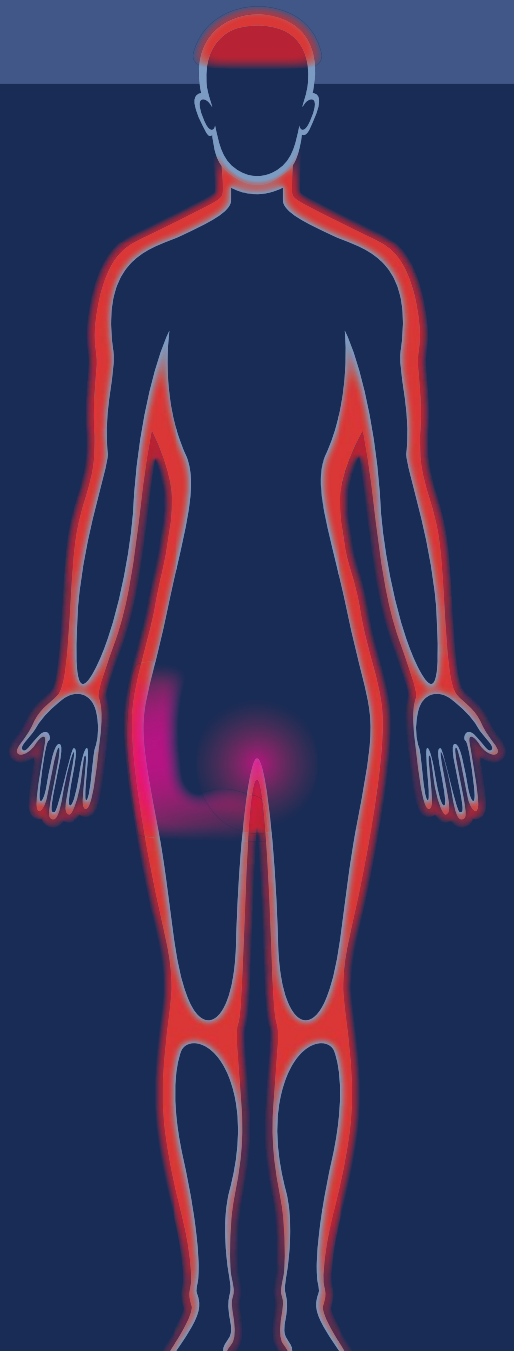
Australian patients

Of which 15% in cancer-related pain, 85% in non-cancer-related pain

Median averages = dosage 4 sprays per day

Significant improvements in pain, QoL scores and Opioid Sparing

NanaBis™ PATIENT Case Report



Patient Initials	TB
Age	35
Sex	F
Indication	Epithelioid Sarcoma of the Vulva, Lymphedema

Medications pre-NanaBis™	**Dosage:**
Nortriptyline 10mg	1 tablet daily
Ibuprofen 200mg	2 tablets TDS PRN
Paracetamol 500mg	2 tablets QID PRN
Sertraline 100mg	1 tablet daily
Oxycodone 5mg	2 tablets QID PRN
Targin 10/5mg	1 tablet BD
Pregabalin 150mg	1 tablet BD

Date NanaBis™ Commenced	09/08/2021
NanaBis™ Initial Dosage	1 spray BD
Changes in current medications	**Dosage:**
Nortriptyline	ceased Oct 2021
Ibuprofen	ceased Nov 2021
Targin	ceased Dec 2021
Endone	ceased Dec 2021
Paracetamol	ceased Dec 2021
Sertraline	ceased Feb 2022
Paracetamol + Diphenhydramine introduced in Dec 2021 as PRN but rarely used	
Current NanaBis™ dose	6-8 sprays nocte before meals

Quote from the patient

I have chronic global and chronic pain as a result of epithelioid sarcoma. I had 5 excision surgeries in 4 months which all had no clear margins. 6 weeks radiation to vulva, right side groin and right bottom of pelvis. I have contact nerve pain and heightened central nervous system sensitivity where a small pain feels like my body is being crushed when the pain is at its worst. I do not sleep well and have PTSD.

Patient outcomes at time of writing

Currently **pain** has gone **down** from 10 out of 10 to **2 out of 10**

Comment from the patient

"This has been life changing for me and my family. I am now doing things I didn't think I'd ever be able to do again with my level of pain and despair I was in.

I am off all pain meds, no more Endone, Targin and pregabalin. No more feeling like my only choice was to throw myself into a brick wall so my body would focus on a different kind of pain.

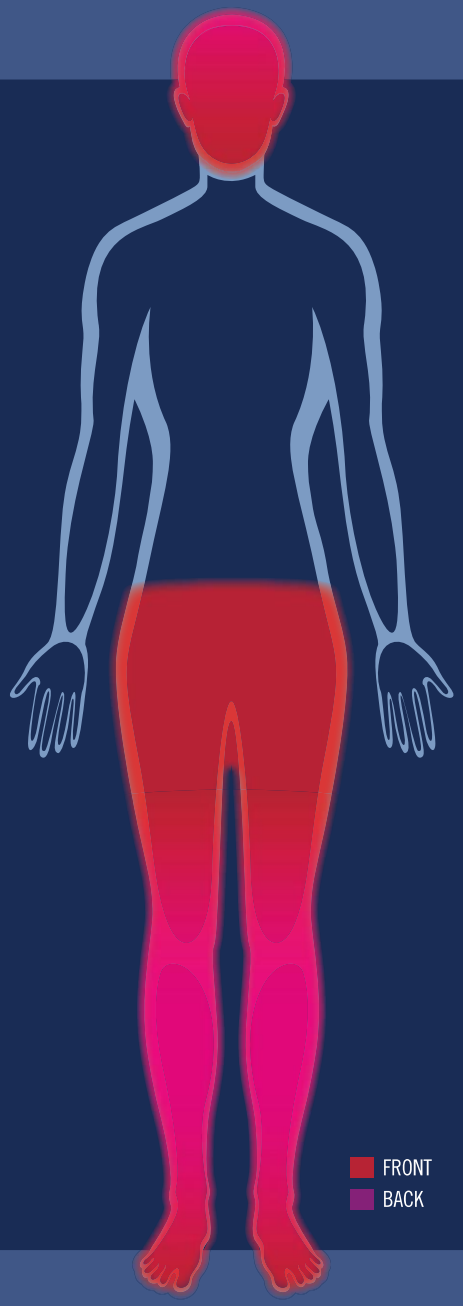
My world is free of brain fog and feeling awful each day. I am now able to focus and think clearly and enjoy my days. I am sleeping so incredibly well which has been a massive blessing.

Our family and friends say I have colour back in my face and light in my eyes again.

I am incredibly grateful for this trial and the doctor who has guided me through the process."

Date data collected	26/07/2022
Continuing medication?	Yes

NanaBis™ PATIENT Case Report



Patient Initials	FA
Age	N/A
Sex	F
Indication	Fibromyalgia, Restless Legs and chronic migraines

Medications pre-NanaBis™	**Dosage:**
Gabapentin	1500mg daily
Endep	75mg daily
Topamax	50mg daily
Paxam	0.5mg daily (anxiety)
Anafrani	25mg daily (depression)

Date NanaBis™ Commenced	15/10/2019
NanaBis™ Initial Dosage	N/A
Medications post-NanaBis™	**Dosage:**
Gabapentin	600mg daily
Endep	25mg daily
Paxam	0.5mg daily
(ceased Topamax, Anafranil)	
Current NanaBis™ dose	3 sprays afternoon, 4-5 sprays night

Symptoms of the patient before NanaBis™ treatment

Fibromyalgia and Restless legs. Chronic migraines daily. Disturbed sleep - waking up 6 times a night due to pain.

Patient outcomes at time of writing

Chronic migraines daily **prior to NanaBis™**

After NanaBis™ **migraines are rare** (maybe once a month)

May have headaches sometimes but no where near the intensity as a migraine

Was **waking up to 6 times a night** due to pain - now able to **sleep through the night**

Currently **pain** has gone **down** from 10 out of 10 to **1-1.5 out of 10**

If no NanaBis™ (ran out for 3 days) = 7-8

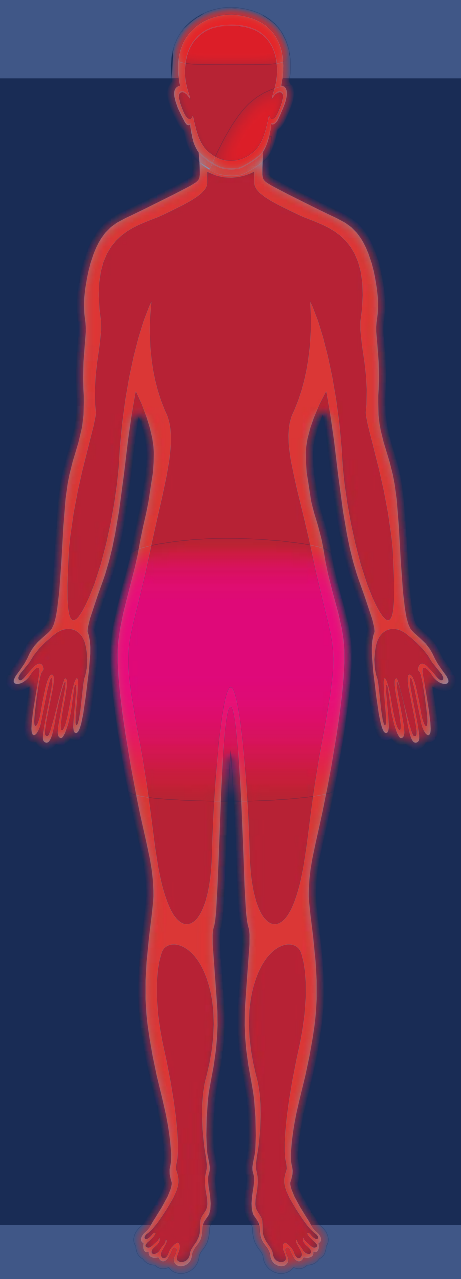
Was initially prescribed **Tilray CBD 25mg, not effective at all**. Besides slight drowsiness, no other adverse events

Date data collected	10/03/2020
Continuing medication?	YES

Results provided under consent. NanaBis™ under clinical investigation as a drug candidate and as such a non-ARTG medicine.

medlab.co

NanoCBD™ PATIENT Case Report



Medications prior to NanoCBD:

- Arthrexin 25mg - 1 tablet BD PRN
- Prednisolone 25mg - 1 tablet PRN
- Asmol (ventolin) 4-6 puffs in line with peak flow chart when required
- Metagenics Neurocalm 1 tab TDS
- Metagenics Pyrrole Protect 1 tab BD
- Life Extension Magnesium L-Threonate 1 tab daily
- Biological Therapies magnesium oral liquid 1ml in juice daily
- Diclofenac 25mg 1-2 tabs TDS PRN
- Valpam 5mg 1 tab TDS PRN
- Mediherb withania complex 1 tab BD
- Vitamin D3 1000IU 2 caps daily
- Paracetamol 2 tablets PRN
- Ibuprofen 200mg 2 tabs PRN
- Aspirin 500mg extra strength 1 tablet with a glass of coke zero for migraine aborter
- Stemetil 5mg 1 tab PRN
- Maltofer Iron tablets one tab every second day (New started 12/04/2021)
- Zeolite powder: ½ teaspoon every second day
- Paleo fibre powder ½ scoop daily
- Metagenics ultraflora intensive 1 tab daily
- Telfast 180mg 1 tab daily
- Senega with Ammonia cough syrup 20 ml when required
- Bioceuticals Armaforce 2 tablets daily during sinus infection

Patient Initials	RC
Age	40
Sex	F
Indication	Hemiplegic Migraines, Insomnia, Anxiety, Scaro-illiac Joint Pain, Left TMJ pain

Changes in current medications:

- Pyrrole protect 1 tab daily
- Magnesium threonate 1 tab daily
- Vitamin D3 1000IU 2 tab daily
- Maltofer Iron 1 tab every second daily
- Zeolite powder: ½ teaspoon every second daily
- Paleo fibre powder ½ scoop once a daily
- Metagenics ultraflora intensive 1 tab a daily
- Telfast 120mg 1 tab PRN

Current NanoCBD™ dose:

4 sprays nocte.

When NanoCBD™ started 22/02/2021
Starting dose - 1 spray nocte

Pain Score out of 10 prior to NanoCBD™	9/10
Pain Score out of 10 with NanoCBD™	2/10

Date data collected	12/04/2021
Continuing medication?	YES

For educational purposes only

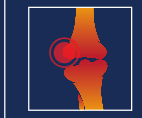
medlab.co

NanoCBD™ PATIENT Case Report

Symptoms of the patient before NanoCBD™ and currently

Before:

- Hemiplegic Migraines 3-4 a month (muscle numbness / weakness in arm or leg it varies on both sides, slow speech, severe head pain (varies from sharp shooting, stabbing to throbbing), visual disturbances, hot heated head, diarrhea, brain fog, ringing in ears, nausea and vomiting



- Chronic Fatigue
- Eczema mild
- Joint stiffness C1-L5 spine, hips, fingers, right knee and ankle during cold days or flare ups

- Muscular & nerve inflammation in these areas during flare ups

- Flare ups are caused by repetitive movements, exercise, high stress & every day activities
- Previous TMJ surgery on left side has nerve pain flare ups

- Moderate clinical anxiety
- December 2020 diagnosed with ASD level 2 - previously known as Aspergers

- Sensory processing - difficulties with touch and light sensitivity
- Insomnia - 3-4 hours sleep
- Restless legs. Night sweats

- Seasonal Allergies & Asthma

Current:

- NO - Hemiplegic Migraines!! There was an episode in March after 2 weeks on NanoCBD™ when I had slow speech, ear ringing and slow movement for 10 minutes yet I could still maintain motor skills (walk) and cognitive functioning (talk to say I'm ok etc). No muscle weakness or numbness, no headache or migraine afterwards, just the slow system malfunction in the one time block

- Significantly increased joint mobility and flexibility improvement, minimal swelling in joints, (contact for Chiropractor information if you would like further information to support this.)
- Increased energy

- Skin eczema and allergies have decreased
- ASD issues. Significant improvement in focusing concentration/ energy on one task as a time compared to previous multiple tasks and scattered focus energy. More tolerance for routine changes

- Sensory Processing - hypersensitivity to touch has decreased to a fantastic coping level. Less light sensitivity

- Anxiety is still moderate however there is more control over it. I can attend appointments, volunteer, have quality active time with family
- NO panic attacks or anxiety attacks

- NO restless legs or night sweats
- Still have seasonal allergies however note the decrease in Antihistamine dose and dosage

Other noticed improvements:

- Circulation on the right side of body has improved. First time in years blood test could be taken from the right arm
- Head heat has decreased

medlab.co

Why Avoid First Pass Metabolism?

For cannabinoids, one problem with oral delivery is the high level of first pass metabolism resulting in systemic exposure to the metabolites rather than THC and CBD.

First pass metabolites may not be as effective (medicinally) as THC and CBD and may have more side effects. For example, the first pass metabolite of THC, 11-hydroxy-tetrahydrocannabinol (11-OH-THC) has worse psychiatric adverse reactions than THC.

Oro-Buccal NanoCelle® spray delivery of THC and CBD provides relative levels of first pass metabolite over 10-fold lower than with ingestion, sublingual delivery, or ethanol vehicle oral buccal spray.

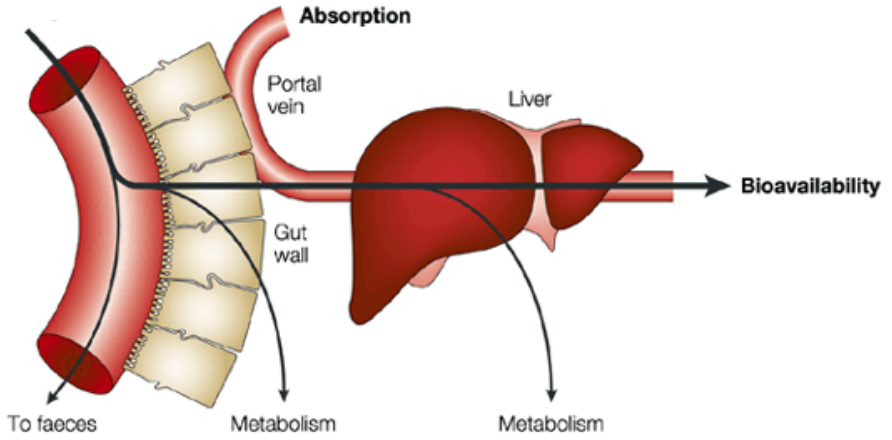


Image Credit: Nature Reviews | Drug Discovery

Stability – NanaBis™ and NanoCBD™

Research Problems and Objectives

The R&D batches of new synthetic cannabinoid preparations are under stability investigation. Two preparations have been secured in controlled temperature chambers at two temperatures each (25°C and 30°C) and a RH% of 65. This report describes the stability investigation performed for **NanaBis-S** and **NanoCBD-S** R and D batches at 9-months after their preparation in our Lab.

Methods

Samples were analysed using HPLC to measure the CBD and THC concentrations against true standards purchased from Cerilliant.

Key Results

The assay for stability is described in this report along with pH measurements. NanoCBD-S met the acceptance criteria for the 9-month CBD concentration with 20.54 mg/mL (25°C) and 19.98 mg/mL (30°C). The NanaBis-S CBD/THC concentration for the 9-month met the acceptance criteria with 10.49/9.73 mg/mL (25°C) and 10.23/9.32 mg/mL (30°C). Acceptance criteria is a change in concentration no more than 10% than the baseline.

Conclusion

The main observations for stability of the synthetic formulations namely for that of NanaBis-S and NanoCBD-S preparations showed no significant reductions (>10%) in CBD and THC concentrations between those results observed and reported at 6-month interval. Samples will be monitored for their stability at 12-month due in September 2022.

Uniqueness of the NanoCelle® Technology

Simplicity and Cost Effectiveness in Manufacturing

- The processing method used does not require specialized mechanical means, such as homogenization or sonication.
- The equipment needed is very common: steam jacketed tanks with stirring capabilities and transfer pumps.
- There is heat involved, but not high temperatures.
- Processing time is relatively short, a few hours depending on volumes.
- The processing method requires specific ratios of oil carriers, non-ionic surfactants, and co-surfactants to create the nanoparticle.
- Combinations of surfactants and multiple carriers often used in other nanoparticle methods are not required.
- All the excipient materials are approved, readily available and relatively inexpensive.
- The procedure is scalable, from 50 ml to over 1000 liters.

Physical Stability

- The **NanoCelle®** formulations are clear, aqueous solutions and they can maintain this stability for over two years without special handling. Chemical stability of specific formulations may require special storage conditions.

Versatility

- This methodology allows its use with a wide variety of hydrophobic small molecules.
- Selected large molecules (e. g. insulin)
- Hydrophilic molecules (e. g. methylcobalamin).
- Certain organically bound mineral compounds (e. g. calcium atorvastatin).

Flexibility in Application

- Due to the stable, clear, aqueous solutions, there are a wide variety of dose applications.
- Oro-buccal Sprays
- Oral Muco-adhesive Gels
- Nasal Sprays
- Topical Sprays
- Topical Gels, Lotions, Creams
- Ocular Solutions
- Dermal Patch Applications
- Adsorption onto Carrier Agents

Inflammopharmacology (2021) 29:1361–1370
https://doi.org/10.1007/s10787-021-00859-y

Inflammopharmacology

ORIGINAL ARTICLE

A pilot safety, tolerability and pharmacokinetic study of an oro-buccal administered cannabidiol-dominant anti-inflammatory formulation in healthy individuals: a randomized placebo-controlled single-blinded study

Luis Vitetta[1,2] · Belinda Butcher[3,4] · Jeremy D.

Received: 7 April 2021 / Accepted: 27 July 2021 / Published onlin

Abstract

Background The cannabis plant presents a complex h
have been classified as cannabinoids binding to canna
and preliminary pharmacokinetics of a nanoparticle
Methods The cannabis-based medicine was elabora
cle CBD-dominant anti-inflammatory cannabis med
and on day 2 administered 6 sprays to alternating ri
participants administered 2 and 6 sprays on days 1 a
Results The study met the primary outcomes of safety
dominant anti-inflammatory extract for oro-buccal ad
IQR) was 0.87 and 8.9 ng h mL^{-1}, respectively. The n
once per day occurred at 60 min for both concentrat
and 5.45 h, respectively. The apparent clearance of (
Conclusion The oro-buccal nanoparticle formulatio
commercial and investigated formulations relative t
adverse effects associated with unfavorable inflamm

Asia-Pacific Journal of Clinical Oncology

ABSTRACT

Volume 16, Issue S8
COSA's 47th Annual Scientific Meeting, Quality and Safety, Implementation Science, Cardio-Oncology, 11–13 November 2020

Wiley Online Library
The Journal is endorsed by the Chinese Society of Clinical Oncology (CSCO), Clinical Oncology Society of Australia (COSA), Korean Association for Clinical Oncology (KACO), Medical Oncology Group of Australia (MOGA) and Singapore Society of Oncology (SSO)

219. Pilot clinical and pharma water soluble nanoparticle ca advanced cancer with intracta

Stephen Clarke[1,2,3], Belinda Butcher[4,5], Andrew J McLachlan[6], Jer

[1]Sydney Medical School, The University of Sydney, Sydney, New South Wales, Austra
[2]Northern Clinical School Kolling Institute of Medical Research, Sydney, NSW, Austral
[3]Oncology, GenesisCare, Sydney, New South Wales, Australia
[4]WriteSource Medical Pty Ltd.,, Lane Cove, New South Wales, Australia
[5]The University of New South Wales, School of Medical Sciences, Sydney, New South
[6]The University of Sydney, School of Pharmacy, Sydney, NSW, Australia
[7]The University of New South Wales, Prince of Wales Clinical School, Sydney, NSW, A
[8]Medlab Clinical, Sydney, NSW, Australia

Relief from chronic pain has been a common reason cited by
open label single arm study (n = 30) assessed a single ascend
(MAD; Stage 2) of a standardised and purified mixture of Δ9-
water-soluble nanoparticle oro-buccal spray formulation for t
advanced cancer. On day 1 Stage I participants received 2.5 m
7.5 mg Δ9-THC and 7.5 mg CBD (six sprays) on day 2. In Stage
spray containing 1.25 mg Δ9-THC and 1.25 mg CBD; two spra
9-THC and CBD were rapidly absorbed. As single and multiple
concentrations (Cmax) of all analytes were proportional to dc
water-soluble nanoparticle formulation was approximately tw
spray that uses ethanol as the vehicle. The water-soluble canr
of Δ9-THC than CBD (bioavailability from 2.5 mg each of Δ9-T
respectively). In a subgroup of participants diagnosed with b
mean pain scores improvement from baseline was approxima
medication use. For all patients the most commonly reported
affecting 11 (44%) and 4 (6%) patients, respectively and naus
water-soluble cannabis-based medicine provided adequate b
tolerable in people with cancer and uncontrolled pain with pr

1. Fraguas-Sánchez, A.I.; Torres-Suárez, A.I. Medical Use of Cannabinoids. Drugs 2018, 78, 1665–1703.
2. Borgelt, L.M.; Franson, K.L.; Nussbaum, A.M.; Wang, G.S. The pharmacologic and clinical effects of medical ca
3. National Academies of Sciences, E.; Medicine, Health; Medicine, D.; Board on Population, H.; Public Health, P.
Collection: Reports funded by National Institutes of Health. In The Health Effects of Cannabis and Cannabinoi
2017 by the National Academy of Sciences. All rights reserved.: Washington (DC).

The volume 16, Issue S8 supplement is an
via https://onlinelibrary.wiley.com/doi/10.

bioengineering

MDPI

Type of the Paper (Communication)

NanoCelle™: A novel delivery platform for pharmaceutical grade cannabis medicines.

Kamini Divakarla[1], Michelle Quezada[2], Tomas Andersen[2], Jere Hall[2], David Rutolo[2], Wojciech Chrzanowski[1], Luis Vitetta [1,2]*

[1] The University of Sydney
[2] Medlab Clinical
[3] The University of New South Wales.

* Correspondence: luis_vitetta@medlab.co and luis.vitetta@sydney.

Received: date; Accepted: date; Published: date

Abstract: Cannabinoid molecules derived from *Cannabis sativa* L. ameliorate conditions such as pain, multiple sclerosis associated sp chemotherapy induced), cancer, cachexia, post-traumatic stress di glaucoma. CBD and THC are highly lipophilic compounds and as a re low aqueous solubility, which in turn results in low bioavailability. makes drug delivery and preparation challenging. Micelle formulatio of drug delivery of such drugs through orientation of surfactant hydrophobic core. Furthermore, novel delivery mechanisms may a standard routes of administration (e.g., oral / gastrointestinal, inh mucosa) through bypassing of first pass metabolism by the liver. nanomicellar formulation in an orobuccal spray format for rapid del

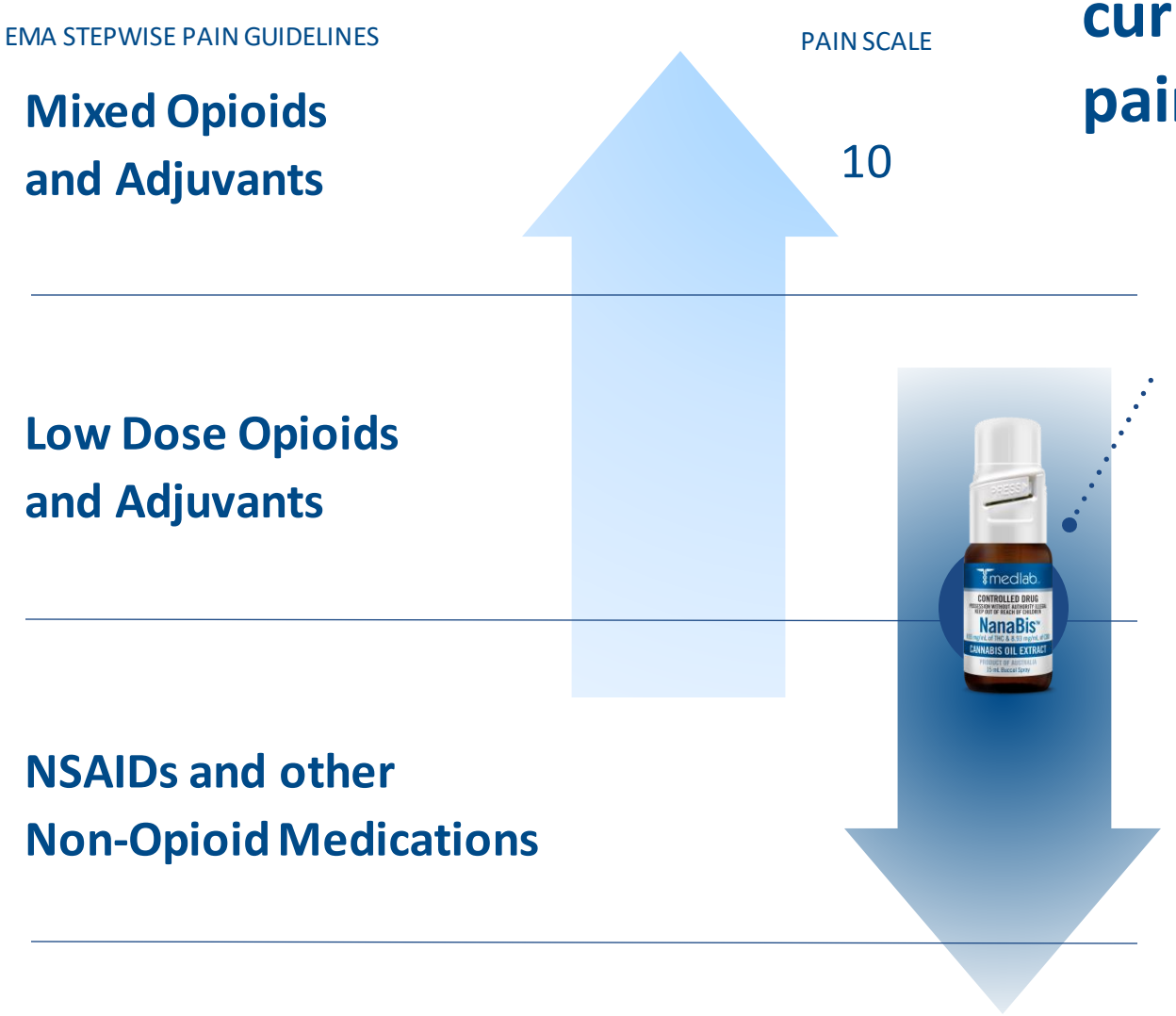
PLOS ONE

Pilot Clinical and Pharmacokinetic Study of Δ9-Tetrahydrocannabinol (THC) / Cannabidiol (CBD) Nanoparticle Oro-Buccal Spray in Patients with Advanced Cancer Experiencing Uncontrolled Pain

--Manuscript Draft--

Manuscript Number:	PONE-D-21-02741R3
Article Type:	Clinical Trial
Full Title:	Pilot Clinical and Pharmacokinetic Study of Δ9-Tetrahydrocannabinol (THC) / Cannabidiol (CBD) Nanoparticle Oro-Buccal Spray in Patients with Advanced Cancer Experiencing Uncontrolled Pain
Short Title:	Cannabis-based medicine of a nanoparticle oro-buccal spray
Corresponding Author:	Luis Vitetta The University of Sydney Sydney, AUSTRALIA
Keywords:	Δ9-Tetrahydrocannabinol; cannabidiol; Pharmacokinetics; NanoCelleTM; MDCNB-01; Oro-Buccal; advanced cancer; Intractable Pain
Abstract:	In this pilot study we 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. The study was a non-blinded single arm 2 stage study. Stage I was a single escalating dose (n=5) [2.5 mg D9-THC and 2.5 mg CBD) versus a 3x escalating dose. Whereas stage II was an up-titrated dose in patients diagnosed with advanced cancers and intractable pain (n=25). During Stage I with an increased cannabis-based medicine dose, maximum observed plasma concentrations of all analytes were not proportional to dose. The bioavailability of D9-THC and CBD in this water-soluble nanoparticle formulation was comparable (at a lower administered dose) to the bioavailability reported for a D9-THC/CBD mouth spray with ethanol. The water-soluble formulation in the current study (MDCNB-01) resulted in a higher median (min, max) bioavailability of D9-THC than CBD (AUC from 2.5 mg each of D9-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. During stage II

The Importance



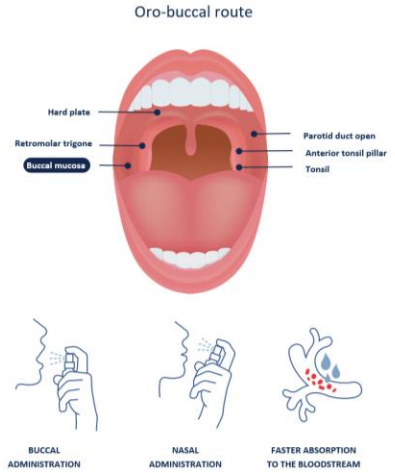
64% of all bone cancer patients are currently not supported by existing pain therapy

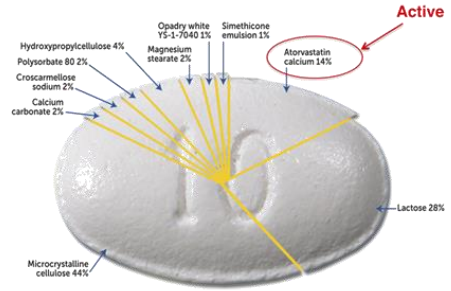
- THC / CBD provides a viable alternative that can delay or alleviate the need to use opioids for pain management
- Effective and safe, preferably used before progression to opioids
- Efficacious in patients with *unmanageable pain* that is not being controlled by opioids and other pain medication

NanoCelle® Opportunities are beyond Cannabinoid-based Medicines

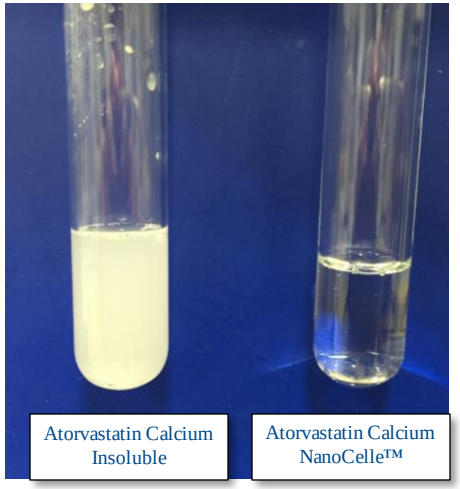
Typical bioavailability and characteristics of different routes of administration are[1]:

Route	Speed[2]	Bioavailability	Characteristics
Intravenous	30-60 seconds	100%	Most rapid.
Intramuscular	10-20 minutes	75≤100%	Large volume may be injected but painful method.
Subcutaneous	15-30 minutes	75≤100%	Smaller volume than IM. May be painful.
Oral - ingested	30-90 minutes	5% or more	Convenient, first pass metabolism occurs.
Oral - sublingual	**3-5 minutes**	**c.35%[3]**	
Oral - buccal	**3-5 minutes**	**30% or more**	**Direct access to systemic circulation - bypassing the portal system. First pass metabolism is avoided.**
Rectal	5-30 minutes	30<100%	Less first pass metabolism than oral route.
Inhalation	2-3 minutes	5<100%	Rapid onset.
Transdermal	Highly varied	80≤100%	Usually slow absorption, lack of first pass metabolism and prolonged duration of action.





Lowers dosage requirement of Atorvastatin (Lipitor)



[1] http://howmed.net/pharmacology/bioavailability-of-drugs/
[2] https://pharmawiki.in/routes-of-drug-administration-ppt-pdf-10-routes-of-drug-administration/
[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3513449/#:~:text=The%20bioavailability%20of%20a%205,doses%20exceed%20around%205%20mg.

NanoCelle® Particle Sizes PoC

Article	Particle Size (nm)	Concentration	Dosage
Ampicillin Sodium Salt (2162016AMP)-antibiotics	12.85	2 mg/mL	0.6 mg/0.3mL
Atorvastatin (1022015ATO)	11.41	10 mg/mL	3 mg/0.3mL
Atorvastatin (1232015ATO)	89.31	0.1 mg/mL	0.03 mg/0.3mL
Atorvastatin (03212017ATO)	14.4	8.3 mg/mL	2.49 mg/0.3mL
Atorvastatin (3152017ATO)	19.37	13.3 mg/mL	3.99 mg/0.3mL
Atorvastatin-25 (12142015ATO25)	14.62	1.67 mg/mL	0.5 mg/0.3mL
Atorvastatin-30 (12142015ATO30)	14.37	1.67 mg/mL	0.5 mg/0.3mL
Atorvastatin (2162016ATO)	12.71	10 mg/mL	3 mg/0.3mL
Beta-Estradiol (2162016EST)-hormones	16.43	1 mg/mL	0.3 mg/0.3mL
Fexofenadine (Telfast™)	10.6	4 mg/mL	1.2 mg/0.3mL
Dexamethasone (2162016DEX)-hormones	13.17	2.6 mg/mL	0.78 mg/0.3mL
Insulin (1022015INS)	3.843	15 IU/mL	4.5 mg/0.3mL
Perindopril Erbumine (2162016PER)-ACEi	12.7	7 mg/mL	2.1 mg/0.3mL
Progestogen (2162016PEO)-hormones	15.48	2 mg/mL	0.6 mg/0.3mL
Rosuvastatin (1022015ROS)-statin	12.19	2 mg/mL	0.6 mg/0.3mL
Rosuvastatin (1022015ROS)-statin	12.19	2 mg/mL	0.6 mg/0.3mL
Sertraline Hydrochloride (2162016SER)-SSRI	15.21	0.5 mg/mL	0.15 mg/0.3mL
Testosterone Propionate (123015TES)-hormones	14.31	15 mg/mL	4.5 mg/0.3mL
CoQ10 (2182916CoQ10)	32.3	100 mg/mL	30 mg/0.3mL
D3	86.3	3333 IU/ mL	5000 IU/0.3 mL
D3 & K2 (2182016D3K2)	28	3333 IU+150mcg/0.3 mL	1000 IU+45 mcg/0.3 mL
Melatonin (2182016MEL)	23	8.3 mg/mL	2.5mg/0.3mL
Cyanocobalamin B12	24.8	3333 IU/ mL	1000 IU/0.3 mL
MethylcobalaminB12 (2182016B12)	18.9	3333 IU/ mL	1000 IU/0.3 mL
NanaBidial™(<1:20 THC:CBD (20mg/mL CBD and less than 1 mg/mL THC)	20.13 nm	8.3 mg/mL	2.5mg/0.3mL
NanaBis™1:1 THC:CBD (8.33mg/mL THC 8.33mg/mL	33.33 nm	8.3 mg/mL	2.5mg/0.3mL
NanoCBD™(16.66 mg/mL CBD)	21.99	5mh/0.3mL	5mg/0.3mL
Chloroquine	31.5 nm	5mg/mL	-

Innovative Patent Technology

NanoCelle®
57 patents worldwide

Our research into nano-sized particles has spanned years of rigorous development

The science behind the unique NanoCelle® delivery system was validated with an Australian Patent granted in September 2020, providing protection until March 2036. The US Patent was granted in November 2021.

9 September 2016

USPTO published the patent Transmucosal and transdermal delivery systems (WO2O16141069).

21 November 2016

A second patent, 'Protection of plant extracts and compounds from degradation', also entered National Phase into the above countries.

November 2020

A provisional patent, 'absorbing characteristics of NanoCelle®' was launched in Australia

Australia
United States
Canada
Europe

- Albania
- Austria
- Belgium
- Bulgaria
- Switzerland
- Liechtenstein
- Cyprus
- Czech Republic
- Germany
- Denmark
- Estonia
- Spain
- Finland
- France
- United Kingdom
- Greece
- Croatia
- Hungary
- Ireland
- Iceland
- Italy
- Lithuania
- Luxembourg
- Latvia
- Monaco
- North Macedonia
- Malta
- Netherlands
- Norway
- Poland
- Portugal
- Romania
- Serbia
- Singapore
- Sweden
- Slovenia
- Slovakia
- San Marino
- Turkey

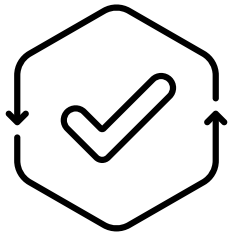
Hong Kong — Registration of Grant requested

New Zealand — Accepted

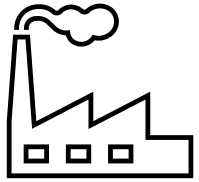
Summary – Benefits Specific to NanoCelle®

API's bypass first pass metabolism and allows for use via non-traditional routes of delivery.

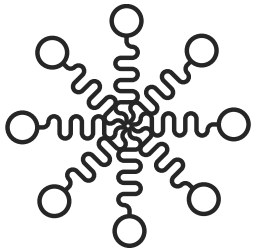
Avoids exposure to gastric acid and/or avoids need for patient to ingest.



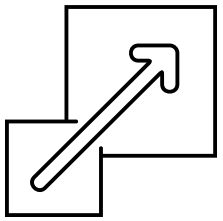
Convenient and easy to use.



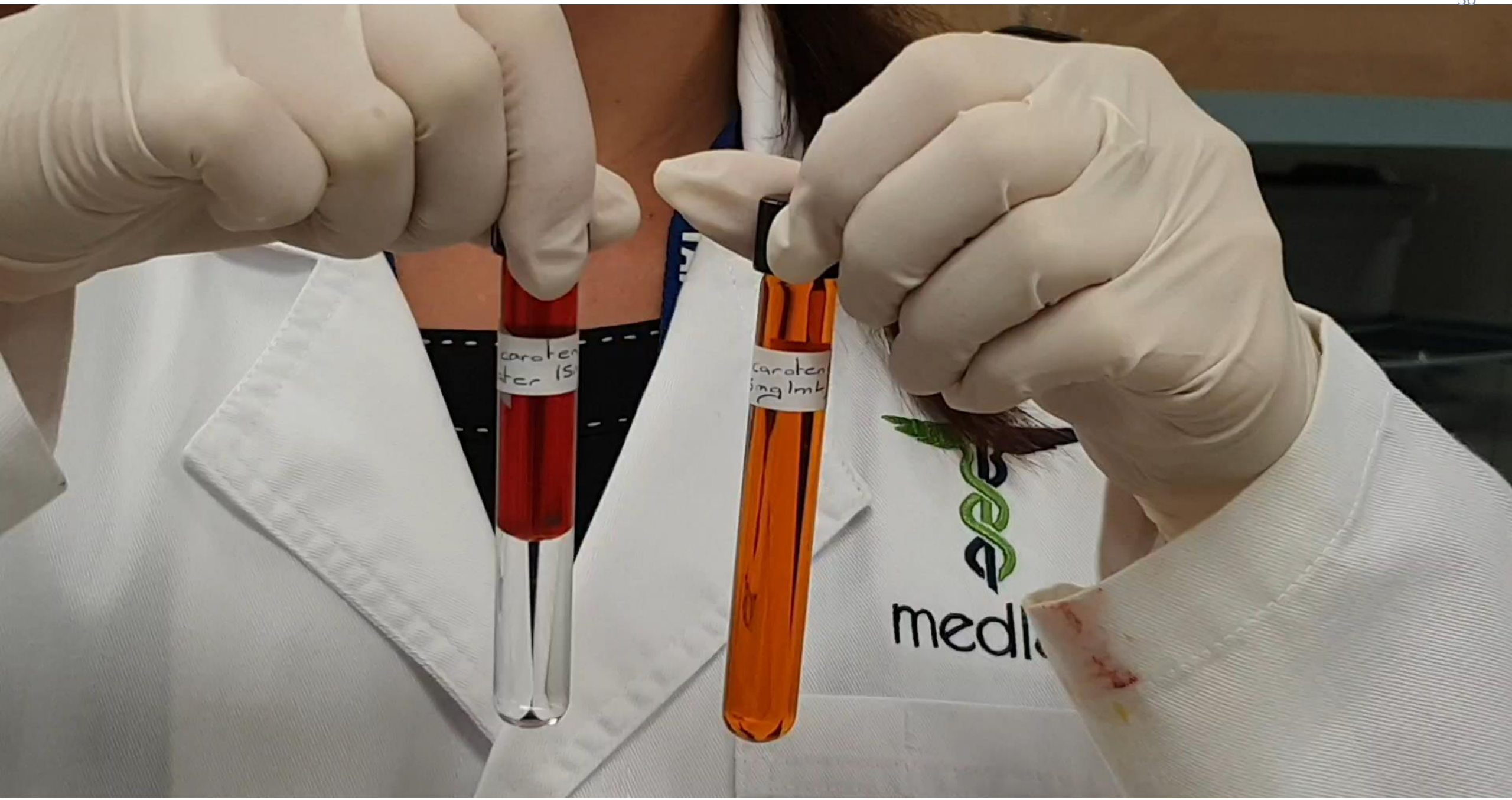
Production is an easy bolt-on to liquid manufacturing.



For use as buccal, nasal or topical delivery.



Shown to enhance shelf life/stability for certain API, inclusive of CBD and THC.



Thank You

ASX : MDC

HEAD OFFICE

Medlab Clinical Limited
Units 5 & 6, 11 Lord St, Botany
NSW 2019, Australia
P +61 2 8188 0311
E sean_hall@medlab.co

CALIFORNIA OFFICE (USA)

Medlab Clinical US, Inc
30021 Tomas
Suite 150
Rancho Santa Margarita, CA
92679, USA
P +1 949 202 1088

US INVESTOR RELATIONS

Edison Group
1185 Avenue of the Americas, New
York NY
P: +1 646 653 7035
E: lyonker@edisongroup.com