Medical Cannabis and Cannabinoids

Preclinical Science and Clinical Studies - Research Article

Med Cannabis Cannabinoids 2023;6:66–76
DOI: 10.1159/000531232

Received: February 21, 2023
Accepted: May 17, 2023
Published online: July 7, 2023

Tolerability and Efficacy of a 10:25 Preparation of Δ9-Tetrahydrocannabinol and Cannabidiol for Treatment of Chronic Back or Neck Pain: A Multiple-Dose Escalation Study

Paul Glare[a] Richard Chye[b, c] Mark Bloch[d] Mark Arya[e] Andrew Moore[e] John Montgomery[f, g]

[a]Northern Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia; [b]School of Clinical Medicine, UNSW, Sydney, NSW, Australia; [c]Supportive & Palliative Care, St Vincent's Hospital, Sydney, NSW, Australia; [d]Holdsworth House Medical Practice, Sydney, NSW, Australia; [e]Australian Clinical Research Network, Sydney, NSW, Australia; [f]Cymra Life Sciences, Sydney, NSW, Australia; [g]Pharmacy Department, University of Technology, Sydney, NSW, Australia

Keywords
Cannabidiol · Delta-9-tetrahydrocannabinol · Safety · Pharmacokinetics

Abstract

Introduction: The aim was to demonstrate the safety and tolerability of cannabidiol (CBD) with Δ9-THC in patients with moderate to severe chronic back or neck pain unresponsive to over-the-counter non-opioid analgesics. ***Methods:*** This was a non-randomized, single-arm, open-label study. Participants received escalating doses of an oromucosal-administered combination containing 10 mg/mL of Δ9-THC, 25 mg/mL of CBD. On day 1, patients received once-daily 0.5 mL Cybis® 10:25 (5 mg Δ9-THC plus 12.5 mg CBD daily), escalated at days 8, 15, and 22 to 0.5 mL twice-daily (bd) (10 mg Δ9-THC plus 25 mg CBD daily), 1.0 mL bd (20 mg Δ9-THC plus 50 mg CBD daily), and 1.5 mL bd (30 mg Δ9-THC plus 75 mg CBD daily), respectively. The primary outcome was safety and tolerability, with secondary objectives including pharmacokinetic and efficacy outcomes. ***Results:*** 28 patients were enrolled in the study. Their median age was 63.3 years, and half were female. The median history of neck/back pain was 10 years. The pharmacokinetics following single doses of 0.5 mL were variable; however, there were dose-dependent increases in trough levels of CBD and Δ9-THC. Cybis® 10:25 was well tolerated, with the majority of adverse events of mild severity. The most common adverse events were nausea, vomiting, fatigue, dizziness, headache, paresthesia, and anxiety. There were dose-dependent improvements in numerical pain rating scores ($p < 0.001$), with clinically significant reductions in pain at 1.0 mL bd and 1.5 mL bd doses (28.8% and 34.1% reductions, respectively, $p < 0.001$). Depressive symptoms and stress had dose-dependent reductions ($p = 0.0182$, $p < 0.01$, respectively). ***Conclusion:*** In patients with chronic neck/back pain, CBD and Δ9-THC are well tolerated and doses of 1.0 mL bd and 1.5 mL bd showed clinically significant reductions in pain compared to baseline pain scores.

karger@karger.com
www.karger.com/mca

Correspondence to:
Paul Glare, paul.glare@sydney.edu.au

Introduction

Chronic back pain is one of the leading causes of disease burden, causing moderate interference with daily activities for almost two in five sufferers [1]. It affects between 1 and 16% of the population [1, 2]. Current treatment of chronic back pain includes non-pharmacological approaches (exercise, rehabilitation, acupuncture, mindfulness, etc.) [3], and in patients with inadequate response, pharmacological treatment is used [3]. Paracetamol and nonsteroid anti-inflammatory drugs (NSAIDs) are first-line therapies.

However, given the large variability in the presentation and outcomes of patients with chronic back and neck pain [4], treatment can be challenging, particularly when simple analgesia is ineffective. Given this, in addition to limitations on opioid prescribing resulting from concerns about their long-term effectiveness and the limited evidence supporting their effectiveness, there has been increasing interest in finding alternative treatments for patients with chronic pain [5, 6].

One such option is medicinal cannabis. Evidence for medicinal cannabis in chronic non-cancer pain is limited, but it suggests that cannabis is more likely than placebo to produce between 30% and 50% reductions in pain scores and is more likely than placebo to produce significantly greater reduction in pain intensity rating, although the differences are small [7, 8]. The summary of evidence of THC:cannabidiol (CBD) extract, for which there was only one study, provided a moderate level of evidence of 30% reduction in pain scores and a low level of evidence for change in pain scores [7]. Efficacy results are heterogenous, likely due to the different combinations and formulations included in the analysis. Sublingual or orobuccal preparations are useful as they may provide rapid absorption and avoid a first-pass effect [9–11].

In this study, Cybis® 10:25, an oromucosal-administered THC and CBD combination, was assessed. Cybis® 10:25 contains a 10:25 ratio of THC:CBD in medium-chain triglycerides. The CBD is present in order to counteract the psychoactive effects of THC and may also contribute to the analgesic effect [12]. This was the first study of Cybis® 10:25 in humans. The overall aim was to demonstrate the safety and tolerability of Cybis® 10:25 in participants with moderate to severe chronic back or neck pain that was unresponsive to over-the-counter (OTC) non-opioid analgesics.

Materials and Methods

Trial Design

This was a non-randomized, single-arm, open-label study of Cybis® 10:25 in participants with chronic back or neck pain in which participants received escalating doses of Cybis® 10:25. This study was designed with reference to the IMPACCT consensus guidelines [13] and the European Medicines Agency guidelines [14]. This study was reviewed and approved by the Bellberry Human Research Ethics Committee (approval number 2021-03-305), Clinical Trials Registration (Clinicaltrials.gov NCT04976738).

Participants

This study was conducted between October 2021 and June 2022 at two community sites in Sydney, Australia. Adult (≥18 years of age and <75 years of age) men or women who had a history of back or neck pain of at least 3 months duration were invited to participate. They had an average back or neck pain score of between five and nine on a 10-point visual analogue scale; had to have failed to achieve self-reported satisfactory pain relief using OTC paracetamol or NSAIDs; and were willing to cease all current pain medications. In addition, they agreed to cease driving a car or operating heavy machinery from the date of the first dose, until 7 days after the last dose of Cybis® 10:25. All participants were required to provide written informed consent.

Potential participants were excluded if they had a history of cannabis use disorder or other substance abuse disorders, were currently using cannabis or other medicinal cannabis products, or had significant other illness. Participants were not permitted to use any pain medications beyond the study intervention for at least 3 days prior to commencing study intervention and throughout the trial period, with the exception of rescue medication (two tablets, each tablet containing 500 mg paracetamol with 150 mg ibuprofen, every 6 h as clinically necessary, with a maximum of six tablets in 24 h).

Interventions

Participants took multiple ascending doses of Cybis® 10:25, containing 10 mg/mL of D9-THC, 25 mg/mL of CBD, formulated in medium-chain triglyceride oil. Administration occurred oromucosally. On days 1–7, participants received 0.5 mL once-daily (od); on days 8–14, they received 0.5 mL twice-daily (bd), on days 15–21, they received 1.0 mL bd; and on days, 22–28 they received 1.5 mL bd. Participants were followed up again on day 35 (7 days after the last dose of Cybis® 10:25).

Outcomes

The primary objective of this trial was to assess the safety and tolerability of Cybis® 10:25 at low (0.5 mL od), medium-low (0.5 mL bd), medium (1.0 mL bd), and high (1.5 mL bd) doses in participants with chronic back or neck pain refractory to OTC non-opioid analgesics. Secondary objectives were to investigate the pharmacokinetics of Cybis® 10:25; to investigate the dose-response relationship between Cybis® 10:25 and pain response as measured by the change from baseline in Numerical Pain Rating Scale (NPRS) and Brief Pain Inventory Short Form (BPI-SF); to investigate the dose-response relationship between Cybis® 10:25 and mood as measured by the change from baseline in Depression Anxiety Stress Scale (DASS), change from baseline in Medical Outcomes Study Sleep Scale (MOS-SS), and change from baseline in Self-Assessment of Treatment (SAT-II) scale; and to investigate rescue medication use in participants prescribed Cybis® 10:25 for chronic back and neck pain.

To assess pharmacokinetics, blood samples were drawn at Day 1 prior to dosing (0 [visit window −15 min]) and at 0.25 h ± 5 min, 0.5 h ± 5 min, 1.0 h ± 5 min, 1.5 h ± 5 min, 2.0 h ± 5 min, 2.5 h ±

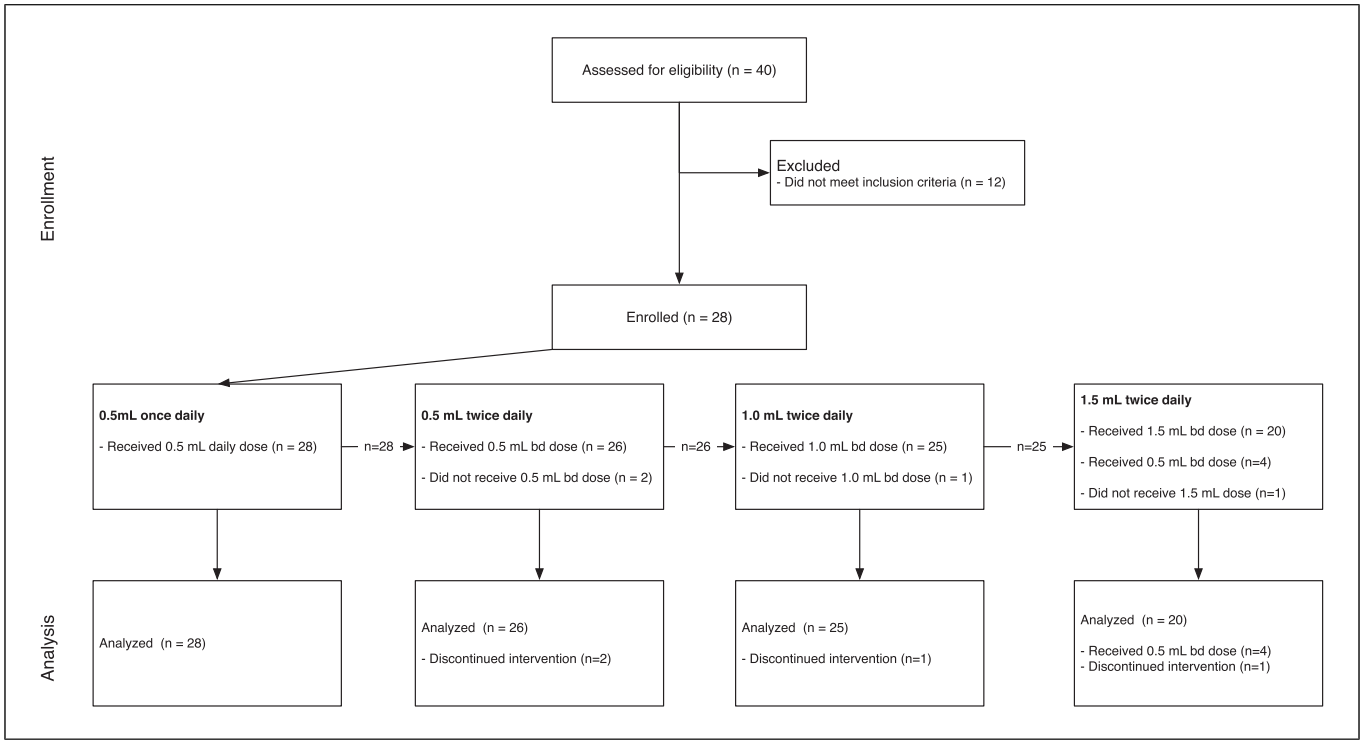

Fig. 1. CONSORT diagram.

5 min, 3.0 h ± 5 min, 3.5 h ± 5 min, 4.0 h ± 5 min, 5.0 h ± 10 min, 6.0 h ± 10 min, 9.0 h ± 30 min, 12.0 h ± 30 min, and on Day 2, 24.0 h ± 1 h post dosing. During the pharmacokinetic sampling, a light lunch was permitted after the 4 h sample, and a light snack was permitted 4 h later. A light dinner was permitted. Alcohol was not permitted throughout the study.

Sample Size

The sample size calculation was based on the secondary objective of investigating the dose-response relationship in terms of change from baseline in NPRS. Assuming a non-linear change in NPRS at each dose, then using a one-sided alpha of 0.05, and assuming a standard deviation of 2.2, and three dose levels with an assumed maximum change in NPRS of 2.1 (the minimum clinically important difference for the NPRS is a two-point change [15]), then 19 participants per dose level were required for 80% power. Allowing for 20% drop out, then 24 participants per dose level were planned to be recruited. The sample size was calculated using a linear contrast test.

Statistical Methods

Analyses were based on the full analysis set (FAS), that is, all participants who enrolled and received at least one dose of Cybis® 10:25. An additional FAS was developed (FAS by dose) which included all participants enrolled who received at least one dose of Cybis® 10:25 but placed participants in dose cohorts only if they received that dose. The latter was used for comparisons by dose. Safety analysis was conducted in the FAS population.

Adverse events were summarized by dose cohort. Pharmacokinetic parameters were estimated using non-compartmental methods. The dose-response relationship between Cybis® 10:25 and efficacy outcomes (NPRS, BPI, DASS, MOS-SS, SAT-II) was assessed using mixed models repeated measures with baseline as a covariate in the model. Sensitivity analyses assessed the impact of rescue medication, by including in the analysis only those participants without rescue medication use.

There was no adjustment for multiple comparisons, and $p < 0.05$ was considered statistically significant. All analyses were conducted using Stata MP v17 for Mac (StataCorp, Texas Station, USA). Although this was a non-randomized study, this study has been reported in accordance with CONSORT [16] and the pain-specific supplement to CONSORT [17].

Results

Participants

Forty people were screened for this study, of whom 28 were included in the study (Fig. 1). The median age of participants was 63.3 years (range 31.3–74.7 years), and half were female (Table 1). Participants had experienced back or neck pain for a median of 10 years (range 7 months–53 years). Only 4 (14%) had previous experience of cannabis, while 26 (93%) had prior analgesic (opioid, paracetamol, NSAID, and other analgesic) use.

Table 1. Participant demographics and clinical characteristics

Demographic	Value
Age, years, median (min, max)	63.3 (31.3, 74.7)
Sex, *n* (%)	
Female	14 (50)
Male	14 (50)
Height, cm, mean (SD)	165.6 (9.7) (*n* = 27)
Weight, kg, mean (SD)	84.2 (17.2)
Ethnic background, *n* (%)	
Asian (including SE Asian, Indian, etc.)	10 (36)
Caucasian	18 (64)
Disease duration, months, median (range)	120.5 (6.9, 637.6)
History of cannabis use	4 (14)
Type of pain (LANSS category)*	
Non-neuropathic	6 (21)
Neuropathic	4 (14)
Missing	18 (64)
Prior opiate use (including tramadol)	8 (29)
Prior analgesic use (including complementary medicine)	26 (93)
Washout period for those with analgesic medication during screening, days, median (range)	2.5 (0.0, 14.0) (*n* = 8)
Pain level at baseline, *n* (%)	
Moderate	8 (31)
Severe	14 (54)
Very severe	4 (15)
Depressive symptoms (based on DASS), *n* (%)	
Normal mood	6 (23)
Mild depressive symptoms	4 (15)
Moderate depressive symptoms	8 (31)
Severe depressive symptoms	1 (4)
Very severe depressive symptoms	7 (27)

DASS, Depression Anxiety Stress Scale; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs. *This assessment was introduced in a protocol amendment, so is missing for approximately one-third of patients.

Drug Exposure

The percentage adherence to investigational medicine product (IMP) was high (median 100%) for all four doses, although there was some variability, particularly at the highest dose (adherence range 28.6–100%). The proportion of participants who were compliant with 80% or more of doses was higher in lower doses (93% for 0.5 mL od to 67% in 1.5 mL bd). Of the original cohort (*n* = 28), 20 (71%) participants reached the highest dose cohort.

Pharmacokinetics

The pharmacokinetics of single doses of 0.5 mL Cybis® 10:25 showed significant interpatient variability (Table 2); briefly, THC C_{max} was 1.84 ng/mL CBD C_{max} was 2.49 ng/mL. T_{max} occurred at 9.58 h (THC) and 11.78 h (CBD). There were dose-dependent increases in median trough concentrations of Cybis® 10:25.

Pain

There were significant reductions in pain in patients administered all doses of Cybis® 10:25 compared to baseline, and the linear effect of dose was significant ($p < 0.001$, Table 3). Clinically significant reductions in NPRS scores (>2 point reduction in NPRS) were observed for 1.0 mL bd and 1.5 mL bd doses (both $p < 0.001$, Fig. 2). The mean and median NPRS reductions were 2.3 and 2.0 points, respectively, for 1.0 mL bd dose, and 2.7 and 3.0 points, respectively, for 1.5 mL bd dose. This equated with a mean 28.8% (median 28.6%) reduction for the 1.0 mL dose and a mean 34.1% (median 37.5%) reduction for the 1.5 mL dose. This pattern remained when excluding any participants who had been administered rescue medication (see Fig. 2b). Similarly, there were dose-dependent improvements in pain levels as assessed by the BPI. Significant improvements from baseline were observed in *Pain Now* and *Pain Average* for all

Table 2. Pharmacokinetics of THC, CBD, and 11-OH-THC following single doses of 0.5 mL of Cybis™ 10:25

Parameter	THC (*n* = 22)	CBD (*n* = 22)	11-OH-THC (*n* = 22)
C_{max}, ng/mL, median (min, max)	1.84 (0.43, 6.97)	2.49 (0.78, 11.40)	2.49 (0.44, 9.05)
t_{max}, hours, median (min, max)	9.58 (9.03, 24.87)	11.78 (9.18, 25.12)	23.79 (9.18, 25.23)
Area under curve, ng/mL.hours, median (min, max)	7.45 (2.83, 72.83) (*n* = 18)	17.95 (4.80, 34.62) (*n* = 18)	13.64 (4.53, 31.96) (*n* = 21)
Half-life, hours, median (min, max)	1.56 (0.46, 268.90) (*n* = 18)	3.35 (0.87, 71.03) (*n* = 18)	7.06 (1.90, 17.74) (*n* = 21)
Trough concentration, ng/mL, median (min, max)			
0.5 mL od	0.0 (0.0, 0.3) (*n* = 26)	0.2 (0.0, 0.6) (*n* = 26)	0.2 (0.0, 0.4) (*n* = 26)
0.5 mL bd	0.2 (0.0, 0.7) (*n* = 28)	0.8 (0.1, 2.6) (*n* = 28)	0.6 (0.0, 1.7) (*n* = 28)
1.0 mL bd	0.5 (0.1, 1.3) (*n* = 24)	1.6 (0.6, 4.2) (*n* = 24)	1.3 (0.2, 4.1) (*n* = 24)
1.5 mL bd	0.9 (0.3, 2.9) (*n* = 19)	3.2 (0.7, 5.3) (*n* = 19)	2.2 (0.1, 4.2) (*n* = 19)

CBD, cannabidiol; THC, Δ9-tetrahydrocannabinol; 11-OH-THC, 11-hydroxy-Δ9-tetrahydrocannabinol.

Table 3. Efficacy outcomes

Endpoint	Baseline (*n* = 26)	0.5 mL od (*n* = 26)	0.5 mL bd (*n* = 25)	1.0 mL bd (*n* = 24)	1.5 mL bd (*n* = 19)
Numerical Pain Rating Scale, mean (SD)					
Score†††	7.6 (1.2)	6.6 (1.5)***	6.3 (1.2)***	5.4 (1.3)***	5.0 (1.5)***
Change from baseline		−1.0 (1.3)	−1.4 (1.6)	−2.3 (1.5)	−2.7 (1.6)
% change from baseline		−13.1 (16.8)	−15.8 (23.9)	−28.8 (17.9)	−34.1 (19.4)
Brief Pain Inventory, mean (SD)					
Pain now†††	7.4 (1.3)	6.5 (1.8)	6.2 (1.3)***	5.2 (1.4)***	4.6 (1.8)***
Change from baseline pain now		−1.0 (1.8)	−1.3 (1.7)	−2.2 (1.7)	−3.1 (1.6)
Average pain in last 24 h†	7.2 (1.2)	6.6 (1.6)	6.1 (1.4)**	5.5 (1.4)***	4.9 (1.4)***
Change from baseline in average pain		−0.6 (1.6)	−1.1 (2.0)	−1.7 (1.8)	−2.4 (1.5)
Depression Anxiety Stress Scale, mean (SD)					
Depressive symptoms†	16.9 (10.5)	14.5 (10.0)	13.0 (10.7)	11.6 (11.5)*	13.1 (10.8)*
Change from baseline depressive symptoms		−2.5 (6.4)	−4.0 (10.5)	−5.7 (9.6)	−5.2 (10.3)
Anxiety	13.5 (9.5)	10.4 (7.6)	9.5 (8.5)	10.8 (9.3)	9.7 (9.3)
Change from baseline anxiety		−3.2 (4.7)	−4.1 (7.0)	−2.9 (6.8)	−3.8 (9.7)
Stress	18.6 (10.8)	14.5 (10.1)**	14.6 (10.3)**	13.1 (11.1)***	12.9 (11.5)***
Change from baseline stress		−4.1 (7.3)	−4.2 (7.7)	−5.7 (7.3)	−6.5 (9.1)
Medical Outcomes Study – Sleep Survey, Sleep Problems Index II, mean (SD)					
MOS-SS Sleep Problems Index II	55.0 (16.4)	66.4 (14.8)***	66.0 (15.2)***	60.4 (19.0)	64.8 (17.2)**
Change from baseline in MOS-SS Sleep Problems Index II		11.4 (14.3)	11.9 (16.4)	6.3 (20.1)	13.2 (19.9)
SAT-II, mean (SD)					
Pain ability	3.5 (0.9)	2.1 (0.7) (*n* = 25)	2.5 (0.8) (*n* = 29)	2.7 (0.8) (*n* = 22)	3.1 (0.8) (*n* = 18)
Pain impact	3.3 (1.0)	2.3 (1.0, 4.0) (*n* = 25)	2.3 (1.0, 5.0) (*n* = 29)	2.8 (1.3, 4.3) (*n* = 22)	2.8 (1.7, 5.0) (*n* = 18)
Rescue medication use					
Median no. doses (min, max) ††††		2.0 (0.0, 37.0)	0.0 (0.0, 40.0)	0.0 (0.0, 32.0)	0.0 (0.0, 34.0)
Number (%) patients with rescue medication use		15 (58)	12 (48)	8 (33)	6 (32)

††† Mixed model repeated measures (MMRM) for linear effect compared to baseline significant at $p < 0.001$. ***Significantly different from baseline at $p < 0.001$. **Significantly different from baseline at $p < 0.01$. † MMRM for linear effect compared to baseline significant at $p < 0.05$. *Significantly different from baseline at $p < 0.05$. †† MMRM for linear effect compared to baseline significant at $p < 0.01$. ††††A rescue medication dose is considered one Maxigesic tablet.

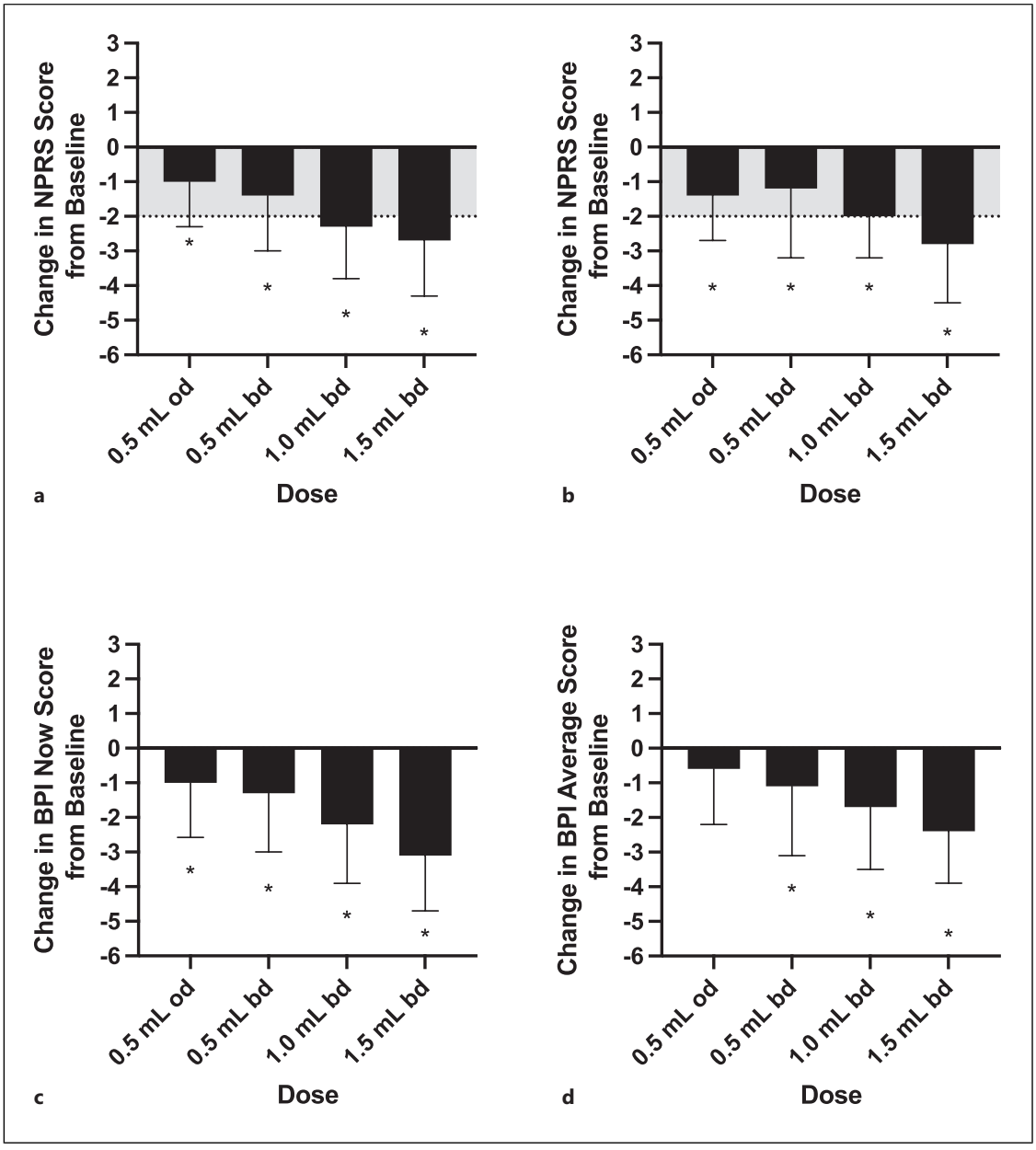

Fig. 2. Change from baseline in NPRS (**a**); NPRS in those with no rescue medication use (**b**); BPI Now (**c**); BPI Average (**d**). * Significant difference from baseline pain score. For panels A and B, line at −2 represents the minimum clinically important difference in NPRS score.

doses (Table 3). The proportion of participants who experienced pain other than minimal headache, sprain, or toothache reduced from 81% at baseline to 53% during the 1.5 mL bd dose. There was also a reduction in pain interference in all domains including general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life by dose (see Table 4).

Approximately two-thirds of participants (61%) required rescue medication at some point during the study. Rescue medication was more commonly required by participants during treatment with lower doses of Cybis® 10:25 (58% required rescue medication at 0.5 mL od dose, 48% at 0.5 mL bd dose, 33% at 1.0 mL bd dose, and 32% at 1.5 mL bd dose). The median number of tablets of rescue medication (500 mg paracetamol + 150 mg ibuprofen)

Table 4. Brief pain inventory and medical outcomes study – sleep survey

	Baseline	0.5 mL od	0.5 mL bd	1.0 mL bd	1.5 mL bd
	26	26	25	24	19
Brief Pain Inventory, mean (SD)					
Pain other than min. headache, sprain, and toothache today?, %	21 (81)	15 (58)	16 (64)	13 (54)	10 (53)
Worst pain in last 24 h	8.1 (1.0)	7.0 (1.3)	6.4 (1.3)	6.0 (1.3)	5.2 (1.5)
Least pain in last 24 h	6.7 (1.6)	5.7 (1.8)	5.2 (1.7)	4.8 (1.6)	4.4 (1.6)
Average pain in last 24 h	7.2 (1.2)	6.6 (1.6)	6.1 (1.4)	5.5 (1.4)	4.9 (1.4)
Change from baseline in average pain		−0.6 (1.6)	−1.1 (2.0)	−1.7 (1.8)	−2.4 (1.5)
Pain now	7.4 (1.3)	6.5 (1.8)	6.2 (1.3)	5.2 (1.4)	4.6 (1.8)
Change from baseline pain (now)		−1.0 (1.8)	−1.3 (1.7)	−2.2 (1.7)	−3.1 (1.6)
BPI Pain Severity	7.4 (1.1)	6.4 (1.5)	6.0 (1.2)	5.4 (1.3)	4.8 (1.4)
How much relief have pain medications provided?	2.7 (11.9)	35.8 (25.3)	42.8 (21.7)	43.8 (22.4)	55.3 (17.8)
Pain interference					
General activity	7.2 (1.7)	5.7 (2.6)	5.2 (2.0)	4.7 (2.5)	4.3 (2.0)
Mood	6.3 (2.6)	5.3 (2.7)	4.3 (2.4)	4.0 (2.5)	3.6 (2.3)
Walking ability	6.1 (2.1)	4.9 (2.5)	4.3 (2.5)	4.5 (2.7)	3.9 (2.4)
Normal work	6.7 (2.0)	5.8 (2.2)	5.4 (2.0)	4.8 (2.5)	4.0 (2.1)
Relationships	5.2 (2.5)	4.9 (2.9)	3.9 (2.7)	4.1 (2.7)	3.7 (2.6)
Sleep	6.6 (2.5)	5.1 (2.9)	4.4 (2.5)	4.7 (2.4)	4.4 (2.7)
Enjoyment of life	6.7 (1.9)	5.3 (2.8)	4.7 (2.7)	4.5 (2.7)	4.4 (2.8)
BPI pain interference	6.4 (1.6)	5.3 (2.3)	4.6 (2.1)	4.5 (2.3)	4.0 (2.2)
Medical Outcomes Study – Sleep Survey, mean (SD)[a]					
Sleep disturbance	52.5 (27.4)	72.4 (21.0)	76.1 (20.1) (n = 29)	71.3 (21.1)	75.8 (23.1)
Snoring	51.4 (35.8) (n = 18)	47.1 (31.7) (n = 17)	51.2 (35.8) (n = 21)	52.9 (39.4) (n = 17)	50.0 (28.9) (n = 13)
Short of breath or headache	63.2 (26.7) (n = 17)	66.7 (20.4) (n = 15)	72.2 (27.0) (n = 18)	71.7 (24.8) (n = 15)	79.5 (24.5) (n = 11)
Sleep adequacy	64.8 (26.6)	63.9 (22.1)	57.6 (27.1) (n = 29)	51.2 (31.1)	57.6 (29.4)
Sleep somnolence	61.3 (20.7)	62.6 (22.0)	61.7 (21.9) (n = 29)	52.7 (27.6)	67.7 (23.7)
Adequate sleep, %	18 (69)	18 (69)	19 (66)	14 (58)	9 (47)
Sleep Problems Index I	53.3 (21.5)	63.9 (19.2)	62.4 (21.8) (n = 29)	57.2 (25.1)	61.8 (24.3)
Sleep Problems Index II	55.0 (16.4)	66.4 (14.8)	65.6 (16.6) (n = 29)	60.4 (19.0)	64.8 (17.2)

[a]For MOS-SS, all patients who had an assessment at a dose level, including those who dose reduced are included in the overall number – thus, some patients had more than one assessment in the 0.5 mL bd dosing group.

taken during the 0.5 mL od dose was 2 (range 0–37), while at the 0.5 mL bd dose and higher, the median number of rescue medication doses taken was zero.

Depression, Anxiety, and Stress

Cybis® 10:25 appeared to reduce levels of depressive symptoms from baseline in a dose-dependent manner (p = 0.0182), with significant reductions in DASS depression scores for baseline observed at 1.0 mL bd and 1.5 mL bd doses (Table 3). Numerical reductions in anxiety compared to baseline were observed for 0.5 mL od, 0.5 mL bd, 1.0 mL bd, and 1.5 mL bd doses; however, this did not appear to be dose dependent (p = 0.0505). Reductions in stress from baseline were dose dependent (p = 0.0053), with reductions significant for all doses (p < 0.01).

Sleep

Participants self-reported numerical increases in sleep disturbance but improvements in sleep adequacy with increasing doses of Cybis 10:25. However, significant

changes only occurred compared to baseline for 0.5 mL od, 0.5 mL bd, and 1.5 mL bd doses (Table 3). This contrasts to the results from the BPI, which suggested there may have been improvements in sleep, although these did not appear to be dose dependent (see Table 4).

Treatment Satisfaction

Although not statistically significant ($p = 0.12$), there were greater proportions of participants who reported that treatment improved pain "quite a lot" or "very much" at higher dose levels (0.5 mL od 4%, 0.5 mL bd 17%, 1.0 mL bd 32%, and 1.5 mL bd 45%). Seven days after the cessation of treatment, most felt that Cybis® 10:25 was either somewhat better (35%) or very much better (39%) than their previous treatments.

Safety

Overall Cybis® 10:25 was well tolerated. Most participants (82%) experienced at least one adverse event, typically of mild or moderate severity. More participants experienced adverse events at lower dose levels than at higher doses. Vomiting, dizziness, and headache did not appear to be dose-dependent. Related adverse events are presented by severity in Table 5. One severe adverse event was reported: nephrolithiasis, which occurred in one participant 7 days after the last dose of Cybis® 10:25. Three adverse events led to dose withdrawal: constipation, anxiety, and syncope. The episode of syncope was reported as the only serious adverse event. It occurred in a participant administered 1.0 mL bd. There were no clinically significant changes in systolic or diastolic blood pressure, QTc interval, or clinically important hematological and clinical chemistry values. There were no deaths and no pregnancies reported.

Discussion

Chronic pain, particularly chronic back and neck pain, remains a significant challenge for patients and clinicians alike [18]. Given its prevalence and impact on mood and function, finding new treatment options is important [19]. A recent review has highlighted the need for "*safer and more effective pharmaceutical options to provide pain relief and improvement in function while minimizing the risks of currently available analgesics*" [19]. Medicinal cannabis may provide one such therapeutic option; however, to date, there is limited high-quality clinical trial evidence on the use of medicinal cannabis in chronic pain. Our study was conducted to address this gap. This was the first clinical study of Cybis® 10:25 in people with chronic back or neck pain. Our study has shown that doses of up to 1.5 mL bd are well tolerated, with clinically significant reductions in pain for 1.0 mL bd and 1.5 mL bd doses. This represents, to our knowledge, the first published dose-response study of a THC:CBD combination.

We found significant heterogeneity in pharmacokinetics following single dose of 0.5 mL Cybis® 10:25. THC and CBD are highly lipophilic with poor oral bioavailability. There are several possible reasons for interpatient differences in pharmacokinetic parameters, including differences in body fat, rapid distribution into tissues, potential swallowing of the product, or differential absorption in different parts of the oral mucosa [20]. Another potential contributing factor is the age of the included patients with long disease duration who were previously treated with other analgesic agents. Maximal concentrations of CBD (C_{max}) were higher than those reported following doses of CBD in a different CBD:THC formulation (5 mg CBD +5.4 mg THC): median 2.49 ng/mL in the present study versus 0.39 ng/mL in the 5 mg CBD +5.4 mg THC study [10]. However, THC levels were similar (2.49 ng/mL in the present study compared to 2.50–3.75 n/mL in the 10 mg CBD +10.8 mg THC) [10]. Peak concentrations occurred later in the present study compared to other studies [10, 20]. This delayed peak was influenced heavily by a number of participants with bimodal peak concentrations or with delayed peak concentrations.

A similar finding has been reported previously [20]. However, in that study, the time to maximal concentration was much shorter (median CBD t_{max} was 4.5 h and THC t_{max} was also 4.5 h following doses of 16.2 mg THC +15 mg CBD) [20].

Our study reported a mean NPRS pain reduction of 28.8% (median 28.6%) following 1.0 mL bd doses and a mean 34.1% (median 37.5%) reduction following 1.5 mL bd doses. This is similar to that published in systematic reviews of reductions of pain of between 30% and 50% following use of medicinal cannabis in the chronic non-cancer pain setting [7]. The NPRS results were echoed by the BPI results, along with dose-dependent reductions in depressive symptoms and stress but not anxiety. There is preliminary evidence supporting the efficacy of CBD as an anxiolytic and antidepressant and in improving sleep disturbance [21]. Improvement in BPI interference scores was encouraging, given that this is a surrogate for function. The sleep results in the present study were contradictory, with improvements in pain interference with sleep reported in the BPI but paradoxical increases in self-reported sleep disturbance with the MOS-SS. The

Table 5. Related adverse events, by severity

Adverse events	*n* (%)	
At least one AE	23 (82)	
At least one AE during 0.5 mL od dosing	19 (68)	
At least one AE during 0.5 mL bd dosing	12 (46)	
At least one AE during 1.0 mL bd dosing	13 (52)	
At least one AE during 1.5 mL bd dosing	3 (15)	
Adverse event by System Organ Class and Preferred Term, *n* (%)	Mild	Moderate
Gastrointestinal disorders	6 (21.4)	3 (10.7)
Constipation		2 (7.1)
Dry mouth	2 (7.1)	
Nausea	2 (7.1)	1 (3.6)
Vomiting	3 (10.7)	
General disorders and admin site conditions	4 (14.3)	6 (21.4)
Asthenia		1 (3.6)
Chest pain		1 (3.6)
Fatigue	4 (14.3)	2 (7.1)
Feeling abnormal		2 (7.1)
Hunger	1 (3.6)	
Thirst	1 (3.6)	
Metabolism and nutrition disorders	2 (7.1)	
Decreased appetite	1 (3.6)	
Increased appetite	1 (3.6)	
Musculoskeletal and connective tissue disorders		1 (3.6)
Back pain		1 (3.6)
Nervous system disorders	13 (46.4)	7 (25.0)
Balance disorder		1 (3.6)
Disturbance in attention		1 (3.6)
Dizziness	8 (28.6)	2 (7.1)
Headache	6 (21.4)	1 (3.6)
Lethargy	1 (3.6)	2 (7.1)
Memory impairment	1 (3.6)	
Mental impairment	1 (3.6)	1 (3.6)
Paresthesia	1 (3.6)	2 (7.1)
Somnolence	2 (7.1)	
Syncope		1 (3.6)
Psychiatric disorders	1 (3.6)	1 (3.6)
Anxiety	1 (3.6)	
Depression		1 (3.6)
Mood altered	1 (3.6)	

System organ class totals may not sum to the total of preferred terms as patients may have had more than one event of that type. There were no severe adverse events.

reason for this is unclear but may be related to the study being underpowered to detect a difference in this endpoint, or differences in the underlying sleep construct each survey is designed to assess [22].

Encouragingly, the efficacy observed was in the setting of typically mild adverse events, as has been reported previously [23, 24]. As with other studies [23, 25], the most common adverse events were headache, dizziness, fatigue, paresthesia, vomiting, nausea, and anxiety. It was of clinical interest that the majority of adverse events occurred during the lower doses of Cybis® 10:25, which suggests that there is a level of tolerance observed to treatment with CBD:THC combinations. Whether inclusion of CBD in CBD:THC combinations reduces THC-related toxicity requires additional clinical research.

This study has several limitations. First, as it was designed as a first-in-human study, it is not randomized, and therefore the relative efficacy to placebo or active control has not yet been established. Second, dosing was unblinded. Assessment of the efficacy of Cybis® 10:25 compared to placebo or active control is planned in future larger randomized controlled studies.

Acknowledgments

The authors thank Belinda Butcher, BSc (Hons), MBiostat, PhD, AStat, CMPP, for providing medical writing assistance on this manuscript in accordance with GPP 2022 [26].

Funding Sources

This study was funded by Cymra Life Sciences Ltd., the developer of Cybis® 10:25. Medical writing services were funded by Cymra Life Sciences Ltd.

Statement of Ethics

This study protocol was reviewed and approved by the Bellberry Human Research Ethics Committee, approval number 2021-03-305. Written informed consent was obtained from all participants.

Author Contributions

P.G., R.C., and J.M. were involved in the design of the study. M.B., M.A., and A.M. implemented the study at their institutions. All authors were involved in the drafting and review of the manuscript and approved its submission.

Conflict of Interest Statement

The authors declare the following conflicts of interest: Paul Glare and Richard Chye are medical advisors to Cymra Life Sciences Ltd. Mark Bloch, Mark Arya, and Andrew Moore's institutions received research funding from Cymra Life Sciences Ltd. to perform this study. John Montgomery is an employee of Cymra Life Sciences Ltd.

Data Availability Statement

The datasets that support the findings of this study are not publicly available due to ethical restrictions. Data requests can be made to the corresponding author which, subject to ethics approval, will not be unreasonably withheld.

References

1 Australian Institute of Health and Welfare. Back problems. Cat no PHE 231. Canberra: AIHW; 2020. https://www.aihw.gov.au/reports/chronic-musculoskeletal-conditions/back-problems.
2 Fatoye F, Gebrye T, Odeyemi I. Real-world incidence and prevalence of low back pain using routinely collected data. Rheumatol Int. 2019 Apr;39(4):619–26.
3 Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American college of physicians. Ann Intern Med. 2017 Apr 4;166(7):514–30.
4 Vlaeyen JWS, Maher CG, Wiech K, Van Zundert J, Meloto CB, Diatchenko L, et al. Low back pain. Nat Rev Dis Primers. 2018 Dec 13;4(1):52.
5 Tompkins DA, Hobelmann JG, Compton P. Providing chronic pain management in the "Fifth Vital Sign" Era: historical and treatment perspectives on a modern-day medical dilemma. Drug Alcohol Depend. 2017 Apr 1;173(Suppl 1):S11–21.
6 Campbell G, Stockings E, Nielsen S. Understanding the evidence for medical cannabis and cannabis-based medicines for the treatment of chronic non-cancer pain. Eur Arch Psychiatry Clin Neurosci. 2019 Feb;269(1):135–44.
7 Goods Administration T. Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia; 2017.
8 Fisher E, Moore RA, Fogarty AE, Finn DP, Finnerup NB, Gilron I, et al. Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials. Pain. 2021 Jul 1;162(Suppl 1):S45–66.
9 Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 "N of 1" studies. Anaesthesia. 2004 May;59(5):440–52.
10 Goods Administration T. Australian Public Assessment Report for Nabiximols. Available from: https://www.tga.gov.au/sites/default/files/auspar-nabiximols-130927.pdf. 2013.
11 Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. Br J Clin Pharmacol. 2018 Nov;84(11):2477–82.
12 Argueta DA, Ventura CM, Kiven S, Sagi V, Gupta K. A balanced approach for cannabidiol use in chronic pain. Front Pharmacol. 2020;11:561.
13 Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain. 2010 May;149(2):177–93.
14 European Medicines Agency. Guidelines on the clinical development of medicinal products intended for the treatment of pain. EMA/CHMP; 2016.
15 Suzuki H, Aono S, Inoue S, Imajo Y, Nishida N, Funaba M, et al. Clinically significant changes in pain along the Pain Intensity Numerical Rating Scale in patients with chronic low back pain. PLoS One. 2020;15(3):e0229228.
16 Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS Med. 2010;7(3):e1000251.
17 Gewandter JS, Eisenach JC, Gross RA, Jensen MP, Keefe FJ, Lee DA, et al. Checklist for the preparation and review of pain clinical trial publications: a pain-specific supplement to CONSORT. Pain Rep. 2019 May-Jun;4(3):e621.
18 Jovanovic F, Pirvulescu I, Knezevic E, Candido KD, Knezevic NN. Comparative safety review of current treatment options for chronic low back pain and unmet needs: a narrative review. Expert Opin Drug Saf. 2021 Sep;20(9):1005–33.
19 Gudin J, Kaufman AG, Datta S. Are opioids needed to treat chronic low back pain? A review of treatment options and analgesics in development. J Pain Res. 2020;13:1007–22.
20 Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration. Clin Chem. 2011 Jan;57(1):66–75.
21 Garcia-Gutierrez MS, Navarrete F, Gasparyan A, Austrich-Olivares A, Sala F, Manzanares J. Cannabidiol: a potential new alternative for the treatment of anxiety, depression, and psychotic disorders. Biomolecules. 2020 Nov 19;10(11):1575.
22 Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in anxiety and sleep: a large case series. Perm J. 2019;23:18–041.

23 Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456–73.
24 Huestis MA, Solimini R, Pichini S, Pacifici R, Carlier J, Busardo FP. Cannabidiol adverse effects and toxicity. Curr Neuropharmacol. 2019;17(10):974–89.
25 Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018 Oct;159(10):1932–54.
26 DeTora LM, Toroser D, Sykes A, Vanderlinden C, Plunkett FJ, Lane T, et al. Good publication practice (GPP) guidelines for company-sponsored biomedical research: 2022 update. Ann Intern Med. 2022 Sep;175(9):1298–304.