Cannabis and Cannabinoid Research
Volume X, Number X, 2022

DOI: 10.1089/can.2022.0135

A Single-Blind, Randomized, Placebo Controlled Study to Evaluate the Benefits and Safety of Endourage Targeted Wellness Formula C Sublingual +Drops in People with Post-Acute Coronavirus Disease 2019 Syndrome

Thomas P. Young,[1,*] Joel S. Erickson,[1] Shannon L. Hattan,[1] Serge Guzy,[2] Fabienne Hershkowitz,[2] and Michael D. Steward[3]

Abstract

Introduction: Coronavirus Disease 2019 (COVID-19) causes a wide range of symptoms, including death. As persons recover, some continue to experience symptoms described as Post-Acute COVID-19 Syndrome (PACS). The objectives of this study were to measure the efficacy of Formula C™, a cannabidiol (CBD)-rich, whole-flower terpene-rich preparation in managing PACS symptoms.

Materials and Methods: This randomized, placebo-controlled, single-blind, open-label crossover study was conducted in 2021. Informed consent was obtained from participants, and they were randomized to two treatment groups. Group 1 ($n = 15$) received blinded active product for 28 days, and Group 2 ($n = 16$) received blinded placebo for 28 days (Treatment Period 1). Both groups crossed over to open-label active product for 28 days (Treatment Period 2) with a safety assessment at day 70. Patient-Reported Outcomes Measurement Information System (PROMIS®) scores and the Patient Global Impression of Change (PGIC) score were used to assess primary and secondary objectives. Safety assessments were also done at each visit.

Results: Twenty-four participants completed study, with 8 withdrawals, none related to study product. PGIC and PROMIS scores improved across both groups at day 28. This raised questions about the placebo. A reanalysis of the placebo confirmed absence of CBD and unexpected medical concentration of terpenes. The study continued despite no longer having a true placebo. The improved scores on outcome measures were maintained across the open label treatment period. There were no safety events reported throughout the study.

Discussion: For persons with PACS who are nonresponsive to conventional therapies, this study demonstrated symptom improvement for participants utilizing Formula C. In addition, the benefits seen in Group 2 suggest the possibility that non-CBD formulations rich in antioxidants, omega-3, and omega-6 fatty acids, gamma-linoleic acid, and terpenes may also have contributed to the overall improvement of the partial active group through the study.

Conclusion: Given that both groups demonstrated improvement, both formulations may be contributing to these findings. Limitations include the small number of participants, the lack of a true placebo, and limited time on study products. Additional studies are warranted to explore both CBD-rich hemp products and hempseed oil as treatment options for PACS.

Trial Registration ClinicalTrials.gov Identifier: NCT04828668.

Keywords: COVID-19; long-hauler; PACS; CBD; integrative medicine; cannabidiol

[1]Joel S Erickson, MD+Thomas P Young, PhD, NP, Inc., Novato, California, USA.
[2]ProPharma, Inc., Hillsborough, New Jersey, USA.
[3]Endourage, LLC, Wheatridge, Colorado, USA.

*Address correspondence to: Thomas P. Young, PhD, Joel S. Erickson, MD+Thomas P. Young, PhD, NP, Inc., 165 Rowland Way, Ste 212, Novato, CA 94945, USA, E-mail: thomas@younghab.com

Introduction

Coronavirus disease 2019

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2.[1] First identified in Wuhan, China in 2019 COVID-19 was declared a global pandemic by the World Health Organization (WHO) in March 2020. Over the last 2 years, the virus has mutated, and variants identified, impacting patterns of infection and reinfection. In some individuals, a cytokine storm is triggered, resulting in multiorgan, multisystem disease. Ultimately, the cytokine storm causes more harm than the primary infection, and some postulate that this is one of many underlying etiologies associated with post-acute COVID-19 syndrome (PACS).[2] Despite the introduction of several vaccines to prevent infection, as of early 2022, more than 472,816,657 people have been diagnosed with COVID-19 and more than 6,099,380 deaths have been reported.[3]

Post-acute COVID-19 syndrome

Clinicians have observed that some patients infected with COVID-19 go on to experience symptoms after resolution of acute infection. This condition is referred to as PACS. The exact prevalence for PACS is unknown; however, it is estimated that over 23 million people have experienced post-COVID-19 complications.[4] Studies estimate that between 5% and 80% of the infected population are experiencing symptoms of PACS. Severity and number of symptoms experienced are related to a person's overall premorbid health status. Patients who were hospitalized or have preexisting pulmonary conditions, are of older age, or are obese are at greater risk of being diagnosed with PACS. Women are also more likely to experience symptoms beyond 6 months after infection.[5,6]

The most common symptoms reported include fatigue, headache, shortness of breath, chest pain or discomfort, cough, persistent loss of smell and/or taste, joint pain, muscle aches/pains/weakness, sore throat, memory loss, brain fog, dizziness, low-grade intermittent fever, rapid/irregular heartbeat, anxiety, depression, post traumatic stress disorder (PTSD), insomnia, earache/hearing loss, abdominal discomfort, diminished appetite, and hair loss.[7] While the exact number of people suffering from PACS is unknown, it is worth noting that PACS is now a qualified condition for long-term disability insurance. Presently, there is no known cure for PACS, and treatment options have been focused on managing symptoms. Many suffering with PACS have reported that they are nonresponsive to conventional medical therapies. Research shows that integrating alternative medicine modalities can provide relief to many with chronic illnesses that mimic the symptoms associated with PACS.

Hemp-derived cannabidiol formulations and the endocannabinoid system

The endocannabinoid system (ECS) is a physiologic system that plays important roles in central nervous system development, immune modulation, synaptic plasticity, and the response to endogenous and environmental insults. The ECS is composed of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids. In PACS, saturating the ECS has the potential to impact symptoms associated with post-COVID conditions, including inflammation and immune responses, mood, learning and memory, sleep, cardiovascular function, and stress.[8,9]

Hemp is the low THC version of the cannabis plant. Humans have been using cannabis, rich in phytocannabinoids, for more than 10,000 years to treat a broad range of ailments. Cannabidiol (CBD), the second most abundant cannabinoid in the cannabis plant, has been used to manage symptoms, including inflammation, anxiety, stress, PTSD, insomnia, and depression.[10,11] CBD can also attenuate many of the inflammatory markers that are implicated in the cytokine storm that occurs with COVID-19 infection.[3] CBD's potential to interact at cellular entry at angiotensin-converting enzyme 2, a critical pathway for COVID-19, infection has also been demonstrated *in vivo*.[8,9,12–15]

In addition, terpenes, the fragrant components of the cannabis plant, have shown therapeutic benefits. Together with cannabinoids, terpenes illustrate a synergistic effect and their interactions have been observed for decades. *Limonene* is a monoterpene that boosts serotonin and dopamine levels, thereby inducing the anxiolytic, anti-stress, and sedative effects of CBD.[16,17] β-*Caryophyllene* possesses gastroprotective, analgesic, anticancerogenic, antifungal, antibacterial, antidepressant, anti-inflammatory, antiproliferative, antioxidant, anxiolytic, analgesic, and neuroprotective effects.[18,19] β-*Myrcene* has analgesic effects similar to THC and CBD by stimulating the release of endogenous opioids through the α2-adrenergic receptor dependent mechanism.[19] *Pinene* is known to aid memory and minimize cognitive dysfunction, as well as being used for its antiseptic properties.[19] It has been used to treat respiratory tract infections for centuries.[20]

Endourage, Formula C™, the focus of this study, is a CBD-rich, hemp-derived, whole-flower preparation with trace amounts of THC and other minor cannabinoids and a robust terpene profile. The continuum of potential benefits of full-spectrum hemp formulas supports exploration in persons with PACS because there is documented benefit in the use of cannabis preparations in other ailments with similar symptoms.

We hypothesize that there will be no change in symptoms for those persons receiving placebo versus those receiving study product, Formula C.

Materials and Methods

Design and objectives

This is a postmarketing, randomized, open-label, placebo-controlled with an open-label extension clinical trial evaluating Formula C in persons with PACS. The primary objectives of this study were to evaluate the clinical benefits of Formula C on symptoms in adults who have documented PACS or persistence of effects consistent with COVID-19 and to assess the impact of Formula C on quality-of-life (QOL) in persons with PACS. The secondary objective was to assess the safety of Formula C in persons with PACS. This single-site clinical trial was conducted from March to December 2021 and was intended as an exploratory, proof-of-concept study. Target number for enrollment was 60, and informed consent was obtained from all participants. Recruitment was aided by an Institutional Review Board (IRB)-approved study flyer used at post-COVID treatment centers. Flyers directed interested parties to clinicaltrials.gov IRB approval was obtained (Sterling IRB, Atlanta, GA; approval no. 8327).

Baseline demographic profile, medical history, date of diagnosis, hospital admission and discharge dates, laboratory and imaging test results, persistent symptoms, and QOL information were collected (Table 1). Although some data were limited in availability given telemedicine format of visits, we utilized the WHO Post-Acute COVID Syndrome (WHO PACS) Questionnaire. Information was also gathered on employment status utilizing the COVID-19 Employment Change Questionnaire at the beginning and end of study. This form includes questions regarding employment post-COVID diagnosis and, if relevant, loss of employment and impact on seeking employment. Participants were required to meet protocol defined inclusion/exclusion criteria (Supplementary Table S1).

This study was conducted in 2021. Informed consent was obtained from participants, and they were randomized to two treatment groups. Group 1 ($n=15$) received blinded active product for 28 days, and Group 2 ($n=16$) received blinded placebo product for 28 days (Treatment Period 1). Both groups crossed over to open-label active product for 28 days (Treatment Period 2) with a safety assessment at day 70. PROMIS® and Patient Global Impression of Change (PGIC) scores were used to determine primary and secondary objectives. Safety assessments were completed at each visit. Full schedule of events and study schematic are found in Supplementary Tables S2 and S3.

Table 1. Study Demographics

	Full-active ($n=12$)	Part-active ($n=11$)
Age: *M* (SD)	45.7 (10.78)	43.1 (15.64)
Sex (females): *N* (%)	7 (58.3)	6 (54.5)
Ethnic origin: *N* (%)		
White	11 (91.7)	6 (54.5)
Black	1 (8.3)	0 (0)
Latino	0 (0)	1 (9.1)
Mixed	0 (0)	4 (36.4)
Smoking status: *N* (%)		
Current	1 (8.3)	0 (0)
Former	1 (8.3)	3 (27.3)
No	10 (83.3)	7 (63.6)
Unknown	0 (0)	1 (9.1)
Weight (pounds): *M* (SD)	158.64 (29.91)	170.20 (33.30)
Height (inches): *M* (SD)	66.27 (3.23)	65.31 (5.40)

SD, standard deviation.

Dosing was aimed at utilizing the minimally effective dose to avoid the biphasic dose–response curve that can occur in CBD based therapies. Each participant was started on 0.25 mL of assigned product and titrated up to effect. The PGIC score was used to manage dose titrations up and down. For dose titration schedule, see Supplementary Table S4.

End-points and criteria for evaluation

Primary end-points were assessed applying the comparative changes in PROMIS and PGIC scores from baseline to the end of each treatment period, including the COVID-19 Employment Change Questionnaire (Supplementary Table S5). Participants were seen at 7-day intervals, and assessments for safety and adverse events were completed at each visit.

The PROMIS instrument developed by the NIH provides a roadmap for patient-reported outcomes. The PROMIS battery provides systematic measures across physical, mental health, and social domains. These include but are not limited to physical function; pain assessment; QOL, fatigue, and sleep hygiene; anxiety, depression, job and relationship satisfaction; and

others. PROMIS metrics have been well validated and aim to quantify patient experiences in a consistent systematic way. The format is generic and can be adapted to various disease states and data collection formats. Scoring is based on standard deviations against population norms.[21]

The PGIC was published in 1976 by the National Institute of Mental Health. It's adapted to the patient and aims to measure change in clinical status. Over the years, PGIC scales were used in a broad range of diseases and were modified for the purpose of clinical settings.[22] The PGIC assesses patient perception of changes after treatment and is tied to the conceptual framework of improvement.[23,24]

The COVID-19 Employment Change Questionnaire is a scale composed of eight items assessing change in employment status during the COVID-19 epidemic. This tool was administered at the day 0, day 28, and day 56 time points.

Formula C is the active product for this study. It is a CBD-rich, hemp-derived, whole-flower preparation with noneuphoric trace amounts of THC and other minor cannabinoids and a robust terpene profile that utilizes organic medium chain triglycerides from coconuts to achieve the desired dosage of CBD per mL. The protocol supply was tested by a third-party laboratory to ensure the accuracy of labeling and to ensure the absence of residual solvents, pesticides, heavy metals, and microbes. The placebo was organic hempseed oil and is known to be rich in antioxidants, omega-3 and omega-6 fatty acids, gamma-linoleic acid, and other amino acids. After observing improvements in Group 2 during the Period 1, a decision was made to submit the placebo for additional laboratory testing and it was determined that therapeutic levels of terpenes were present in the hempseed oil. The cannabinoid and terpene breakdown for both products can be seen in Table 2. One batch of product was maintained for the entire study.

Table 2. Cannabinoid and Terpene Profile of Formula C

Terpene	Formula C™ (μg/mL)	Placebo (μg/mL)
R-(+) limonene	2270	579
Trans-caryophyllene	1850	
Beta-myrcene	1750	399
Alpha-humulene	949	
(-)-Alpha-bisabolol (Levomenol)	479	
Alpha-cedrene	440	
(-)-Caryophyllene oxide	418	
Alpha-pinene	407	138
Linalool	220	
Valencene	216	
Beta-pinene	202	
(1R) Endo-(+)-fenchyl	182	
Gamma-terpineol	180	
Trans-nerolidol	142	
Cis-nerolidol	84	
Cannabinoid	**Formula C (mg/ml)**	**Placebo (mg/ml)**
Cannabidivarin	< 0.2	< 0.2
Cannabidiolic acid	3.63	< 0.2
Cannabigerolic acid	< 0.2	< 0.2
Cannabigerol	0.935	< 0.2
Cannabidiol	40.7	< 0.2
Tetrahydrocannabivarin	< 0.2	< 0.2
Cannabinol	< 0.2	< 0.2
Delta 9-Tetrahydrocannabinol	2.91	< 0.2
Delta 8-Tetrahydrocannabinol	< 0.2	< 0.2
Delta 9-Tetrahydrocannabinol Acid	< 0.2	< 0.2
Cannabichromene	2.28	< 0.2
(6aR, 9S)-delta-10-THC	Not tested	< 0.3
(6aR, 9R)-delta-10-THC	Not tested	< 0.3
Max active THC	2.91	< 0.20
Max active CBD	43.88	0

Measures taken to minimize/avoid bias

Randomization was managed centrally by a third-party consultant; subjects were randomized in treatment blocks of six. Study product dispensing and return were managed by the study site (all blinded). To maintain the placebo blind across Group 1 and Group 2, study product for the first 28 days (Treatment Period 1) was mask labeled for both groups. Both groups received open-label (commercially available) product in Treatment Period 2. Participants maintained a daily diary of dosing. All enrolled were eligible to participate in Treatment Period 2; therefore, participants had no incentive to not accurately report data. Telemedicine visits were conducted weekly to review symptoms, adverse events, and dosing diary entries. Blinding was maintained for the study administrators for all participants for the duration of the study completing on day 70.

Analysis and results

Patient characteristics were summarized as counts and percentages or mean and standard deviation. Given that some categorical variable frequencies were small, they were recoded into 2×2 tables and compared using chi-square with a Yates correction. Continuous normally distributed variables were compared using *t*-test for independent samples. For testing the hypotheses, continuous normally distributed variables between groups were compared using the Student's *t*-test. Comparisons of continuous normally distributed variables within groups were compared using paired

t-test, and ordinal non-normally distributed variables were compared using the Related-Samples Wilcoxon Signed Rank Test. All statistical analyses were carried out using SPSS version 27 (SPSS, Inc., Chicago, IL). Within statistical tests were one sided, between statistical tests were two sided, and *p*-values lower than 0.05 were statistically significant.

Ten PROMIS questionnaires were completed at designated visits. Table 3 shows the mean and standard deviation of each test and for each group timepoint of interest. The assumption of normality, in each group and time point, was tested with the Shapiro–Wilk test. The assumption was not violated, except for the PGIC scores because this measure is an independent measure not standardized against a population. Parametric tests (*t*-tests) were performed for the PROMIS results. Nonparametric tests were done for the PGIC results. Results demonstrate the consistency of the PROMIS measures across both groups through the study.

Group 1 (blinded active to open label)

Analysis of Group 1 includes three repeat measures at day 0, day 28, and day 56. An increase in the result of positive direction symptoms, such as ability in social roles, was described as an improvement (+). Decrease in negative direction symptoms such as anxiety also appears as an improvement (+). As all the hypotheses were one tailed, the table contains only one-tailed significance and the significance value figures only when the effect was in the direction expected.

The effects between day 0 and day 28 and the effects between day 0 and day 56, except one (pain), were consistent with the hypotheses. Statistical significance was reached for dyspnea, anxiety, and sleep disturbance with $p < 0.013$, 0.006, and 0.041, respectively, at day 28, this effect held through day 56 for anxiety $p < 0.009$ and sleep disturbance $p < 0.021$. It appears that the improvement from day 0 to day 56 occurred predominantly between day 0 and day 28 (Table 4). The largest effect was reduction of anxiety between day 0 and day 28, and it was still noticeable when comparing day 0 to day 56.

Group 2 (blinded placebo to open label)

We saw improvements in the following negative direction symptoms as expected (1) anxiety, (2) dyspnea, (3) depression, (4) fatigue, (5) sleep disturbance, and (6) pain but none reached statistical significance. Two

Table 3. Mean and Standard Deviation of PROMIS Battery of Tests by Treatment Group and Treatment Period, Day 0, Day 28, and Day 56

	Group 1								
	Day 0			Day 28			Day 56		
Tests	***N***	***Mean***	***SD***	***N***	***Mean***	***SD***	***N***	***Mean***	***SD***
Patient global impression of change	13	1.4	1	12	2.8	1.8	12	3.1	1.7
Ability to participate in social roles	12	41.8	9.8	12	43.9	8.8	12	45.6	11.9
Cognitive function	12	36.9	8.5	12	38.2	9.6	12	38.3	10.4
Satisfaction with social roles and activities	12	39.5	9.7	12	42	9.8	12	41.9	12
Dyspnea severity	12	46.5	9.7	12	43.3	8.6	12	45.6	11.7
Emotional distress anxiety	12	56.5	8.8	12	49.8	8.8	12	51.7	8.3
Emotional distress depression	12	54.5	10.2	12	53.5	10.5	12	52.7	10.6
Fatigue	12	62.2	10.5	12	58.7	10.1	12	59.4	13.2
Pain	12	52.6	9.2	12	51.8	6.3	12	53.7	11.1
Sleep Disturbance	12	54.3	6.4	12	51	2.8	12	51.1	6.9
	Group 2								
	Day 0			Day 28			Day 56		
Tests	***N***	***Mean***	***SD***	***N***	***Mean***	***SD***	***N***	***Mean***	***SD***
Patient global impression of change	11	2.3	1.7	11	3.1	2.1	10	4.7	1.6
Ability to participate in social roles	11	42.1	9.3	11	47.3	7.7	11	46.3	8.1
Cognitive function	11	41.4	13.1	11	47.2	12	11	46	12.3
Satisfaction with social roles and activities	11	41.5	9	11	44.8	11.3	11	43.6	11.3
Dyspnea severity	11	45.1	8.6	11	42.7	7.6	11	42.2	6.1
Emotional distress anxiety	11	55	11.9	11	49.8	8.7	11	47.7	8.2
Emotional distress depression	11	54.3	8.6	11	50.6	7.6	11	50.2	7.3
Fatigue	11	59.8	10.6	11	53	11.4	11	52.1	11.4
Pain	11	52.1	7.9	10	47.6	6.9	11	48.4	7.1
Sleep disturbance	11	55.4	6.9	11	52.9	10	11	48.7	7

Table 4. Differences Between Day 0, Day 28, and Day 56 Among Full Active Group ($n=12$)

Tests	Day 28 vs. day 0				Day 56 vs. day 28				Day 56 vs. day 0			
	Difference in means	SD	Improvement	Relevant Sig. 1-tailed	Difference in means	SD	Improvement	Relevant Sig. 1-tailed	Difference in means	SD	Improvement	Relevant Sig. 1-tailed
Ability to participate in social roles	2.1	6.11	(+)	0.127	1.7	9.2	(+)	0.269	3.8	7.63	(+)	*0.056*
Cognitive function	1.3	7.11	(+)	0.271	0.1	6.18	(+)	0.475	1.4	7.37	(+)	0.261
Satisfaction with social roles and activities	2.5	4.83	(+)	*0.051*	−0.2	6.29	(−)		2.3	7.69	(+)	0.158
Dyspnea severity	−3.2	4.3	(+)	**0.013**	2.3	5.74	(−)		−0.9	5.48	(+)	0.291
Emotional distress anxiety	−6.8	7.9	(+)	**0.006**	1.9	4.06	(−)		−4.9	6.14	(+)	**0.009**
Emotional distress depression	−1.1	4.26	(+)	0.206	−0.8	3.76	(+)	0.245	−1.8	5.5	(+)	0.137
Fatigue	−3.6	6.94	(+)	*0.051*	0.7	9.36	(−)		−2.9	9.25	(+)	0.154
Pain	−0.8	6.46	(+)	0.337	1.9	8.05	(−)		1.1	6.72	(−)	
Sleep disturbance	−3.3	6	(+)	**0.041**	0.2	5.91	(−)		−3.1	4.71	(+)	**0.021**

Bold values represent significance ($p<0.05$). Italic values represent Marginal significance ($p<0.1$).

symptoms were marginally significant with a $p<0.1$, anxiety, and dyspnea. Three positive directional symptoms (1) ability in social roles, (2) cognitive function, and (3) satisfaction with social roles did not reach statistical significance. A visual representation for negative and positive direction of symptoms is seen on Figure 2. It could be that these symptoms were being modulated by other symptoms or that the PROMIS assessments were overlapping with various symptomatologies. Participants did note during interviews that the battery of tests was fatiguing, contributed to brain fog, and a decreased sense of physical well-being (Table 5).

Differences of the differences (group 1 and 2 comparison)

These analyses revealed differences within each group. Since Group 2 received blinded placebo from day 0 to day 28 and crossed over to open-label product, the analysis compares both groups, from day 0 to day 28, when Group 2 served as a control group. The question is whether there is a significant difference between the groups, from day 0 to day 28. Positive direction symptoms, such as (1) ability to participate in social roles, (2) satisfaction with social roles, and (3) cognitive function, improved in both groups, but slightly favored Group 2.

Negative direction symptoms improved in Group 1, and for Group 2, these were not statistically significant but, clinically, there was an even distribution of improvement for both groups. Full description and directional comparisons are shown in Figure 1.

Table 5. Differences Between Day 28 and Day 56 Among Part-Active Group

PROMIS® Battery/test	Day 56 vs. day 28			
	Diff means	SD	Improvement	Relevant sig. 1-tailed
Ability to participate in social roles and activities	−0.9	2.70	(−)	
Cognitive function	−1.3	2.04	(−)	
Satisfaction with social roles and activities	−1.2	10.22	(−)	
Dyspnea severity	−0.5	4.03	(+)	**0.096**
Emotional distress anxiety	−2.1	8.31	(+)	**0.066**
Emotional distress depression	−0.4	5.05	(+)	0.245
Fatigue	−0.9	8.50	(+)	0.396
Pain	1.5	8.98	(−)	
Sleep disturbance	−4.2	7.87	(+)	0.462

Bold values represent marginal statistical significance at the $p < 0.1$, for dyspnea and emotional distress.

PROMIS, Patient-Reported Outcomes Measurement Information System.

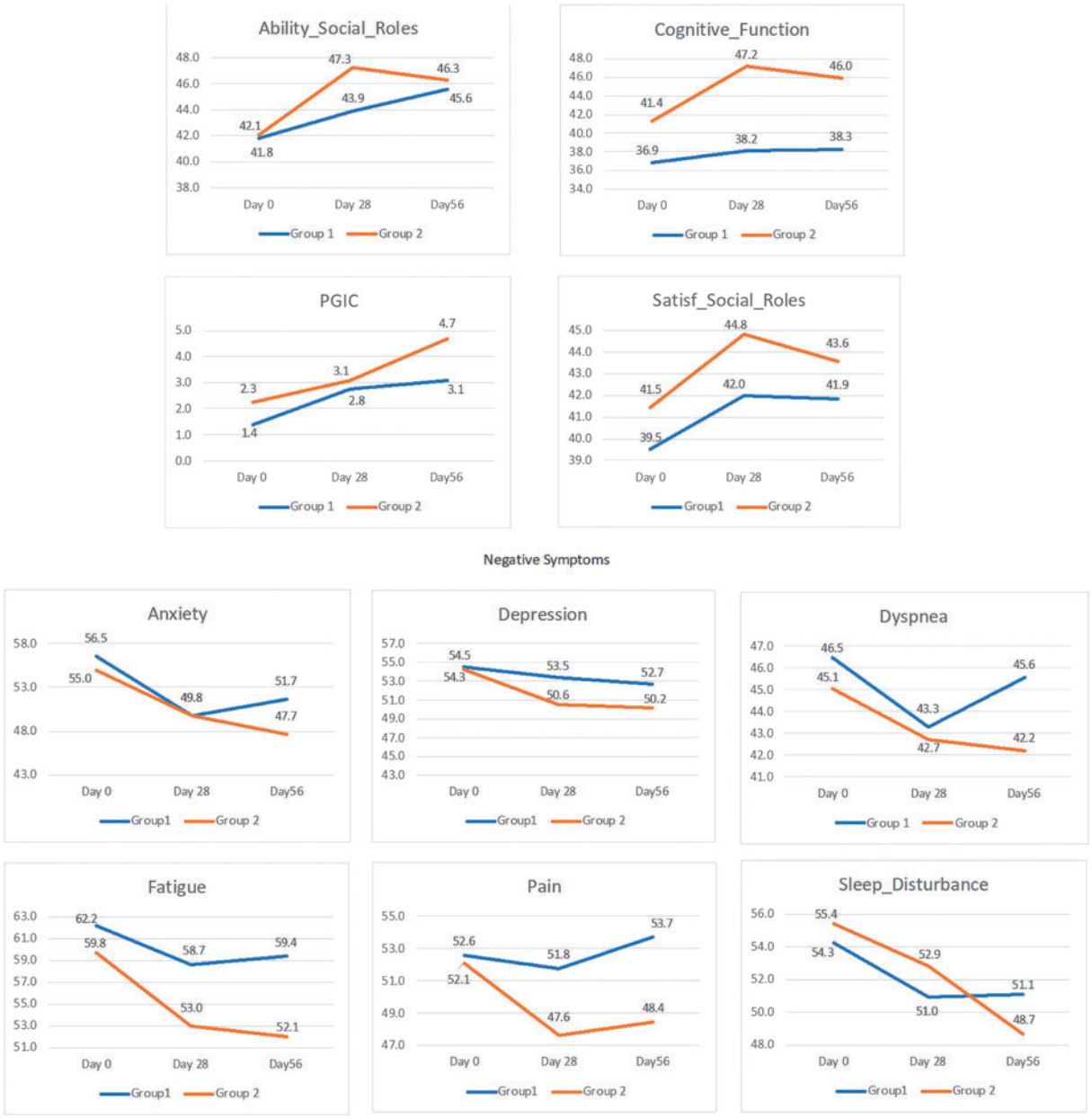

FIG. 1. Group 1 and 2 positive direction symptoms (1) ability to participate in social roles and activities, (2) satisfaction with social roles and activities, and (3) cognitive function. Negative direction symptoms (1) dyspnea, (2) anxiety, (4) depression, (5) fatigue, (6) pain, (7) sleep disturbance at day 0, 28, and 56.

The PGIC score also improved in this group suggesting that although statistical significance was not achieved for this measure across groups, clinically, participants reported feeling better. A PGIC score drop for both groups was seen at day 35, 7 days after the cross over to open label product. This is likely the result of re-baselining study product dose at day 28 as noted above. In addition, as previously discussed, the observation at day 28 between Group 1 and 2 raised questions about the placebo as both groups had similar improvements in their PGIC score. PGIC scores from day 0 to day 56 for both groups can be seen in Figures 2 and 3. Decision was made to continue the study despite no longer having a true placebo.

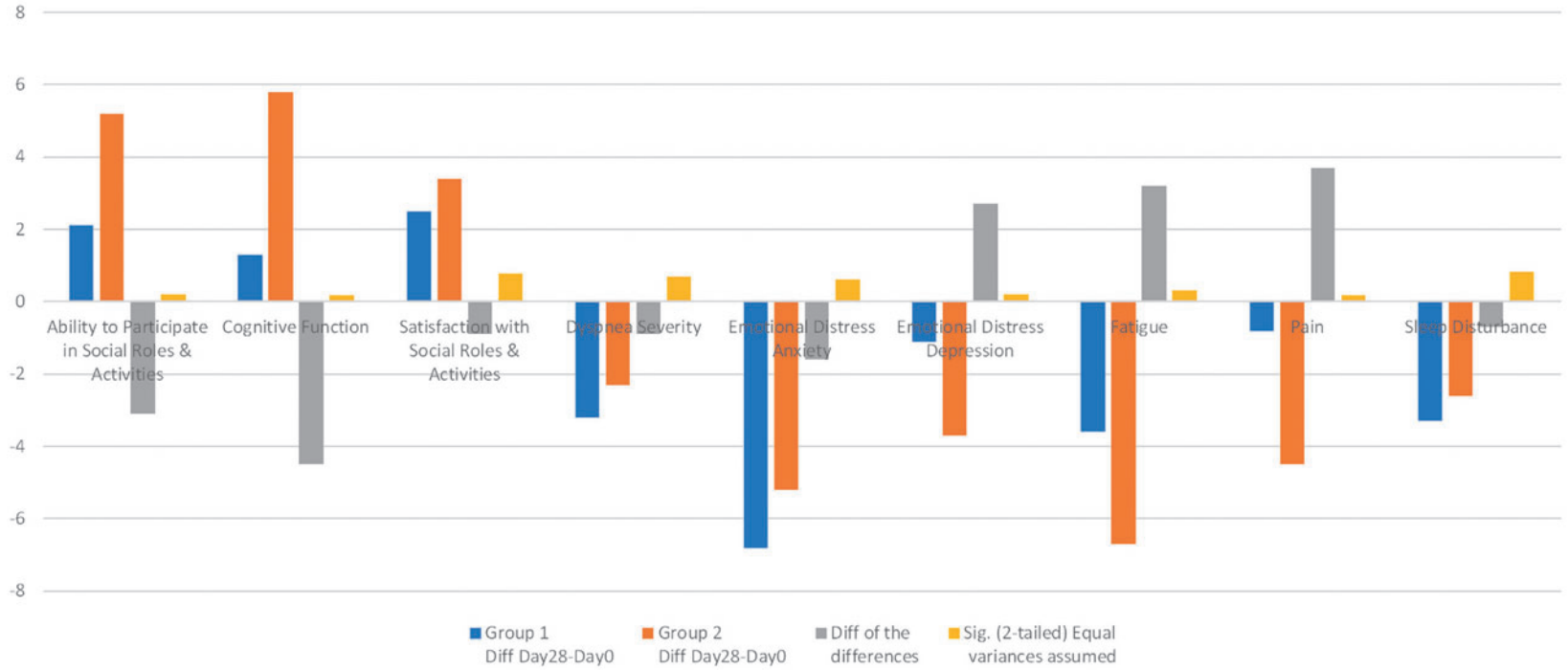

Fig. 2. Negative direction symptoms improved in group 1 and for group 2, these were not statistically significant but clinically, there was an even distribution of improvement for both groups.

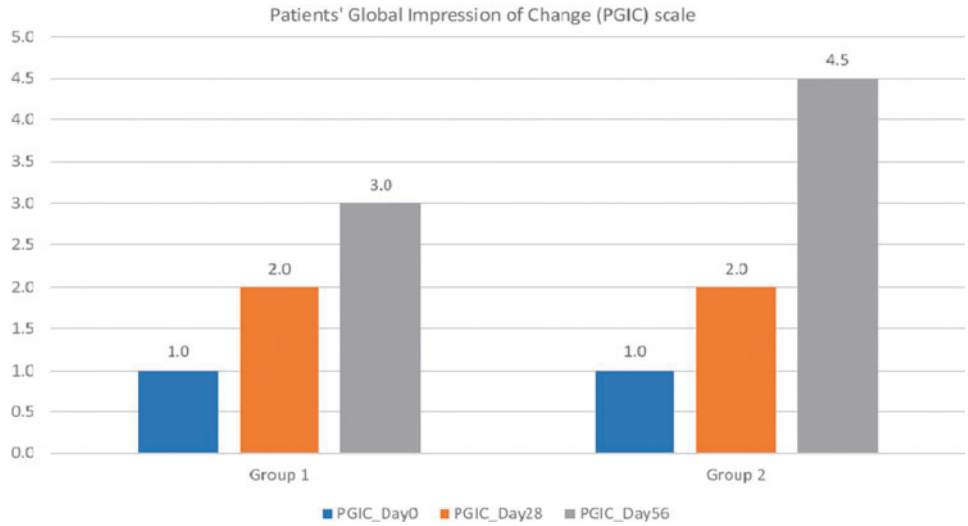

FIG. 3. Patient global impression of change scores group 1 and 2 increased across, for both the groups. The increase within repeated measure in the full-active group was significant between day 0 and day 28 and between day 0 and day 56 (related-samples wilcoxon signed rank test, $p < 0.005$ and $p < 0.05$, respectively). The increase within repeated measure in the group 2 was significant between day 28 and day 56 (related-samples wilcoxon signed rank test, ($p < 0.05$). There was no benefit to group 1 compared to the group 2 between day 0 to day 28, since the increase in median in both groups was the same.

There were eight withdrawals, (3/15) from Group 1 and (5/16) from Group 2. In Group 1, two participants were randomized but not dosed, one declined due to time commitment and one on the advice of their primary care provider; one participant was randomized but had concerns about the random urine drug screens at work and opted out. In Group 2, three participants withdrew due to noncompliance with study visits. One participant dropped out due to time commitment and complexity of the study forms. One participant withdrew due to an adverse event of lightheaded sensation and euphoria but assessed by the investigator as not related to study product as he had a previous history of vertigo. Later communication with the participant's primary care provider confirmed this assessment.

There were no safety concerns observed during the study. There were no serious adverse events reported, no sustained changes in baseline symptoms versus treatment evolved symptoms over the course of the study, and no pregnancies were reported.

Discussion

As an effective standard of care is yet to be developed for persons with PACS, an alternative approach should be considered for those persons not responding to conventional therapy. Improvement in several symptoms associated with the use of study product (Formula C) did reach statistical significance. However, the use of the placebo also achieved relief for some symptoms, also reaching statistical significance. It is possible that non-CBD formulation of hempseed oil, also containing therapeutic levels of terpenes, may offer benefits. It is possible that some of the symptoms observed would have improved over time but given that many of the participants had suffered with PACS for greater than 6 months it's unlikely as many remained on multiple medications for symptom management. The concern over long-term polypharmacy continues to impact participants QOL and activities of daily living.

Although we did not achieve complete statistical significance as outlined in the protocol, clinical benefits were observed. Although not all symptoms evaluated with the PROMIS measures reached statistical significance, the overall PGIC scores improved across both groups through both treatment periods; therefore, the relevance of statistical significance versus clinical significance is important to consider.

Conclusion

Formula C is an easy to use, commercially available product which appears to be safe and efficacious in

people with PACS. There were no adverse events or safety concerns with utilizing Formula C in this patient population. Limitations of the study, including the small number of subjects, the lack of a true placebo arm, and relatively short time on study products, may all impact generalizability. In addition, as this study was conducted through telemedicine technology, therefore no laboratory data were collected except that provided through medical history. Additional exploration is warranted whether both CBD and non-CBD containing hemp formulations may be of benefit to those with PACS. In summary, PACS has emerged as a patient population requiring extended periods of chronic care. The failure to identify an effective treatment with the use of traditional western medicinal products suggests the need to explore alternative and integrative approaches to improving the lives of those people affected with ongoing post-COVID conditions.

Authors' Contributions

T.P.Y.: Conceptualization, formal analysis, investigation, methodology, project administration, software, supervision, validation, visualization, writing—original draft, writing—review and editing. J.S.E.: Conceptualization, draft, writing—review and editing, supervision. M.D.S.: Conceptualization, methodology. S.L.H.: Data curation, writing—original draft. Pharma Pro: Software, validation; Endourage, LLC: Funding, Resources.

Author Disclosure Statement

T.P.Y. has equity holdings in Endourage, LLC. M.D.S. is a founder, member of the board of directors and chief medical officer of Endourage, LLC. There were no other disclosures reported.

Funding Information

Funding for this study was provided by Endourage, LLC.

Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4
Supplementary Table S5

References

1. COVID-19: Frequently Asked Questions. Available from: https://www.cdc.gov/coronavirus/2019-ncov/faq.html [Last accessed: March 25, 2022].
2. WHO Coronavirus (COVID-19) Dashboard. 2022. Available from: https://covid19.who.int/table [Last accessed: March 25, 2022].
3. Fara A, Mitrev Z, Rosalia RA, et al. Cytokine storm and COVID-19: A chronicle of pro-inflammatory cytokines. Open Biol 2020;10(9):200160; doi: 10.1098/rsob.200160
4. AAPM&R: PASC Dashboard. 2022. Available from: https://pascdashboard.aapmr.org/ [Last accessed: March 25, 2022].
5. Kim Y, Bitna-Ha, Shin-Woo Kim, et al. Post-acute COVID-19 syndrome in patients after 12 months from COVID-19 infection in Korea. BMC Infect Dis 2022;22(1):93; doi: 10.1186/s12879-022-07062-6
6. Post-acute sequelae of SARS-CoV-2 infection among adults aged ≥18 years—Long Beach, California, April 1–December 10, 2020. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7037a2.htm [Last accessed: March 25, 2022].
7. Long COVID (Post-Acute Sequelae of SARS CoV-2 infection, PASC). Available from: https://www.yalemedicine.org/conditions/long-covid-post-acute-sequelae-of-sars-cov-2-infection-pasc [Last accessed: March 25, 2022].
8. Tagne AM, Pacchetti B, Sodergren M, et al. Cannabidiol for viral diseases: Hype or hope. Cannabis Cannabinoid Res 2020;5(2):121–131; doi: 10.1089/can.2019.0060
9. Ruhaak LR, Felth J, Karlssson CK, et al. Evaluation of the cyclooxygenase inhibiting effects of six major cannabinoids isolated from cannabis sativa. Biol Pharm Bull 2011;34(5):774–778; doi: 10.1248/bpb.34.774
10. Malfait AM, Gallily R, Sumariwalla, PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A. 2000;97(17):9561–9566; doi: 10.1073/pnas.160105897
11. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology 2006; 45(1):50–52; doi: 10.1093/rheumatology/kei183
12. Lu D, Vemuri VK, Duclos RI, et al. The cannabinergic system as a target for anti-inflammatory therapies. Curr Top Med Chem 2006;6(13):1401–1426; doi: 10.2174/15680266106061401
13. Russo EB. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuro Endocrinol Lett 2008;29(2):192–200.
14. Nagarkatti P, Pandey R, Riede, SA, et al. Cannabinoids as novel anti-inflammatory drugs. Future Med Chem 2009; doi: 10.4155/fmc.09.93
15. Russo EB. Clinical endocannabinoid deficiency reconsidered: current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. Cannabis Cannabinoid Res 2016; 1(1):154–165; doi: 10.1089/can.2016.0009
16. Maayah ZH, Takahara S, Ferdaoussi M, et al. The molecular mechanisms that underpin the biological benefits of full-spectrum cannabis extract in the treatment of neuropathic pain and inflammation. Biochem Biophys Acta Mol Basis Dis 2020;1866(7):165771; doi: 10.1016/j.bbadis.2020.165771
17. Meschler J, Howlett AC. Thujone exhibits low affinity for cannabinoid receptors but fails to evoke cannabimimetic responses. Pharmacol Biochem Behav 1999;62(3):473–480; doi: 10.1016/S0091-3057(98)00195-6
18. Takeda S, Misawa K, Yamamoto I, et al. Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis. Drug Metab Dispos 2020;36(9):1917–1721; doi: 10.1124/dmd.108.020909
19. Sommano SR, Chittasupho C, Ruksiriwanich W, et al. The cannabis terpenes. Molecules 2020;25(24):5792; doi: 10.3390/molecules25245792
20. Allenspach M, Steuer C. α-Pinene: A never-ending story. Phytochemistry 2021;190:112857; doi: 10.1016/j.phytochem.2021.112857
21. Gershon RC, Wagster MV, Hendrie HC, et al. NIH toolbox for assessment of neurological and behavioral function. Neurology 2013;80(11 Suppl 3): S2–S6; doi: 10.1212/WNL.0b013e3182872e5f
22. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. US Department of Health, Education, and Welfare Publication (ADM), 76-338. National Institute of Mental Health: Rockville, MD; 1976.
23. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94(2):149–158; doi: 10.1016/S0304-3959(01)00349-9

24. Perrot S, Lantéri-Minet M. Patients' global impression of change in the management of peripheral neuropathic pain: Clinical relevance and correlations in daily practice. Eur J Pain 2019;23(6):1117–1128; doi: 10.1002/ejp.1378

Cite this article as: Young TP, Erickson JS, Hattan SL, Guzy S, Hershkowitz F, Steward MD (2022) A single-blind, randomized, placebo controlled study to evaluate the benefits and safety of endourage targeted wellness Formula C sublingual +drops in people with post-acute COVID-19 syndrome, *Cannabis and Cannabinoid Research* X:X, 1–11, DOI: 10.1089/can.2022.0135.

Abbreviations Used

CBD = cannabidiol
COVID-19 = coronavirus disease 2019
ECS = endocannabinoid system
IRB = Institutional Review Board
PACS = post-acute COVID-19 syndrome
PGIC = Patient Global Impression of Change
PROMIS = Patient-Reported Outcomes Measurement Information System
PTSD = post traumatic stress disorder
QOL = quality-of-life
SD = standard deviation
THC = tetrahydrocannabinol
WHO = World Health Organization