pharmaceuticals

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A Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Effectiveness and Safety of Melatonin and Three Formulations of Floraworks Proprietary TruCBN™ for Improving Sleep

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RADICLE™ SCIENCE

Radicle Discovery™ Rest Report

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About this report

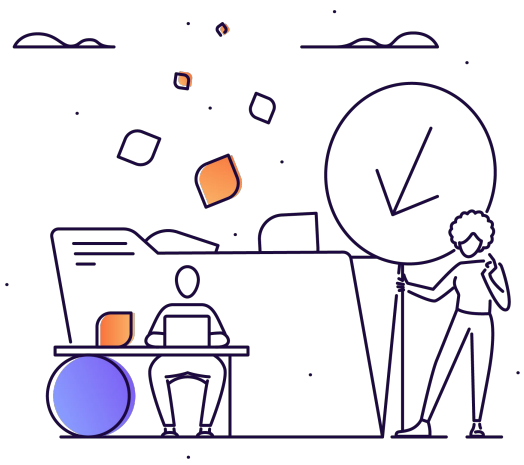
This report summarizes key insights drawn from the *Radicle Discovery™ Rest Study*, a randomized, blinded, placebo controlled study to evaluate the effects of three FloraWorks TruCBN softgels and 4 mg melatonin on sleep and overall health outcomes, relative to placebo control. Through a rigorous examination of the data, we sought to answer the following:

Does the effect of these TruCBN Softgel formulations extend beyond that of the placebo?

Do we find evidence suggesting that higher doses of CBN leads to greater therapeutic effects?

Summary of key findings

- We observed **significant difference** in effect on sleep between 50 mg CBN and placebo and between 4 mg Melatonin and placebo.
- We observed **marginally significant difference** in effect on sleep between 25 mg CBN and placebo and between 100 mg CBN and placebo.
- **No significant differences** in effect on any other health outcomes were observed between the active product arms and placebo control.
- All **side effects** were **mild or moderate**. There were no significant differences in the frequency of reported side effects between the active and placebo arms.



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About the study

The primary aim of the study was to assess the effects of three formulations of TruCBN softgels and 4 mg melatonin on sleep quality, relative to placebo control. There were 5 arms within the study; (1) TruCBN softgel A (containing 4 mg melatonin), (2) TruCBN softgel B (containing 25 mg CBN), (3) TruCBN softgel C (containing 50 mg CBN), (4) TruCBN softgel D (containing 100 mg CBN) and (5) Placebo control (see **Table 1** below for further details on study arm formulations). All were softgels. Participants were informed to take their 1 softgel 1-2 hours before bed.. To ensure that results were not biased, participants were randomly assigned to product, were blinded to the contents, and were not told what they were taking until the conclusion of the study.

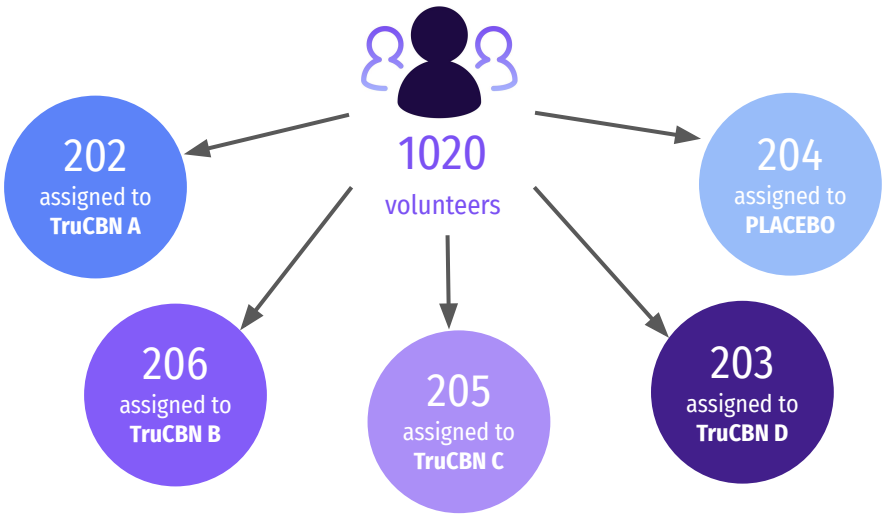

TABLE 1: RADICLE DISCOVERY REST STUDY ARMS

Product ID	Product formula	Instructions
RADX-22D03-01 (FWA)	4 mg melatonin	*Please take 1 softgel 1-2 hours before bed.*
RADX-22D03-04 (FWD)	25 mg CBN	
RADX-22D03-03 (FWC)	50 mg CBN	
RADX-22D03-05 (FWE)	100 mg CBN	
RADX-22D03-02 (FWB)	placebo	

The study process

Participant volunteers were recruited from across the United States. All volunteers were at least 21 years old, endorsed a desire for better sleep quality, and expressed interest in taking a cannabinoid product to improve their sleep. The study was entirely virtual; participants were recruited through online recruitment channels, study product was delivered directly to participants' homes, and all data were collected via online surveys delivered to their mobile device or computer.

Recruitment & Randomization	Baseline (Week 1)	Study period (Weeks 2-5)	Study conclusion
1020 volunteers were recruited from across the US and were randomized to receive either active product or placebo control	Before receiving their study product, participants completed a week of surveys asking about their sleep and overall health.	After receiving their study product, participants completed weekly health and product use surveys. See **Table 2** for descriptions of our primary study measures.	Participants received a final study survey asking about their overall experiences and impressions. Afterwards they also receive a Radicle Health Journey Report containing their individualized data.

TABLE 2: VALIDATED MEASURES FOR KEY OUTCOMES USED IN RADICLE DISCOVERY REST STUDY

Measure	Description	Scoring interpretation	How was this collected?
PROMIS™ Sleep Disturbance 8a	8-item measure assessing sleep disturbance (sleep quality) in the past 7 days	Scoring from 8 to 40, with higher scores translating to greater sleep disturbance (i.e., worse sleep quality)	All participants received this measure within their weekly health surveys
PROMIS™ Anxiety 4a	4-item measure assessing frequency of anxiety symptoms in the past 7 days	Scoring from 4 to 20, with higher scores translating to greater anxiety	Participants who endorsed anxiety symptoms received this measure in their weekly health surveys.
PROMIS™ Stress 4a	4-item measure assessing frequency of stress symptoms in the past 7 days	Scoring from 4 to 20, with higher scores translating to greater anxiety	Participants who endorsed stress symptoms received this measure in their weekly health surveys.
PEG (Pain, Enjoyment, General Activity) scale	3-item measure assessing pain intensity and interference in the past 7 days	Scoring from 0 to 10, with higher scores translating to greater pain	Participants who endorsed pain symptoms received this measure in their weekly health surveys.
World Health Organization (WHO)-5 Well-being index	5-item measure assessing feelings of well-being in the past 7 days	Scoring from 0 to 25, with higher scores translating to greater well-being	All participants received this measure within their weekly health surveys

*For full measures and scoring systems, see **Appendix A**.*

Data analysis

For each outcome under study, we ran regression models to test whether there were significant differences in effect between the active arms and placebo. If the mixed effects regression model showed significant improvement for a given outcome, we also ran generalized linear models to compare the likelihood of experiencing a minimal clinically important difference (MCID) in this outcome. For precision, we adjusted for sex, age, race, ethnicity and body mass index (BMI) in every model. We also ran secondary analyses (correcting for multiple comparisons) to evaluate the significance of health score changes within individual active arms, and whether there were significant differences in the effect between active arms. Analysis was conducted using Stata 17 and R.

We ran an intent-to-treat analysis, meaning that all participants who were assigned product (aside from the aforementioned exclusions) were included in the analysis according to their product assignment, regardless of product adherence or study attrition.

Note: Throughout this report, we provide visuals of the **predicted marginal means** of health scores, rather than the raw mean scores. Predicted marginal means are calculated from our statistical models and better represent the true differences between arms adjusting for any potential imbalances across arms. Also, when we state that certain findings were **'significant'**, we mean that the likelihood of falsely rejecting the null hypothesis that there were no differences between groups is very small (less than 5%; i.e., the p-value is less than 0.05). Put another way, when we state certain findings were "significant" we can be fairly confident that our results are not the result of random variation.

Study Results

Study results are divided into the following sections:

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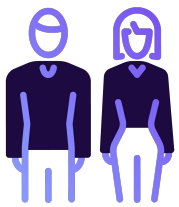
I. Who participated in the study?

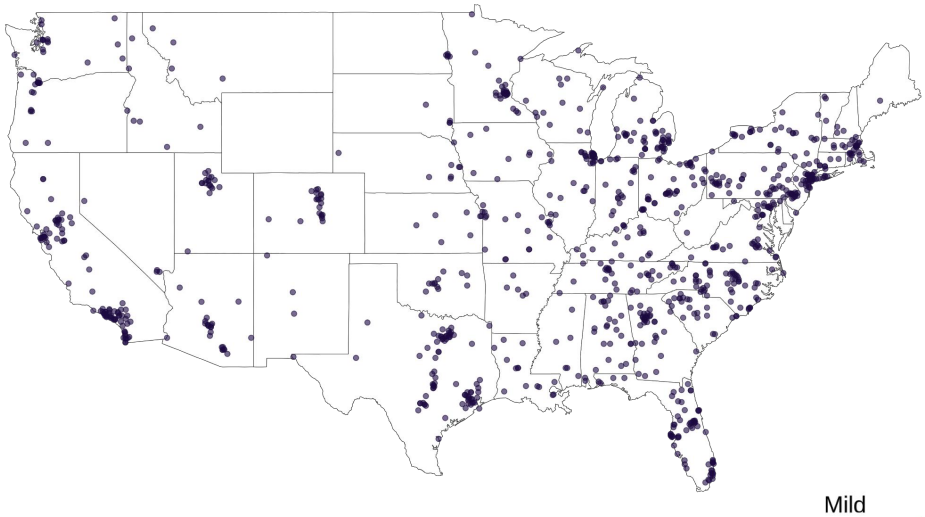


54% of participants were **female**, while **46%** were **male**.

90% Reported that they suffered from **stress.**

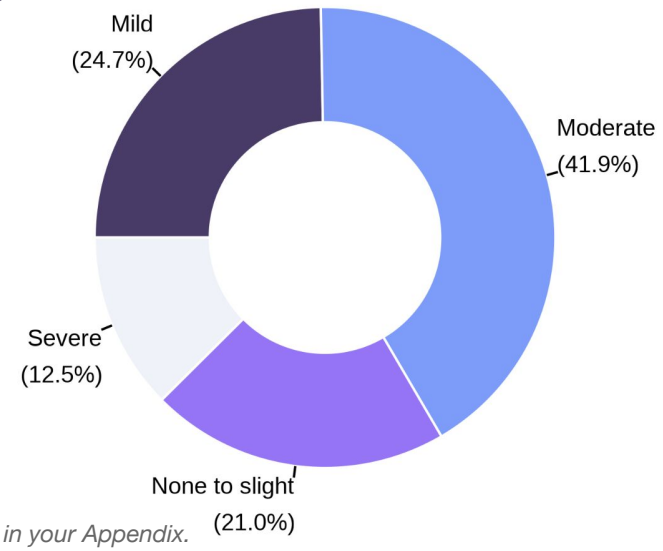
79% Reported that they suffer from **sleep disturbances.**

Geographic distribution of participants



Participants lived all over the U.S., though many resided in **the South and Midwest regions.**

Most (80%) of participants were **White.**



The majority (66.6%) experienced either **mild** or **moderate sleep disturbances** at baseline

*For more detail on participant characteristics/demographics, see **Table 1** in your Appendix.*

Participant engagement

The majority (67.4%) completed at least one follow-up health survey following baseline.

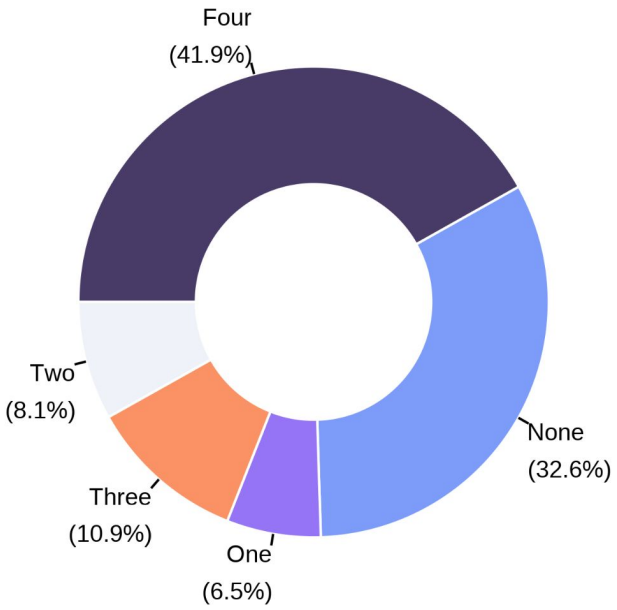
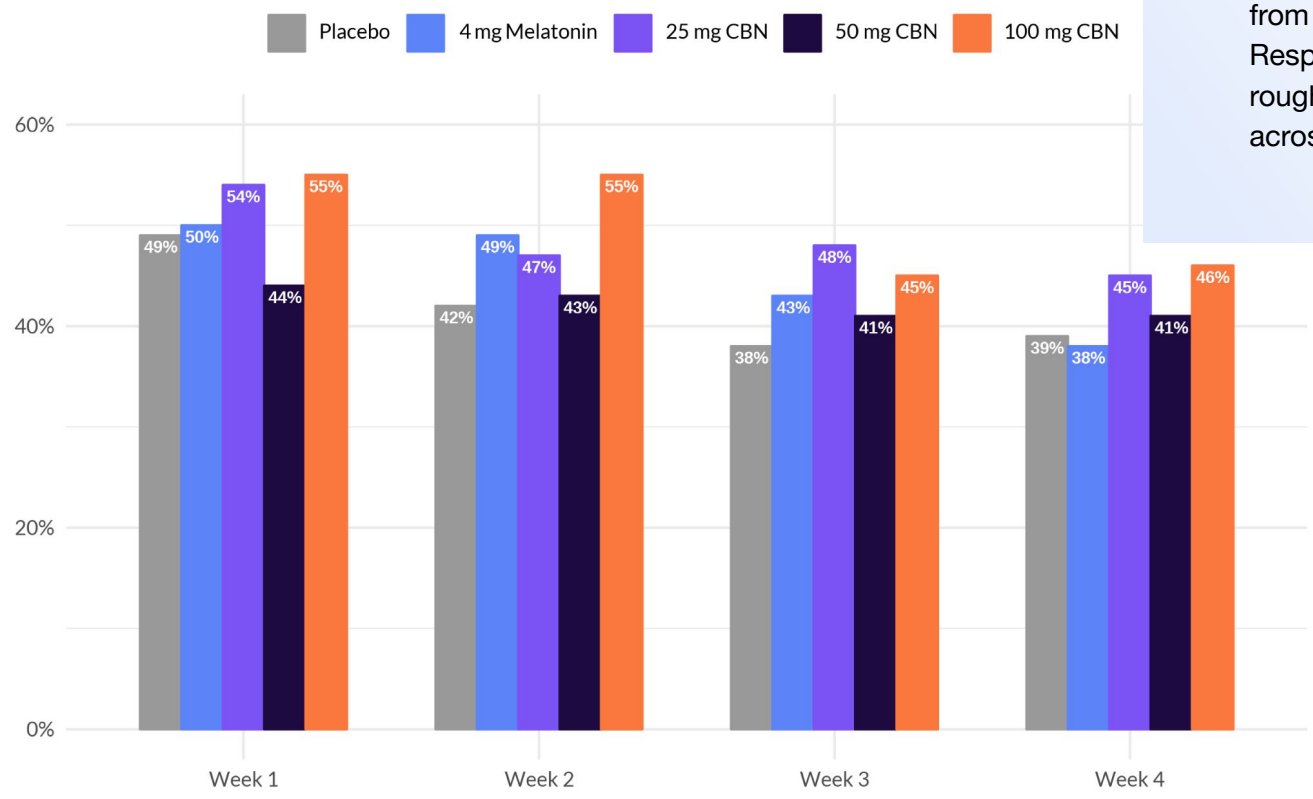


FIGURE 1: Weekly survey completion rates, by study arm

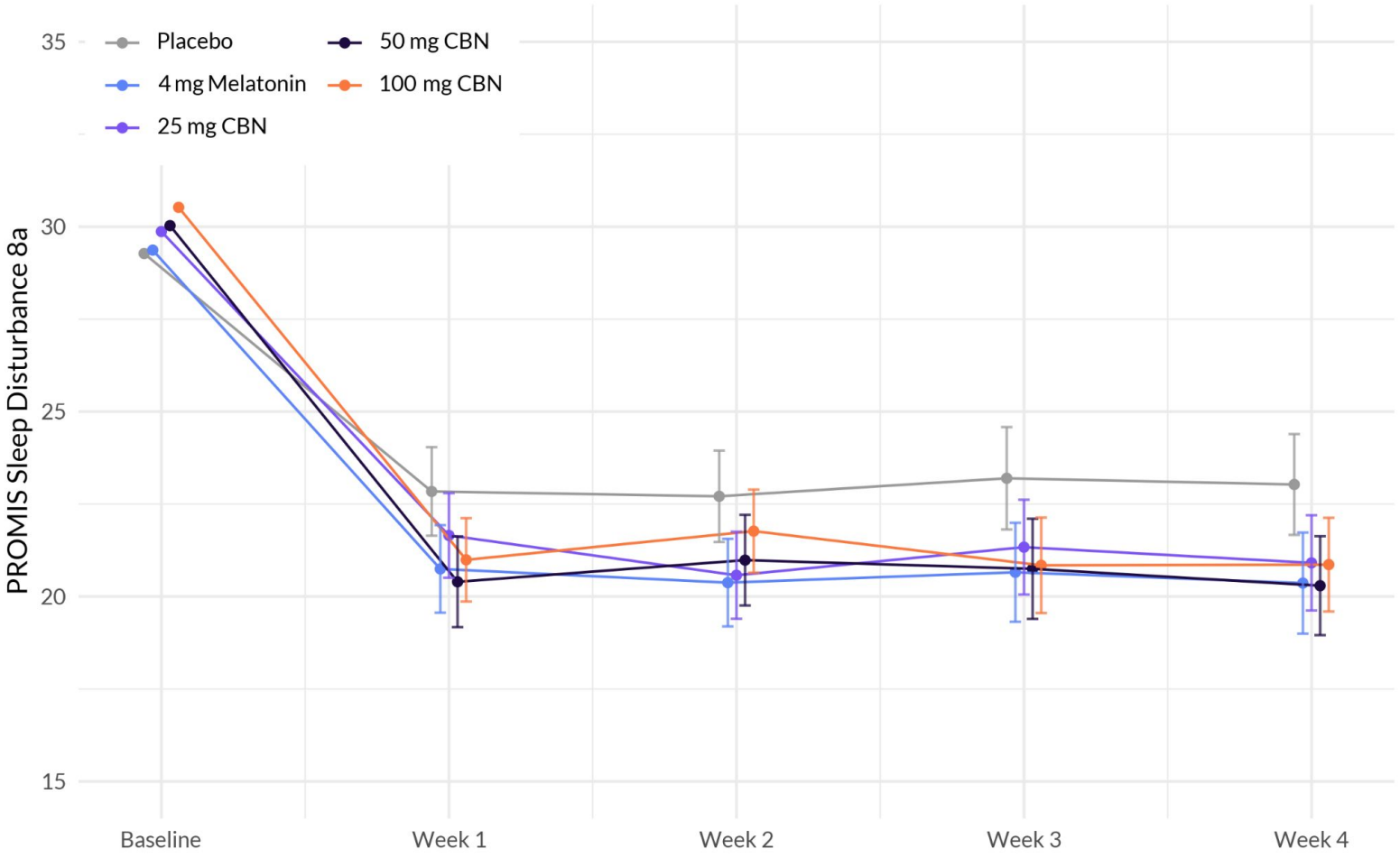
Weekly survey response rates ranged from 39% to 49%. Response rates were roughly equivalent across arms.



II. Main findings: Sleep Quality

Our primary analyses revealed a significant difference in the rate of mean PROMIS Sleep Disturbance 8a score change between 50mg CBN and placebo and between 4 mg Melatonin and placebo (see Table 2 in Appendix). Further, our analysis revealed marginally significant difference in the rate of mean PROMIS Sleep Disturbance 8a score change between 25mg CBN and placebo and between 100mg CBN and placebo (see Table 2 in Appendix).

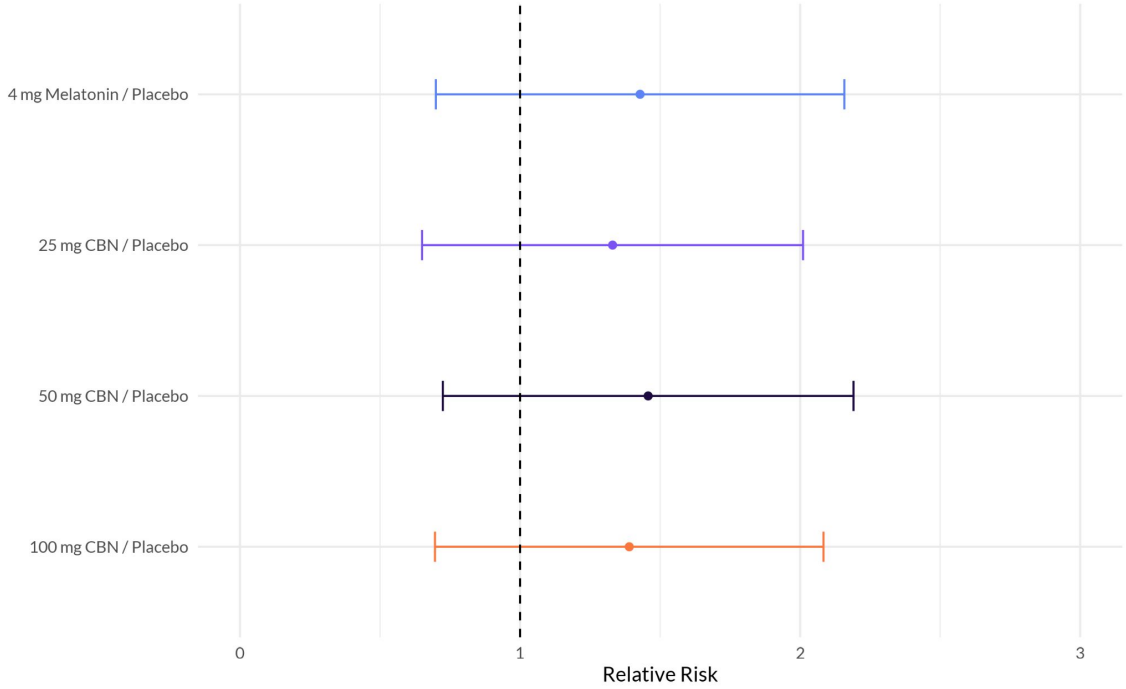
FIGURE 2: PROMIS Sleep Disturbance 8a score through time, by study arm.



Likelihood of achieving MCID

We did not observe any significant differences in the likelihood of achieving a minimum clinically important difference (MCID) in PROMIS Sleep Disturbance 8a score between any of the Arms compared to placebo (see Table 9 in Appendix). Unlike Figure 2, which demonstrated that *average* change in Sleep Disturbance score between two arms compared to placebo is significant, Figure 3 focuses on the amount of change participants experienced. To reach MCID on the Sleep Disturbance scale, participants' scores had to change at least one half the standard deviation of the baseline score. Therefore, while some arms experienced average change that was significantly higher than placebo, the amount of change does not reach the threshold for MCID.

FIGURE 3: Risk ratios for achieving MCID in PROMIS Sleep Disturbance 8a score score by study arm



**Note: A risk ratio of 1 would suggest that there were no difference in risk/likelihood whereas a risk ratio below 1 suggests that the risk/likelihood of the product arm is lower than that of the reference group (placebo).*

About 36-53% of participants in every arm experienced a minimal clinically important improvement in their sleep disturbance, meaning that they experienced a meaningful change that could warrant a change in their symptom management.

TABLE 3: Proportion who experienced a minimal clinically important difference (MCID)[a] in their PROMIS Sleep Disturbance 8a score, by study arm

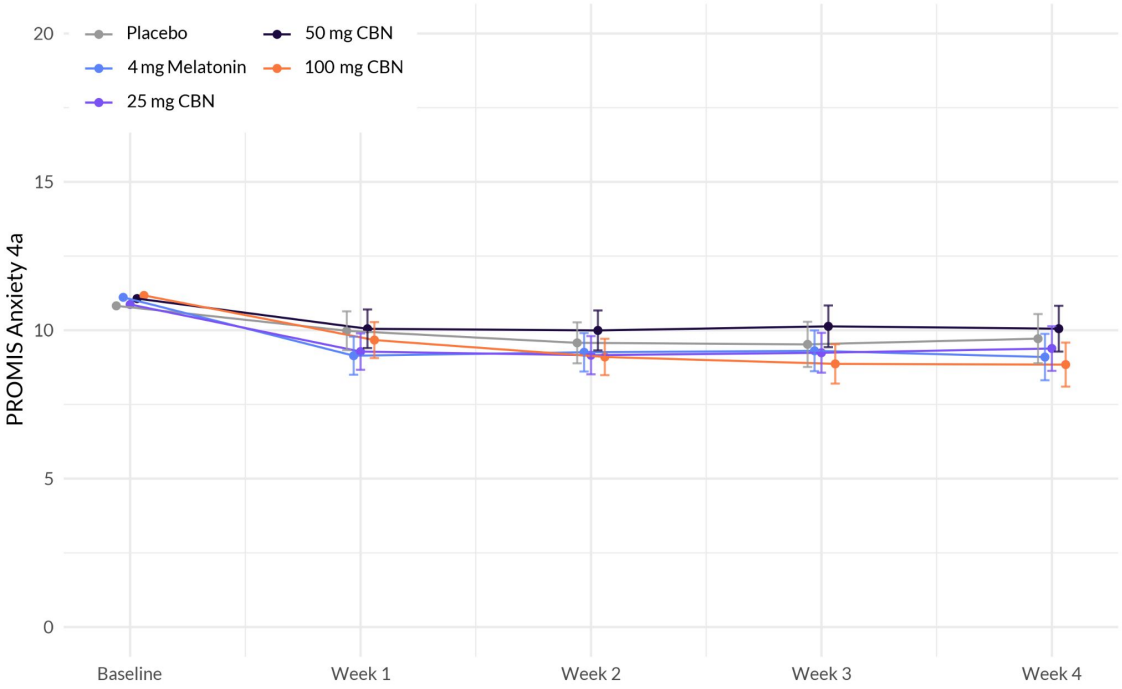
Arm	% experiencing MCID
Placebo	36.2
4 mg melatonin	51.9
25 mg CBN	46.7
50 mg CBN	53.6
100 mg CBN	50.0

[a]A score reduction of one half the standard deviation of the baseline score is considered an MCID

III. Main findings: Anxiety

Our primary analyses revealed no significant differences in the rate of mean PROMIS Anxiety 4a score change between any of the Arms compared to placebo (see Table 22 in Appendix).

FIGURE 4: PROMIS Anxiety 4a score through time, by study arm



About 37-51% of participants in every arm experienced a minimal clinically important improvement in their anxiety score, meaning that they experienced a meaningful change that could warrant a change in their symptom management.

TABLE 4: Proportion who experienced a minimal clinically important difference (MCID)[a] in their PROMIS Anxiety 4a score, by study arm

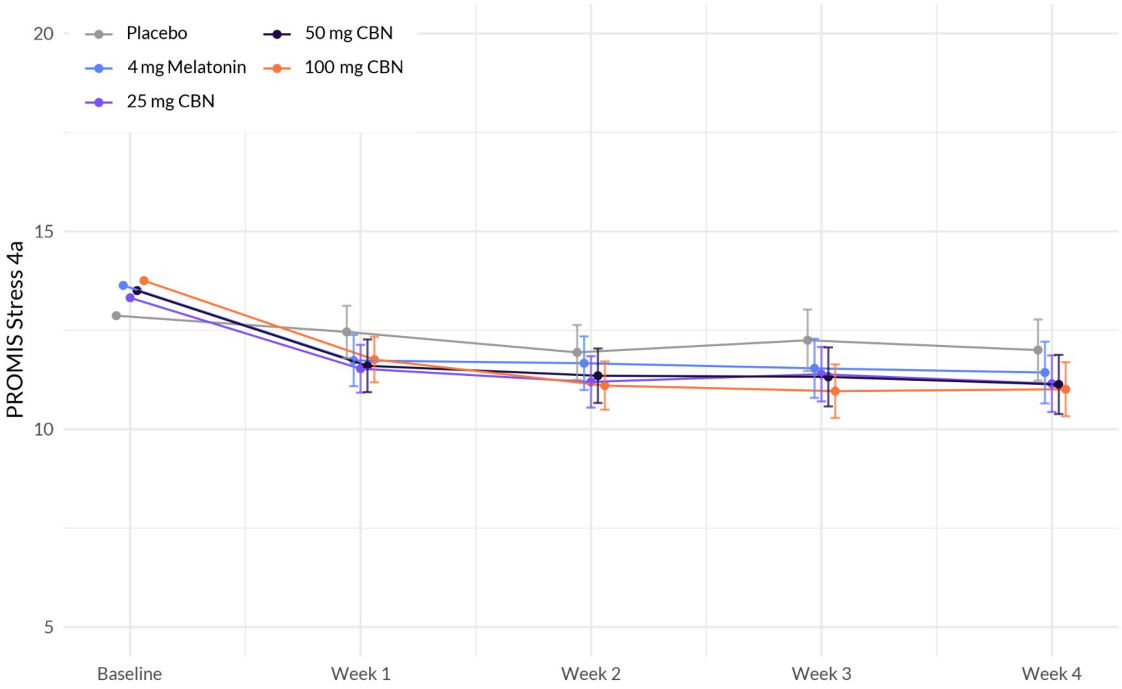
Arm	% experiencing MCID
Placebo	46.6
4 mg melatonin	51.9
25 mg CBN	49.1
50 mg CBN	37.5
100 mg CBN	46.5

[a]A score reduction of one half the standard deviation of the baseline score is considered an MCID

IV. Main findings: Stress

Our primary analyses revealed no significant differences in the rate of mean PROMIS Stress 4a score change between any of the Arms compared to placebo (see Table 30 in Appendix).

FIGURE 5: PROMIS Stress 4a score through time, by study arm



About 22-34% of participants in every arm experienced a minimal clinically important improvement in their stress score, meaning that they experienced a meaningful change that could warrant a change in their symptom management.

TABLE 5: Proportion who experienced a minimal clinically important difference (MCID)[a] in their PROMIS Stress 4a score score, by study arm

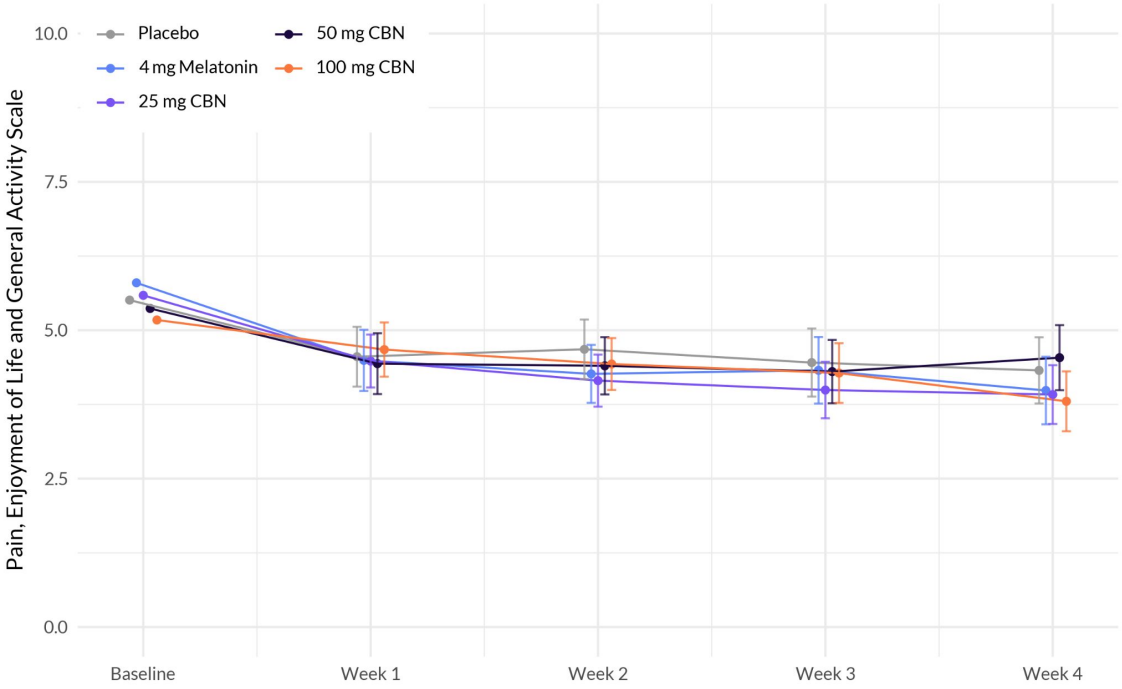
Arm	% experiencing MCID
Placebo	18.9
4 mg melatonin	34.0
25 mg CBN	27.0
50 mg CBN	22.0
100 mg CBN	31.3

[a]A score reduction of one half the standard deviation of the baseline score is considered an MCID

V. Main findings: Pain

Our primary analyses revealed no significant differences in the rate of mean PEG (Pain, Enjoyment, General Activity) score change between any of the Arms compared to placebo (see Table 26 in Appendix).

FIGURE 6: PEG (Pain, Enjoyment, General Activity) score through time, by study arm



About 23-54% of participants in every arm experienced a minimal clinically important improvement in their PEG score, meaning that they experienced a meaningful change that could warrant a change in their symptom management.

TABLE 6: Proportion who experienced a minimal clinically important difference (MCID)[a] in their PEG score, by study arm

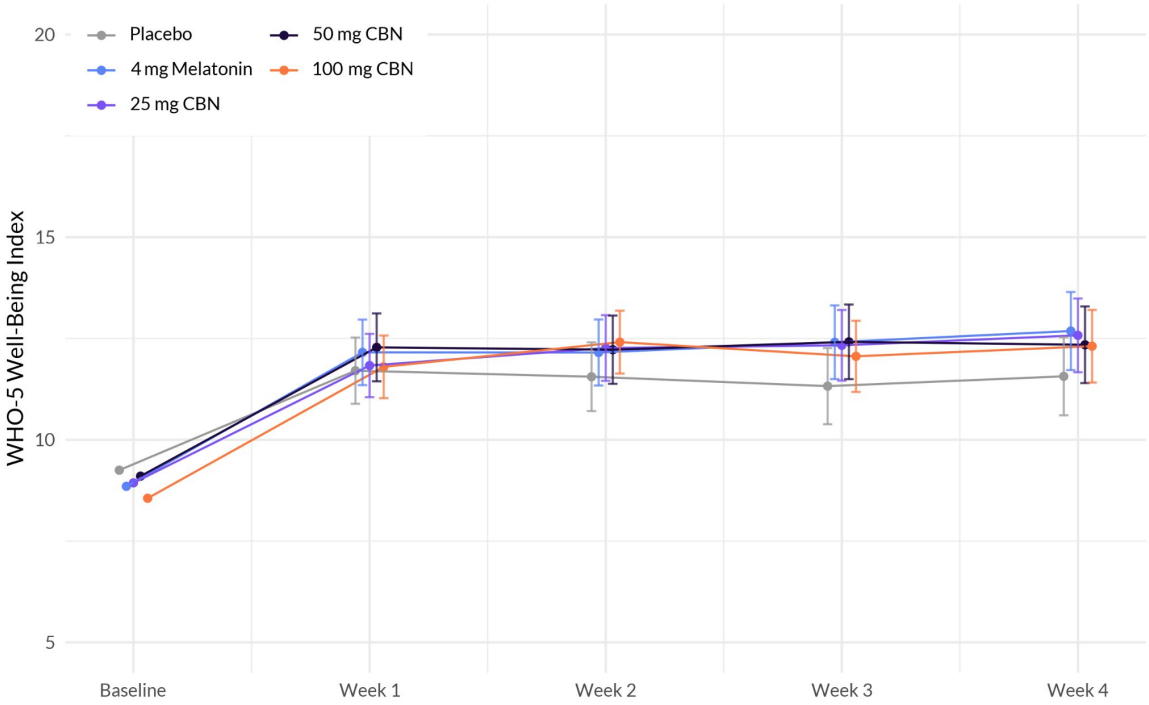
Arm	% experiencing MCID
Placebo	45.2
4 mg melatonin	47.5
25 mg CBN	42.3
50 mg CBN	23.3
100 mg CBN	54.9

[a]A score reduction of one half the standard deviation of the baseline score is considered an MCID

VI. Main findings: Overall well-being

Our primary analyses revealed no significant differences in the rate of mean World Health Organization (WHO)-5 Well-being index score change between between any of the Arms compared to placebo (see Table 15 in Appendix).

FIGURE 7: (WHO)-5 score through time, by study arm



About 7-15% of participants in every arm experienced a minimal clinically important improvement in their (WHO)-5 score, meaning that they experienced a meaningful change that could warrant a change in their symptom management.

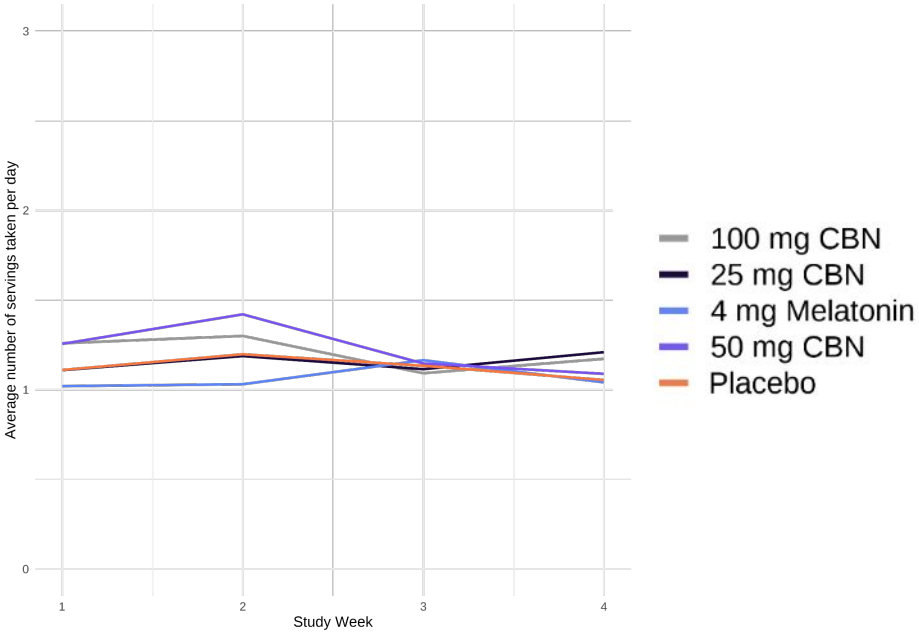
TABLE 7: Proportion who experienced a minimal clinically important difference (MCID)[a] in their (WHO)-5 score, by study arm

Arm	% experiencing MCID
Placebo	12.5
4 mg melatonin	7.8
25 mg CBN	15.2
50 mg CBN	9.5
100 mg CBN	15.9

[a]A score reduction of one half the standard deviation of the baseline score is considered an MCID

VII. Product use

FIGURE 8: Softgels taken each day by study arm



Throughout the study period, daily softgel consumption stayed relatively consistent among all study arms.

Trends in product consumption were roughly equivalent across arms, with average daily dosages staying relatively consistent throughout the study.

TABLE 8: Softgels consumed per day by study week

	Average number of tabs/day	
	First week with product	**Final week with product**
Placebo	1.1	1.0
4 mg melatonin	1.0	1.0
25 mg CBN	1.1	1.2
50 mg CBN	1.2	1.1
100 mg CBN	1.2	1.7

TABLE 9: Average time to effect

Arm	Time (minutes)
Placebo	53.2
4 mg melatonin	49.1
25 mg CBN	54.9
50 mg CBN	55.5
100 mg CBN	46.4

Participants reported experiencing an effect between 46 and 55 minutes after taking their study product.

VIII. Product safety

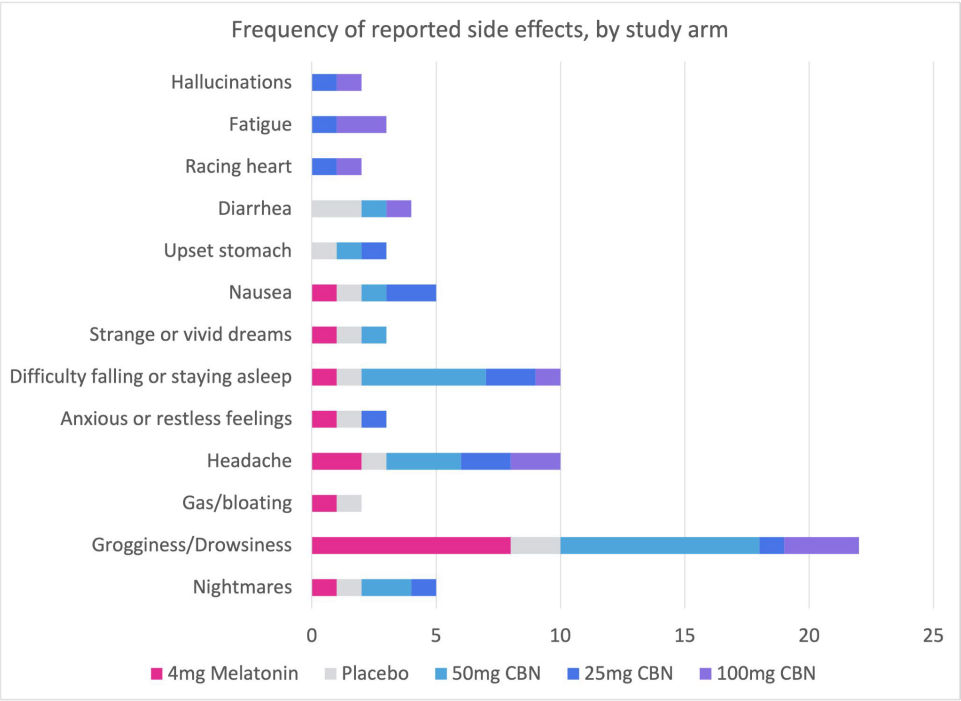
Side effects for all study arms were similar in frequency and mostly mild; none was considered serious or required use of emergency or non-emergency healthcare services.

TABLE 10: Side effect data by study arm

Arm	N (%) reporting any side effects
Placebo	6.4
4 mg melatonin	11.9
25 mg CBN	6.8
50 mg CBN	12.9
100 mg CBN	7.9

No significant difference in the frequency of reporting any side effect were observed between study arms ($\chi^2 = 8.57$, $p = 0.07$)

FIGURE 9: Common side effects (count) reported



Participants most commonly reported experiencing grogginess or drowsiness.

Additionally, each of the following side effects were reported by N=1 participant: Chest pain, Constipation, Urinary Tract Infection, Tingling in lips, Dry mouth, Weight gain, Dry or itchy eyes, Low Libido, Rash, Brain fog.

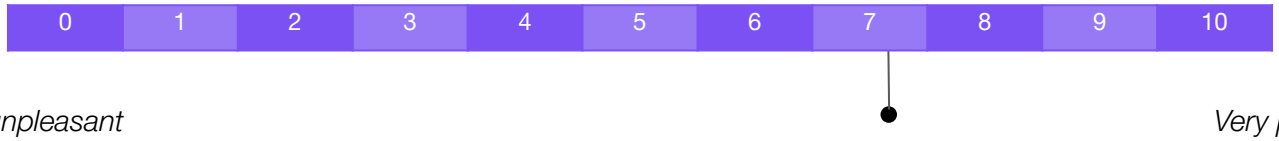
IX. Participant Experience

'How would you describe the smell of your product?'

Very unpleasant *Very pleasant*

Score: 7.4
Participants reported that the smell of their study product was pleasant

'How would you describe the taste of your product?'



Very unpleasant *Very pleasant*

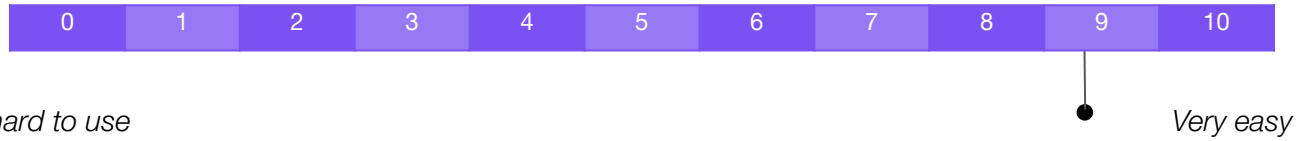
Score: 7.6
Participants reported that the taste of their study product was pleasant

'How satisfied were you with the product packaging?'

Very dissatisfied *Very Satisfied*

Score: 7.3
Participants reported that they were satisfied with the product packaging.

'How would you rate the ease of using this product?'



Very hard to use *Very easy to use*

Score: 9.3
Participants reported that the product was very easy to use.

When asked to provide product feedback, participants in active arms had, on average, positive experiences with their study product. While most claimed that their product improved their sleep, anxiety, and mood, others complained about feeling hungover or groggy the next day, worsening in their sleep disturbances, or general lack of effect.

Selected excerpts:

‘Best thing I’ve tried that’s helped me STAY asleep for more than 3 hrs at a time.’ - 50 mg CBN arm participant

‘Not only did I get longer than 5 hours of great sleep but noticed, upon taking, my body and mind was so relaxed that I felt no body aches and pains.’ - 50 mg CBN arm participant

‘Other than taking the product an hour before bed, nothing in my life changed. I really did not notice a difference with it.’ - 25 mg CBN arm participant

‘It didn't work miracles, but I seemed to fall asleep a little quicker then normal’ - 100mg CBN arm participant

To see all study feedback, please reference your data file.

X. Conclusions

In this randomized, double-blind, placebo-controlled trial to evaluate the effects of TruCBN Softgel formulations relative to placebo, we observed a significant improvement in the rate of mean PROMIS Sleep Disturbance 8a score change between 50mg CBN and placebo and between 4 mg Melatonin and placebo. Further, this study found marginally significant difference in the rate of mean PROMIS Sleep Disturbance 8a score change between 25mg CBN and placebo and between 100mg CBN and placebo. We observed no significant differences in effect on any other health outcome (anxiety, stress, pain, and overall well-being) between the active product arms and placebo control. The active products demonstrated a favorable safety profile; all side effects were mild or moderate, and there were no significant differences in the frequency of reported side effects between the active arms and placebo.

What does this mean?

Our results suggest that this **50mg CBN** product may offer **both significant and clinically meaningful improvement** for those who want to experience higher sleep quality. In this study, the effect of 50mg CBN Softgel formulation on sleep extended beyond the placebo. These effects may be comparable to that of 4 mg melatonin, though further evaluation is needed to directly compare these effects.

Interestingly, products with a lower dose of CBN (25mg) and higher dose of CBN (100mg) also led to greater sleep quality improvement over placebo, though these differences in effect were not statistically significant. Through the lens of product formulation, these results suggest that 50mg CBN may be sufficient to induce significant therapeutic effects. Further, increasing the dose to 100mg does *not* seem to incur additional benefit.

XI. DISCLAIMER

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XII. Appendices

APPENDIX A: Health indices and scoring

PROMIS™ Sleep Disturbance SF 8A
Please select the most appropriate choice for each statement based on your sleep over the last 7 days.

My sleep quality was _____.
[1 = 'very good', 2 = 'good', 3 = 'fair', 4 = 'poor', 5 = 'very poor']

My sleep was refreshing.
[5 = 'not at all', 4 = 'a little bit', 3 = 'somewhat', 2 = 'quite a bit', 1 = 'very much']

I had a problem with my sleep.
[1 = 'not at all', 2 = 'a little bit', 3 = 'somewhat', 4 = 'quite a bit', 5 = 'very much']

I had difficulty falling asleep.
[1 = 'not at all', 2 = 'a little bit', 3 = 'somewhat', 4 = 'quite a bit', 5 = 'very much']

My sleep was restless.
[1 = 'not at all', 2 = 'a little bit', 3 = 'somewhat', 4 = 'quite a bit', 5 = 'very much']

I tried hard to get to sleep.
[1 = 'not at all', 2 = 'a little bit', 3 = 'somewhat', 4 = 'quite a bit', 5 = 'very much']

I was worried about not being able to fall asleep.
[1 = 'not at all', 2 = 'a little bit', 3 = 'somewhat', 4 = 'quite a bit', 5 = 'very much']

I was satisfied with my sleep.
[5 = 'not at all', 4 = 'a little bit', 3 = 'somewhat', 2 = 'quite a bit', 1 = 'very much']

1. Purvis, Taylor E. BA; Neuman, Brian J. MD; Riley, Lee H. III MD; Skolasky, Richard L. ScD Discriminant Ability, Concurrent Validity, and Responsiveness of PROMIS Health Domains Among Patients With Lumbar Degenerative Disease Undergoing Decompression With or Without Arthrodesis, SPINE: November 1, 2018 - Volume 43 - Issue 21 - p 1512-1520

PROMIS™ Sleep Disturbance SF 8A severity thresholds *(based on T-scores, NOT raw scores)*

- Less than 55 = None to slight
- 55.0—59.9 = Mild
- 60.0—69.9 = Moderate
- 70 and over = Severe

PROMIS Sleep Disturbance SF 8A threshold for minimally important difference: One half the standard deviation of the baseline score[1]

1. Norman, G.R.; Sloan, J.A.; Wyrwich, K.W. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. *Med. Care* **2003**, *41*, 582–592.

PROMIS™ Sleep Disturbance SF 4A
Please select the most appropriate choice for each statement based on your sleep over the last 7 days.

My sleep quality was:
5 = Very poor
4 = Poor
3 = Fair
2 = Good
1 = Very good

My sleep was refreshing.
5 = Not at all
4 = A little bit
3 = Somewhat
2 = Quite a bit
1 = Very much

I had a problem with my sleep.
1 = Not at all
2 = A little bit
3 = Somewhat
4 = Quite a bit
5 = Very much

I had difficulty falling asleep.
1 = Not at all
2 = A little bit
3 = Somewhat
4 = Quite a bit
5 = Very much

PROMIS Sleep Disturbance SF 4a threshold for minimally important difference: One half the standard deviation of the baseline score[1]

1. Norman, G.R.; Sloan, J.A.; Wyrwich, K.W. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. *Med. Care* **2003**, *41*, 582–592.

PROMIS™ Anxiety SF 4A
Please select the most appropriate choice for each statement based on your feelings over the last 7 days.

I felt fearful.
1 = never
2 = rarely
3 = sometimes
4 = often
5 = always

I found it hard to focus on anything but my anxiety.
1 = never
2 = rarely
3 = sometimes
4 = often
5 = always

My worries overwhelmed me.
1 = never
2 = rarely
3 = sometimes
4 = often
5 = always

I felt uneasy.
1 = never
2 = rarely
3 = sometimes
4 = often
5 = always

PROMIS™ Anxiety SF 4A threshold for minimally important difference: -2.5 points in T-score[1]

1. Kurt Kroenke, MD, Zhangsheng Yu, PhD, Jingwei Wu, MS, Jacob Kean, PhD, Patrick O. Monahan, Phd, Operating Characteristics of PROMIS Four-Item Depression and Anxiety Scales in Primary Care Patients with Chronic Pain, *Pain Medicine*, Volume 15, Issue 11, November 2014, Pages 1892–1901, https://doi.org/10.1111/pme.12537

PROMIS™ Stress SF 4A
Please select the most appropriate choice for each statement based on your feelings of stress over the last 7 days.

I felt stressed.
1 = Never
2 = Rarely
3 = Sometimes
4 = Often
5 = Always

I felt that my problems kept piling up.
1 = Never
2 = Rarely
3 = Sometimes
4 = Often
5 = Always

I felt overwhelmed.
1 = Never
2 = Rarely
3 = Sometimes
4 = Often
5 = Always

I felt unable to manage things in my life.
1 = Never
2 = Rarely
3 = Sometimes
4 = Often
5 = Always

PROMIS™ Stress SF 4A severity thresholds *(based on T-scores, NOT raw scores)*
- Less than 55 = None to slight
- 55.0—59.9 = Mild
- 60.0—69.9 = Moderate
- 70 and over = Severe

PROMIS™ Stress SF 4A threshold for minimally important difference: One half the standard deviation of the baseline score[1]

1. Norman, G.R.; Sloan, J.A.; Wyrwich, K.W. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. *Med. Care* **2003**, *41*, 582–592.

PEG scale [1]

Thinking about your pain over the last 7 days, please drag the slider to indicate your response. If your response is already reflected in the current position of the slider, simply click the slider once and click 'next.

What number indicates your pain on average in the last 7 days?

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10
no pain — moderate pain — worst possible pain

What number best describes how, during the past 7 days, pain has interfered with your enjoyment of life?

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10
did not interfere — somewhat interfered — completely interfered

What number best describes how, during the past 7 days, pain has interfered with your general activity?

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10
did not interfere — somewhat interfered — completely interfered

PEG threshold for clinically meaningful improvement: 30% reduction[2]

1. Krebs EE, Lorenz KA, Bair MJ, Damush TM, Wu J, Sutherland JM, Asch S, Kroenke K. Development and Initial Validation of the PEG, a Three-item Scale Assessing Pain Intensity and Interference. J Gen Internal Medicine 2009 24:733-738.
2. Dowell, D, Haegerich, T, Chou, R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. Recommendations and Reports. 2016 March 18; 65(1);1–49

WHO-5 scale [1]
Please respond to each item by marking one box per row, regarding how you felt in the last 7 days:

I have felt cheerful in good spirits.
5 = all of the time
4 = most of the time
3 = more than half the time
2 = less than half the time
1 = some of the time
0 = at no time

I have felt calm and relaxed.
5 = all of the time
4 = most of the time
3 = more than half the time
2 = less than half the time
1 = some of the time
0 = at no time

I have felt active and vigorous.
5 = all of the time
4 = most of the time
3 = more than half the time
2 = less than half the time
1 = some of the time
0 = at no time

I woke up feeling fresh and relaxed.
5 = all of the time
4 = most of the time
3 = more than half the time
2 = less than half the time
1 = some of the time
0 = at no time

My daily life has been filled with things that interest me.
5 = all of the time
4 = most of the time
3 = more than half the time
2 = less than half the time
1 = some of the time
0 = at no time

WHO-5 threshold for clinically meaningful improvement [2]

- 10 point or more increase in score

1. Regional Office for Europe WHO. Use of Well-Being Measures in Primary Health Care - The DepCare Project. Health for All, Target 12, 1998 [http://www.who.dk/document/e60246.pdf]
2. World Health Organization (WHO) Regional Office for Europe. Wellbeing Measures in Primary Health Care/the DEPCARE Project. 1998;45.

APPENDIX B: Health indices and scoring

Table 1. Participant characteristics

	Placebo N = 204	4 mg Melatonin N = 202	25 mg CBN N = 206	50 mg CBN N = 205	100 mg CBN N = 203	Overall N = 1020
Age [mean (SD)]	42.68 (12.00)	43.27 (13.60)	43.23 (12.93)	43.97 (12.70)	43.13 (12.59)	43.26 (12.75)
BMI [mean (SD)]	31.23 (9.70)	31.12 (8.78)	29.93 (7.04)	30.27 (8.30)	30.10 (7.26)	30.52 (8.27)
Unknown	3	4	0	3	0	10
BMI category [N (%)]						
Underweight	1 (0.5%)	6 (3.0%)	1 (0.5%)	3 (1.5%)	1 (0.5%)	12 (1.2%)
Normal weight	47 (23%)	50 (25%)	50 (24%)	53 (26%)	47 (23%)	247 (24%)
Overweight	60 (30%)	42 (21%)	68 (33%)	65 (32%)	72 (35%)	307 (30%)
Obesity	93 (46%)	100 (51%)	87 (42%)	81 (40%)	83 (41%)	444 (44%)
Unknown	3	4	0	3	0	10
Sex [N (%)]						
Female	111 (54%)	109 (54%)	112 (54%)	110 (54%)	110 (54%)	552 (54%)
Male	93 (46%)	93 (46%)	94 (46%)	95 (46%)	93 (46%)	468 (46%)
Race [N (%)]						
White	157 (77%)	171 (85%)	165 (80%)	165 (80%)	153 (75%)	811 (80%)
Black	20 (9.8%)	11 (5.4%)	14 (6.8%)	9 (4.4%)	15 (7.4%)	69 (6.8%)
Multi-racial	9 (4.4%)	11 (5.4%)	10 (4.9%)	10 (4.9%)	13 (6.4%)	53 (5.2%)
Asian	4 (2.0%)	2 (1.0%)	5 (2.4%)	12 (5.9%)	9 (4.4%)	32 (3.1%)
Some other race	7 (3.4%)	2 (1.0%)	9 (4.4%)	1 (0.5%)	6 (3.0%)	25 (2.5%)
Prefer not to say	2 (1.0%)	2 (1.0%)	3 (1.5%)	2 (1.0%)	3 (1.5%)	12 (1.2%)
Unknown	3 (1.5%)	3 (1.5%)	0 (0%)	3 (1.5%)	0 (0%)	9 (0.9%)
American Indian or Alaska Native	1 (0.5%)	0 (0%)	0 (0%)	2 (1.0%)	4 (2.0%)	7 (0.7%)
Native Hawaiian or Pacific Islander	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	2 (0.2%)
Hispanic, LatinX, or Spanish origin [N (%)]						
No	183 (90%)	180 (89%)	185 (90%)	179 (87%)	183 (90%)	910 (89%)
Yes	18 (8.8%)	19 (9.4%)	18 (8.7%)	22 (11%)	17 (8.4%)	94 (9.2%)
Prefer not to say	3 (1.5%)	3 (1.5%)	3 (1.5%)	4 (2.0%)	3 (1.5%)	16 (1.6%)
Education level [N (%)]						
Less than high school	1 (0.5%)	4 (2.0%)	5 (2.4%)	0 (0%)	2 (1.0%)	12 (1.2%)
High school diploma, no college	30 (15%)	32 (16%)	33 (16%)	20 (9.9%)	21 (10%)	136 (13%)
Some college, no degree	43 (21%)	51 (26%)	56 (27%)	55 (27%)	57 (28%)	262 (26%)
Trade/technical/vocational degree	12 (6.0%)	15 (7.5%)	17 (8.3%)	15 (7.4%)	9 (4.4%)	68 (6.7%)
Bachelors or associates degree	80 (40%)	70 (35%)	69 (33%)	85 (42%)	83 (41%)	387 (38%)
Masters or professional degree	35 (17%)	27 (14%)	26 (13%)	26 (13%)	31 (15%)	145 (14%)
Prefer not to say	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	1 (<0.1%)
Unknown	3	3	0	3	0	9
PROMIS sleep baseline category [N (%)]						
Within normal limits	47 (23%)	48 (24%)	42 (20%)	42 (20%)	35 (17%)	214 (21%)
Mild	53 (26%)	51 (25%)	50 (24%)	47 (23%)	51 (25%)	252 (25%)
Moderate	82 (40%)	82 (41%)	88 (43%)	93 (45%)	82 (40%)	427 (42%)
Severe	22 (11%)	21 (10%)	26 (13%)	23 (11%)	35 (17%)	127 (12%)
PROMIS stress baseline category [N (%)]						
Within normal limits	28 (14%)	20 (9.9%)	26 (13%)	13 (6.3%)	15 (7.4%)	102 (10%)
Mild	32 (16%)	34 (17%)	34 (17%)	44 (21%)	35 (17%)	179 (18%)
Moderate	118 (58%)	110 (54%)	107 (52%)	114 (56%)	109 (54%)	558 (55%)
Severe	26 (13%)	38 (19%)	39 (19%)	34 (17%)	44 (22%)	181 (18%)
PROMIS anxiety baseline category [N (%)]						
Within normal limits	137 (67%)	130 (64%)	139 (67%)	133 (65%)	136 (67%)	675 (66%)

BMI = Body Mass Index; PEG = Pain, Enjoyment of Life and General Activity Scale

Participant characteristics

Mild	54 (26%)	54 (27%)	51 (25%)	56 (27%)	48 (24%)	263 (26%)
Moderate	12 (5.9%)	17 (8.4%)	14 (6.8%)	15 (7.3%)	17 (8.4%)	75 (7.4%)
Severe	1 (0.5%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	2 (1.0%)	7 (0.7%)
PEG baseline category [N (%)]						
Mild	25 (24%)	21 (21%)	23 (22%)	22 (22%)	34 (32%)	125 (24%)
Moderate	49 (47%)	39 (40%)	49 (46%)	49 (49%)	41 (39%)	227 (44%)
Severe	31 (30%)	38 (39%)	34 (32%)	28 (28%)	31 (29%)	162 (32%)
Unknown	99	104	100	106	97	506
Pain condition [N (%)]						
Yes	105 (51%)	98 (49%)	106 (51%)	99 (48%)	106 (52%)	514 (50%)
No	99 (49%)	104 (51%)	100 (49%)	106 (52%)	97 (48%)	506 (50%)
Sleep condition [N (%)]						
Yes	204 (100%)	202 (100%)	206 (100%)	205 (100%)	203 (100%)	1,020 (100%)
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anxiety condition [N (%)]						
Yes	204 (100%)	202 (100%)	206 (100%)	205 (100%)	203 (100%)	1,020 (100%)
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stress condition [N (%)]						
Yes	204 (100%)	202 (100%)	206 (100%)	205 (100%)	203 (100%)	1,020 (100%)
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatigue condition [N (%)]						
Yes	159 (78%)	166 (82%)	161 (78%)	168 (82%)	146 (72%)	800 (78%)
No	45 (22%)	36 (18%)	45 (22%)	37 (18%)	57 (28%)	220 (22%)

BMI = Body Mass Index; PEG = Pain, Enjoyment of Life and General Activity Scale

Table 2. Comparisons against placebo for PROMIS Sleep Disturbance 8a

Contrast[1]	Difference from Placebo (95% CI)[2]	*t* Statistic	*p* Value[2]
4 mg Melatonin - Placebo	-2.67 (-5.08, -0.25)	-2.71	0.025
25 mg CBN - Placebo	-2.12 (-4.47, 0.23)	-2.22	0.091
50 mg CBN - Placebo	-2.74 (-5.13, -0.34)	-2.81	0.019
100 mg CBN - Placebo	-2.17 (-4.5, 0.17)	-2.29	0.078

[1] Contrast calculated at week 4

[2] Dunnett's test correction used to adjust for multiple comparisons

Table 3. Estimated Marginal Means Across Time Points for PROMIS Sleep Disturbance 8a

Week	Placebo[1]	4 mg Melatonin[1]	25 mg CBN[1]	50 mg CBN[1]	100 mg CBN[1]
Week 1	22.84 (21.64, 24.04)	20.75 (19.56, 21.93)	21.65 (20.51, 22.8)	20.4 (19.17, 21.62)	20.99 (19.86, 22.12)
Week 2	22.71 (21.47, 23.95)	20.38 (19.19, 21.56)	20.58 (19.4, 21.75)	20.98 (19.76, 22.21)	21.77 (20.64, 22.89)
Week 3	23.2 (21.81, 24.58)	20.66 (19.32, 21.99)	21.34 (20.05, 22.62)	20.75 (19.39, 22.1)	20.84 (19.55, 22.14)
Week 4	23.03 (21.67, 24.39)	20.36 (19, 21.73)	20.91 (19.62, 22.2)	20.29 (18.95, 21.63)	20.86 (19.6, 22.13)

[1] Estimated marginal mean (95% confidence interval)

Table 4. Parameter Estimates for Participant Global Impression of Change in Sleep Disturbance

Parameter	Estimate	Standard Error	*z* Statistic	*p* Value
Education Reference: College degree				
No College Degree	0.28	0.16	1.71	0.087
Sex Reference: Female				
Male	−0.22	0.16	−1.37	0.169
Age	0.00	0.01	−0.68	0.498
Race Reference: White				
Non-White	0.28	0.22	1.32	0.187
BMI	−0.01	0.01	−0.78	0.437
Hispanic Reference: Non-Hispanic				
Hispanic	−0.08	0.30	−0.29	0.775
Treatment Reference: Placebo				
4 mg Melatonin	0.79	0.26	3.05	0.002
25 mg CBN	0.63	0.26	2.42	0.015
50 mg CBN	0.85	0.26	3.27	0.001
100 mg CBN	0.85	0.25	3.35	0.001
Intercepts				
Much worse|A little worse	−4.29	0.61	−7.04	0.000
A little worse|No change	−2.48	0.48	−5.13	0.000
No change|A little better	−0.25	0.46	−0.54	0.590
A little better|Much better	1.53	0.47	3.28	0.001

Parameters presented on log-odds scale

Table 5. Estimated Odds Ratio for Sleep Disturbance PGIC

Contrast	Odds Ratio (95% Confidence Interval)[1]	*Z* statistic	*p* Value[1]
4 mg Melatonin - Placebo	2.21 (1.15, 4.21)	3.05	0.009
25 mg CBN - Placebo	1.88 (0.98, 3.62)	2.42	0.054
50 mg CBN - Placebo	2.35 (1.22, 4.51)	3.27	0.004
100 mg CBN - Placebo	2.35 (1.24, 4.44)	3.35	0.003

[1] Adjusted for multiple comparisons using Dunnett's test correction

Table 6. Estimated Marginal Means for Sleep Disturbance PGIC

Treatment Group	Marginal Mean (95% Confidence Interval)
Placebo	3.51 (3.29, 3.72)
4 mg Melatonin	3.88 (3.67, 4.09)
25 mg CBN	3.81 (3.59, 4.02)
50 mg CBN	3.91 (3.7, 4.11)
100 mg CBN	3.91 (3.7, 4.12)

Estimated marginal mean calculated at week 4

Table 7. Estimated Marginal Percentage Achieving Meaningful Clinical Improvement on the PROMIS Sleep 8a

Treatment Group	Estimated Marginal Mean[1]
Placebo	35.4% (25.22%, 49.55%)
4 mg Melatonin	50.5% (37.54%, 67.94%)
25 mg CBN	47.1% (35.41%, 62.66%)
50 mg CBN	51.6% (38.93%, 68.48%)
100 mg CBN	49.1% (36.96%, 65.24%)

[1] Reflects estimated percentage of participants achieving meaningful clinical improvement with 95% confidence intervals in parentheses

Generalized linear model assuming a Poisson distribution with a robust error variance

Clinically meaningful improvement reflects a 30% or greater reduction from baseline

Table 8. Observed Percentage Achieving Meaningful Clinical Improvement on the PROMIS Sleep 8a

Treatment Group	Percent Achieving Meaningful Clinical Improvement
Placebo	36.2%
4 mg Melatonin	51.9%
25 mg CBN	46.7%
50 mg CBN	53.6%
100 mg CBN	50.0%

Clinically meaningful improvement reflects a 30% or greater reduction from baseline

Table 9. Comparisons between study arms for meaningful clinical improvement on the PROMIS Sleep Disturbance 8a

Comparison	Relative Risk[1,2]	*z* Test	*p*-Value[2]
4 mg Melatonin / Placebo	1.43 (0.7, 2.16)	1.60	0.434
25 mg CBN / Placebo	1.33 (0.65, 2.01)	1.33	0.729
50 mg CBN / Placebo	1.46 (0.72, 2.2)	1.71	0.348
100 mg CBN / Placebo	1.39 (0.7, 2.08)	1.54	0.498

[1] Reflects ratio of probability of achieving a clinically meaningful improvement with 95% confidence intervals in parentheses

[2] Bonferroni correction used to adjust for mulitple comparisons

Generalized linear model assuming a Poisson distribution with a robust error variance

Clinically meaningful improvement reflects a 30% or greater reduction from baseline

Table 10. Comparisons against placebo for PROMIS Sleep Disturbance 4a

Contrast[1]	Difference from Placebo (95% CI)[2]	*t* Statistic	*p* Value[2]
4 mg Melatonin - Placebo	-1.21 (-2.39, -0.03)	-2.52	0.043
25 mg CBN - Placebo	-0.9 (-2.05, 0.24)	-1.94	0.169
50 mg CBN - Placebo	-1.43 (-2.6, -0.27)	-3.02	0.010
100 mg CBN - Placebo	-0.98 (-2.12, 0.16)	-2.12	0.115

[1] Contrast calculated at week 4

[2] Dunnett's test correction used to adjust for multiple comparisons

Table 11. Estimated Marginal Means Across Time Points for PROMIS Sleep Disturbance 4a

Week	Placebo[1]	4 mg Melatonin[1]	25 mg CBN[1]	50 mg CBN[1]	100 mg CBN[1]
Week 1	11.8 (11.2, 12.4)	10.77 (10.18, 11.36)	10.97 (10.39, 11.54)	10.69 (10.07, 11.3)	10.82 (10.25, 11.38)
Week 2	11.77 (11.15, 12.39)	10.67 (10.07, 11.26)	10.81 (10.22, 11.4)	10.92 (10.3, 11.53)	11.33 (10.77, 11.89)
Week 3	11.76 (11.05, 12.47)	10.75 (10.06, 11.44)	11.07 (10.42, 11.73)	10.81 (10.11, 11.5)	10.85 (10.18, 11.51)
Week 4	11.76 (11.1, 12.43)	10.55 (9.89, 11.22)	10.86 (10.23, 11.49)	10.33 (9.67, 10.98)	10.78 (10.16, 11.4)

[1] Estimated marginal mean (95% confidence interval)

Table 12. Estimated Marginal Percentage Achieving Meaningful Clinical Improvement on the PROMIS Sleep 4a

Treatment Group	Estimated Marginal Mean[1]
Placebo	34.38% (24.42%, 48.4%)
4 mg Melatonin	51.25% (38.25%, 68.7%)
25 mg CBN	46.28% (34.73%, 61.7%)
50 mg CBN	54.76% (41.80%, 71.7%)
100 mg CBN	50.56% (38.37%, 66.6%)

[1] Reflects estimated percentage of participants achieving meaningful clinical improvement with 95% confidence intervals in parentheses

Generalized linear model assuming a Poisson distribution with a robust error variance

Clinically meaningful improvement reflects a 30% or greater reduction from baseline

Table 13. Observed Percentage Achieving Meaningful Clinical Improvement on the PROMIS Sleep 4a

Treatment Group	Percent Achieving Meaningful Clinical Improvement
Placebo	36.25%
4 mg Melatonin	53.25%
25 mg CBN	47.83%
50 mg CBN	58.33%
100 mg CBN	53.19%

Clinically meaningful improvement reflects a 30% or greater reduction from baseline

Table 14. Comparisons between study arms for meaningful clinical improvement on the PROMIS Sleep Disturbance 4a

Comparison	Relative Risk[1,2]	*z* Test	*p*-Value[2]
4 mg Melatonin / Placebo	1.49 (0.74, 2.25)	1.78	0.302
25 mg CBN / Placebo	1.35 (0.66, 2.03)	1.38	0.673
50 mg CBN / Placebo	1.59 (0.81, 2.37)	2.08	0.149
100 mg CBN / Placebo	1.47 (0.75, 2.19)	1.78	0.297

[1] Reflects ratio of probability of achieving a clinically meaningful improvement with 95% confidence intervals in parentheses

[2] Bonferroni correction used to adjust for mulitple comparisons

Generalized linear model assuming a Poisson distribution with a robust error variance

Clinically meaningful improvement reflects a 30% or greater reduction from baseline

Table 15. Comparisons against placebo for WHO-5 Well-Being Index

Contrast[1]	Difference from Placebo (95% CI)[2]	*t* Statistic	*p* Value[2]
4 mg Melatonin - Placebo	1.12 (-0.59, 2.82)	1.61	0.311
25 mg CBN - Placebo	1.01 (-0.65, 2.67)	1.50	0.372
50 mg CBN - Placebo	0.78 (-0.91, 2.47)	1.13	0.599
100 mg CBN - Placebo	0.74 (-0.9, 2.39)	1.11	0.614

[1] Contrast calculated at week 4

[2] Dunnett's test correction used to adjust for multiple comparisons

Table 16. Estimated Marginal Means Across Time Points for WHO-5 Well-Being Index

Week	Placebo[1]	4 mg Melatonin[1]	25 mg CBN[1]	50 mg CBN[1]	100 mg CBN[1]
Week 1	11.7 (10.89, 12.52)	12.16 (11.35, 12.97)	11.83 (11.05, 12.61)	12.28 (11.44, 13.12)	11.8 (11.03, 12.57)
Week 2	11.56 (10.71, 12.4)	12.15 (11.34, 12.97)	12.26 (11.45, 13.07)	12.22 (11.38, 13.06)	12.41 (11.63, 13.18)
Week 3	11.32 (10.38, 12.26)	12.41 (11.5, 13.32)	12.33 (11.46, 13.2)	12.42 (11.49, 13.34)	12.06 (11.18, 12.94)
Week 4	11.57 (10.6, 12.53)	12.68 (11.72, 13.65)	12.58 (11.67, 13.49)	12.34 (11.4, 13.29)	12.31 (11.41, 13.2)

[1] Estimated marginal mean (95% confidence interval)

Table 17. Estimated Marginal Percentage Achieving Meaningful Clinical Improvement on the WHO-5 Well-Being Index

Treatment Group	Estimated Marginal Mean[1]
Placebo	11.22% (5.33%, 23.62%)
4 mg Melatonin	7.68% (2.72%, 21.66%)
25 mg CBN	14.27% (6.87%, 29.67%)
50 mg CBN	9.06% (3.57%, 23.00%)
100 mg CBN	14.95% (7.43%, 30.08%)

[1] Reflects estimated percentage of participants achieving meaningful clinical improvement with 95% confidence intervals in parentheses

Generalized linear model assuming a Poisson distribution with a robust error variance

Clinically meaningful improvement reflects a 10 point increase from baseline

Table 18. Observed Percentage Achieving Meaningful Clinical Improvement on the WHO-5 Well-Being Index

Treatment Group	Percent Achieving Meaningful Clinical Improvement
Placebo	12.50%
4 mg Melatonin	7.79%
25 mg CBN	15.22%
50 mg CBN	9.52%
100 mg CBN	15.96%

Clinically meaningful improvement reflects a 10 point increase from baseline

Table 19. Parameter Estimates for the Kemp Quality of Life Scale

Parameter	Estimate[1]	Standard Error	*z* Statistic	*p* Value
Education Reference: College degree				
No College Degree	−0.36	0.16	−2.24	0.025
Sex Reference: Female				
Male	−0.04	0.16	−0.27	0.785
Age	0.01	0.01	1.24	0.217
Race Reference: White				
Non-White	0.41	0.22	1.89	0.059
BMI	−0.04	0.01	−3.89	0.000
Hispanic Reference: Non-Hispanic				
Hispanic	0.58	0.29	1.97	0.049
Treatment Reference: Placebo				
4 mg Melatonin	0.19	0.25	0.77	0.440
25 mg CBN	0.17	0.25	0.69	0.492
50 mg CBN	0.08	0.25	0.33	0.743
100 mg CBN	0.11	0.24	0.47	0.640
Intercepts				
1|2	−4.51	0.54	−8.42	0.000
2|3	−3.44	0.49	−7.06	0.000
3|4	−2.35	0.47	−5.06	0.000
4|5	−1.50	0.46	−3.29	0.001
5|6	0.15	0.45	0.33	0.739
6|7	2.27	0.48	4.69	0.000

[1] Parameters presented on log-odds scale

Table 20. Estimated Odds Ratio for the Kemp Quality of Life Scale

Contrast	Odds Ratio (95% Confidence Interval)[1]	*Z* statistic	*p* Value[1]
4 mg Melatonin - Placebo	1.21 (0.65, 2.28)	0.77	0.816
25 mg CBN - Placebo	1.19 (0.63, 2.24)	0.69	0.858
50 mg CBN - Placebo	1.09 (0.58, 2.03)	0.33	0.975
100 mg CBN - Placebo	1.12 (0.61, 2.05)	0.47	0.941

[1] Adjusted for multiple comparisons using Dunnett's test correction

Table 21. Estimated Marginal Means for the Kemp Quality of Life Scale

Treatment Group	Marginal Mean (95% Confidence Interval)
Placebo	4.92 (4.64, 5.2)
4 mg Melatonin	5.05 (4.77, 5.33)
25 mg CBN	5.03 (4.75, 5.32)
50 mg CBN	4.97 (4.69, 5.26)
100 mg CBN	4.99 (4.72, 5.27)

Estimated marginal mean calculated at week 4

Table 22. Comparisons against placebo for PROMIS Anxiety 4a

Contrast[1]	Difference from Placebo (95% CI)[2]	*t* Statistic	*p* Value[2]
4 mg Melatonin - Placebo	-0.62 (-2.05, 0.81)	-1.07	0.641
25 mg CBN - Placebo	-0.33 (-1.73, 1.07)	-0.58	0.903
50 mg CBN - Placebo	0.34 (-1.08, 1.76)	0.58	0.902
100 mg CBN - Placebo	-0.87 (-2.27, 0.52)	-1.54	0.347

[1] Contrast calculated at week 4

[2] Dunnett's test correction used to adjust for multiple comparisons

Table 23. Estimated Marginal Means Across Time Points for PROMIS Anxiety 4a

Week	Placebo[1]	4 mg Melatonin[1]	25 mg CBN[1]	50 mg CBN[1]	100 mg CBN[1]
Week 1	9.98 (9.33, 10.64)	9.14 (8.5, 9.78)	9.28 (8.67, 9.9)	10.05 (9.4, 10.7)	9.67 (9.06, 10.28)
Week 2	9.58 (8.88, 10.27)	9.26 (8.61, 9.91)	9.16 (8.52, 9.8)	9.99 (9.32, 10.67)	9.1 (8.49, 9.71)
Week 3	9.53 (8.76, 10.29)	9.31 (8.62, 10)	9.24 (8.57, 9.91)	10.13 (9.43, 10.83)	8.87 (8.2, 9.53)
Week 4	9.72 (8.89, 10.55)	9.1 (8.32, 9.88)	9.39 (8.63, 10.14)	10.05 (9.28, 10.82)	8.84 (8.1, 9.58)

[1] Estimated marginal mean (95% confidence interval)

Table 24. Estimated Marginal Percentage Achieving Meaningful Clinical Improvement on the PROMIS Anxiety 4a

Treatment Group	Estimated Marginal Mean[1]
Placebo	47.28% (30.58%, 73.1%)
4 mg Melatonin	53.89% (36.71%, 79.1%)
25 mg CBN	52.12% (35.89%, 75.7%)
50 mg CBN	37.61% (24.23%, 58.4%)
100 mg CBN	47.47% (31.73%, 71.0%)

[1] Reflects estimated percentage of participants achieving meaningful clinical improvement with 95% confidence intervals in parentheses

Generalized linear model assuming a Poisson distribution with a robust error variance

Clinically meaningful improvement reflects a 2.5-point or greater reduction from baseline

Table 25. Observed Percentage Achieving Meaningful Clinical Improvement on the PROMIS Anxiety 4a

Treatment Group	Percent Achieving Meaningful Clinical Improvement
Placebo	45.65%
4 mg Melatonin	51.92%
25 mg CBN	49.15%
50 mg CBN	37.50%
100 mg CBN	46.55%

Clinically meaningful improvement reflects a 2.5-point or greater reduction from baseline

Table 26. Comparisons against placebo for the Pain, Enjoyment of Life and General Activity Scale

Contrast[1]	Difference from Placebo (95% CI)[2]	*t* Statistic	*p* Value[2]
4 mg Melatonin - Placebo	-0.34 (-1.34, 0.66)	-0.84	0.782
25 mg CBN - Placebo	-0.41 (-1.34, 0.53)	-1.07	0.637
50 mg CBN - Placebo	0.21 (-0.77, 1.19)	0.54	0.918
100 mg CBN - Placebo	-0.52 (-1.46, 0.42)	-1.36	0.453

[1] Contrast calculated at week 4

[2] Dunnett's test correction used to adjust for multiple comparisons

Table 27. Estimated Marginal Means Across Time Points for the Pain, Enjoyment of Life and General Activity Scale

Week	Placebo[1]	4 mg Melatonin[1]	25 mg CBN[1]	50 mg CBN[1]	100 mg CBN[1]
Week 1	4.55 (4.05, 5.06)	4.49 (3.98, 5.01)	4.48 (4.04, 4.93)	4.44 (3.92, 4.95)	4.67 (4.22, 5.13)
Week 2	4.68 (4.18, 5.18)	4.27 (3.78, 4.75)	4.15 (3.71, 4.59)	4.4 (3.92, 4.88)	4.43 (3.99, 4.87)
Week 3	4.46 (3.88, 5.03)	4.33 (3.76, 4.89)	3.99 (3.52, 4.47)	4.3 (3.77, 4.84)	4.28 (3.78, 4.78)
Week 4	4.32 (3.77, 4.88)	3.99 (3.42, 4.55)	3.92 (3.42, 4.41)	4.54 (3.99, 5.09)	3.8 (3.3, 4.31)

[1] Estimated marginal mean (95% confidence interval)

Table 28. Estimated Marginal Percentage Achieving Meaningful Clinical Improvement on the Pain, Enjoyment of Life and General Activity Scale

Treatment Group	Estimated Marginal Mean[1]
Placebo	43.79% (30.6%, 62.62%)
4 mg Melatonin	49.49% (33.0%, 74.15%)
25 mg CBN	42.90% (29.4%, 62.55%)
50 mg CBN	23.03% (13.1%, 40.56%)
100 mg CBN	53.04% (38.0%, 74.09%)

[1] Reflects estimated percentage of participants achieving meaningful clinical improvement with 95% confidence intervals in parentheses

Generalized linear model assuming a Poisson distribution with a robust error variance

Clinically meaningful improvement reflects a 30% or greater reduction from baseline

Table 29. Observed Percentage Achieving Meaningful Clinical Improvement on the Pain, Enjoyment of Life and General Activity Scale

Treatment Group	Percent Achieving Meaningful Clinical Improvement
Placebo	45.2%
4 mg Melatonin	47.5%
25 mg CBN	42.3%
50 mg CBN	23.3%
100 mg CBN	54.9%

Clinically meaningful improvement reflects a 30% or greater reduction from baseline

Table 30. Comparisons against placebo for PROMIS Stress 4a

Contrast[1]	Difference from Placebo (95% CI)[2]	*t* Statistic	*p* Value[2]
4 mg Melatonin - Placebo	-0.57 (-1.94, 0.81)	-1.02	0.674
25 mg CBN - Placebo	-0.85 (-2.17, 0.47)	-1.58	0.325
50 mg CBN - Placebo	-0.87 (-2.22, 0.48)	-1.59	0.324
100 mg CBN - Placebo	-0.99 (-2.28, 0.31)	-1.88	0.189

[1] Contrast calculated at week 4

[2] Dunnett's test correction used to adjust for multiple comparisons

Table 31. Estimated Marginal Means Across Time Points for PROMIS Stress 4a

Week	Placebo[1]	4 mg Melatonin[1]	25 mg CBN[1]	50 mg CBN[1]	100 mg CBN[1]
Week 1	12.46 (11.8, 13.12)	11.74 (11.09, 12.39)	11.53 (10.92, 12.13)	11.6 (10.93, 12.27)	11.76 (11.19, 12.33)
Week 2	11.94 (11.25, 12.63)	11.67 (10.99, 12.34)	11.19 (10.55, 11.84)	11.35 (10.66, 12.04)	11.1 (10.49, 11.71)
Week 3	12.25 (11.47, 13.02)	11.54 (10.79, 12.28)	11.39 (10.7, 12.08)	11.32 (10.58, 12.07)	10.96 (10.29, 11.64)
Week 4	12 (11.23, 12.77)	11.43 (10.65, 12.21)	11.15 (10.43, 11.87)	11.13 (10.38, 11.88)	11.01 (10.33, 11.69)

[1] Estimated marginal mean (95% confidence interval)

Table 32. Estimated Marginal Percentage Achieving Meaningful Clinical Improvement on the Pain, Enjoyment of Life and General Activity Scale

Treatment Group	Estimated Marginal Mean[1]
Placebo	14.1% (6.50%, 30.7%)
4 mg Melatonin	27.2% (13.88%, 53.2%)
25 mg CBN	21.5% (11.03%, 41.8%)
50 mg CBN	15.5% (6.79%, 35.6%)
100 mg CBN	23.4% (12.06%, 45.2%)

[1] Reflects estimated percentage of participants achieving meaningful clinical improvement with 95% confidence intervals in parentheses

Generalized linear model assuming a Poisson distribution with a robust error variance

Clinically meaningful improvement reflects a .5 standard deviation or greater reduction from baseline

Table 33. Observed Percentage Achieving Meaningful Clinical Improvement on the PROMIS Stress 4a

Treatment Group	Percent Achieving Meaningful Clinical Improvement
Placebo	18.9%
4 mg Melatonin	34.0%
25 mg CBN	27.0%
50 mg CBN	22.0%
100 mg CBN	31.3%

Clinically meaningful improvement reflects a .5 standard deviation or greater reduction from baseline