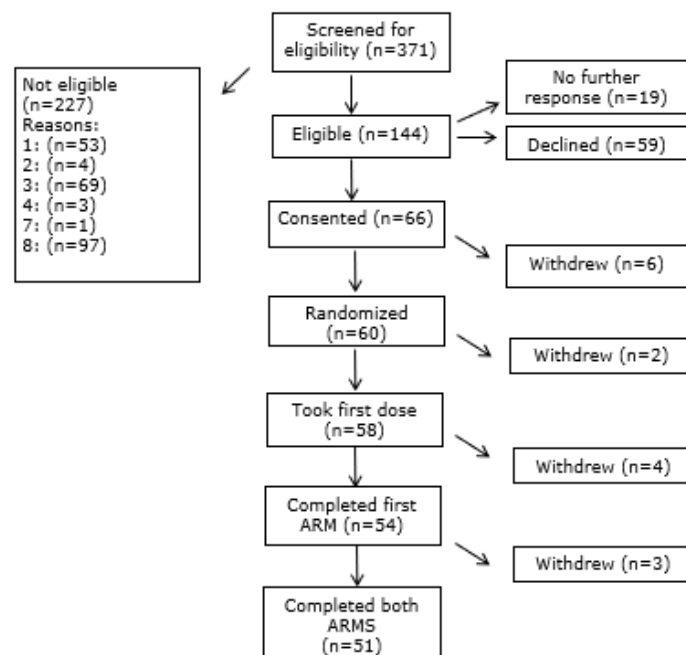


Participant flow



Reasons for non-eligibility

- 1= BPS average pain score <7
- 2= Pain <3 months
- 3= Disallowed drugs
- 4= Liver disease
- 5= Under 16y
- 6= Pregnant/BF/trying
- 7= History of alcohol/drug abuse
- 8= Other/not known

Participant characteristics at baseline

	Intention to Treat		Per Protocol	
	Group A Melatonin first (n=30)	Group B Placebo first (n=28)	Group A Melatonin first (n=26)	Group B Placebo first (n=25)
Age, y (%)	62 [24 -79]	55 [28 -79]	61 [24 -79]	55 [28 - 78]
Sex, n (%)				
Male	10 (33%)	12 (43%)	8 (31%)	10 (40%)
Female	20 (67%)	16 (58%)	18 (69%)	15 (60%)
Pain duration, months	96 [12 - 336]	96 [24 - 480]	96 [12 -336]	120 [24 -480]
Pain Type, n (%)				
Nociceptive/mainly nociceptive	16 (53%)	6 (21%)	14 (54%)	6 (24%)
Neuropathic/mainly neuropathic	12 (40%)	14 (50%)	10 (39%)	12 (48%)
Mixed	2 (7%)	8 (29%)	2 (8%)	7 (28%)
Ethnicity, n (%)				
White	28 (93%)	27 (96%)	24 (92%)	24 (94%)
Other White	1 (3%)	0	1 (4%)	0
Asian	1 (3%)	0	1 (4%)	0
Black	0	1 (3.6%)	0	1 (4%)
Smoking status, n (%)				
Never smoked	10 (33%)	15 (55%)	10 (39%)	13 (52%)
Ex-smoker	13 (43%)	9 (32%)	10 (39%)	8 (32%)
Smoker	7 (23%)	4 (14%)	6 (23%)	4 (16%)
Body mass index, kg/m²	29.8 [22.7 - 51.3]	30.3 [20.4 - 48.0]	30.2 [22.7 -51.3]	30.4 [23.1 - 48.0]
BMI Categories, n (%)				
Normal (18.5-24.9)	3 (10%)	4 (14%)	3 (11%)	3 (12%)
Overweight (25.0-29.9)	12 (40%)	9 (32%)	9 (35%)	8 (32%)
Obese (30 or more)	14 (47%)	15 (54%)	13 (50%)	14 (56%)
Missing value	1 (3%)	0	1 (4%)	0

Outcome measures at baseline

	Group A Melatonin first	Group B Placebo first	Sampling probability
Verran, Snyder-Halpern sleep scale			
Sleep disturbance	480 [67-632]	381 [106-619]	<i>P=0.06</i>
Sleep latency ^a	89 [4-100]	50 [0-100]	<i>P=0.18</i>
Wake after sleep onset ^a	54 [3-100]	43 [0-90]	<i>P=0.24</i>
Brief Pain Inventory			
Pain intensity score ^{b,c}	7 [7-10]	7 [7-10]	<i>P=0.38</i>
Sleep interruption score ^c	8 [1-10]	8 [5-10]	<i>P=0.86</i>
Pittsburgh Sleep Quality Index			
Global Score ^d	12.5 [4.0-17.0]	12.0 [3.0-16.0]	<i>P=0.31</i>
Sleep duration (hours)	5.0 [2.0-7.5]	2.0 [2.0-8.0]	<i>P=0.56</i>
Pain and Sleep Quality 3-Item score^e	242 [57-300]	204 [83-299]	<i>P=0.08</i>

Median [range]

^a maximum score = 100

^b inclusion criteria dictate score of 7 or more at baseline

^c maximum score = 11

^d maximum score = 21

^e maximum score = 300

Intention to treat analysis

Verran, Snyder-Halpern Sleep Scale

VSH Disturbance: Melatonin Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	67	300.3	438.0	560.5	632
Visit 2	74	232.6	308.5	454.6	677
Visit 3	47	295.2	395.0	510.0	684

VSH Disturbance: Placebo Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	96	273.8	430.5	529.2	673
Visit 2	21	256.8	399.0	510.3	677
Visit 3	130	280.3	375.0	460.3	686

Latency: Melatonin Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	2	38.6	79.5	96.1	100
Visit 2	0	12.7	25.0	81.1	100
Visit 3	2	30.9	63.5	90.3	100

Latency: Placebo Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	0	22.7	65.0	95.7	100
Visit 2	0	20.7	55.0	90.0	100
Visit 3	1	32.2	60.0	87.8	100

WASO: Melatonin Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	3	29.8	53.0	72.1	100
Visit 2	3	16.7	37.0	60.7	96
Visit 3	6	32.4	51.5	70.2	98

WASO: Placebo Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	0	22.7	47.0	66.0	100
Visit 2	0	21.3	50.0	66.3	99
Visit 3	10	27.2	47.0	61.7	96

Pittsburgh Sleep Quality Index

PSQI Global Score: Melatonin Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	4	10.0	12.0	15.0	17
Visit 2	3	7.0	10.0	12.1	17
Visit 3	4	8.0	10.0	13.0	17

PSQI Global Score: Placebo Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	3	9.0	12.0	14.0	16
Visit 2	3	8.0	11.0	13.1	17
Visit 3	4	8.7	10.0	13.0	16

Pain and Sleep Quality 3 Item Score

PSQ-3: Melatonin Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	57	186.8	224.5	257.1	300
Visit 2	21	106.7	189.0	231.7	300
Visit 3	19	133.3	179.5	235.1	300

PSQ-3: Placebo Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	42	151.8	203.0	239.8	299
Visit 2	11	141.9	183.0	233.8	291
Visit 3	29	131.0	187.0	217.5	293

Brief Pain Inventory

BPI Average Pain: Melatonin Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	3	7.0	7.0	8.0	10
Visit 2	3	5.0	6.0	7.0	10
Visit 3	3	5.0	6.0	7.0	9

BPI Average Pain: Placebo Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	4	7.0	7.0	8.0	9
Visit 2	3	6.0	6.0	7.0	10
Visit 3	3	5.0	6.0	7.0	10

BPI Sleep Interference: Melatonin Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	1	7.0	8.0	9.0	10
Visit 2	0	5.0	6.0	7.1	10
Visit 3	1	5.0	7.0	8.0	10

BPI Sleep Interference: Placebo Period	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Visit 1	2	6.0	8.0	9.0	10
Visit 2	1	5.0	7.0	8.0	10
Visit 3	1	5.0	7.0	8.0	10

Adverse events

Event	Number of adverse events		
	Melatonin period	Placebo period	Total during treatment
Headache	4	8	12
Drowsiness	1	1	2
Nightmares	3	1	4
Infections	11	11	22
Mental health issues	2	1	3
Gut problems	10	9	19
Skin problems	5	1	6
Joint problems	2	2	4
Other	11	13	24

Serious adverse events

Two serious adverse events (SAEs) occurred in participants allocated to Group B (placebo first) during the washout period (i.e. following placebo treatment) and were considered to be unrelated to trial drug treatment.