Clinical trial results:
The effect of MElatonin on Depression, Anxiety, CIrcadian and Sleep disturbances in patients after acute myocardial syndrome

Summary

EudraCT number	2015-002116-32
Trial protocol	DK
Global end of trial date	15 August 2017

Results information

Result version number	v1 (current)
This version publication date	04 March 2021
First version publication date	04 March 2021

Trial information

Trial identification

Sponsor protocol code	MTM-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02451293
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Center for Surgical Science, Department of Surgery Zealand University Hospital, Køge
Sponsor organisation address	Lykkebækvej 1, Køge, Denmark, 4600
Public contact	Michael Tvilling Madsen, Zealand University Hospital, +4500 27857247, michael_madsen88@hotmail.com
Scientific contact	Michael Tvilling Madsen, Zealand University Hospital, +4500 27857247, michael_madsen88@hotmail.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2017
Global end of trial reached?	Yes
Global end of trial date	15 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to investigate whether prophylactic treatment with melatonin has an effect on depressive symptoms.

Protection of trial subjects:

Participants were monitored with questionnaires throughout the trial and no harm came to the patient in relation to this outcome assessment beside the time used to fill out the questionnaires. Patients had their blood drawn three times throughout the trial, which was associated with minimal discomfort. Furthermore, non-invasive active monitor so called Actigraph was applied to the patient for a two-week period. The discomfort related to this is equivalent to wearing a wrist worn watch.

Background therapy:

Patients were treated according to the national Danish guidelines for acute coronary syndrom (https://nbv.cardio.dk/aks) and cardiac rehabilitation (https://nbv.cardio.dk/hjerterehabilitering).

Evidence for comparator:

Since there is no usual care for prevention of depression following acute coronary syndrome the comparator was a placebo pill. It is common practice in double-blinded randomized trials to apply placebo pill in the current context.

Actual start date of recruitment	18 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 252
Worldwide total number of subjects	252
EEA total number of subjects	252

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	138
From 65 to 84 years	110
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Recruitment were performed on 5 clinical departments of cardiology at Zealand, Denmark. Patients were contacted following admission for ACS before discharge and follow-up contact were made during cardiac rehabilitation during the outpatient clinic. First data of were conducted in Februar 2016 and last inclusion was in May 2017.

Pre-assignment

Screening details:

Screening was performed during weekdays at each department by study investigator. If patients were eligible patients at during primary admissions. Contact information were exchanged for later contact to plan potential inclusion depending on patient consent. . If patient were interest an inclusion interview was planned during outpatient visit.

Pre-assignment period milestones

Number of subjects started	252
Number of subjects completed	252

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The Regional Pharmacy in Region Zealand Denmark handled randomization and allocation concealment. A randomization was produced by applying online software (http://www.randomization.com/) and used a 1:1 allocation in blocks containing six participants (3 melatonin and 3 placebo). To assure allocation concealment during the trial the Regional Pharmacy produced two sets of coded envelopes (an opaque, sealed envelope for each patient, containing the randomization code for each patient).

Arms

Are arms mutually exclusive?	Yes
Arm title	Melatonin 25 mg

Arm description:

25 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Arm type	Experimental
Investigational medicinal product name	Bio-Melatonin
Investigational medicinal product code	ATC: NO5CH01
Other name	Marketing authorisation number - OGYI-T-8974/01/02/03, CAS 73-31-4
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 12,5 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks.

Arm title	Placebo

Arm description:

Placebo tablet (oral) administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	PL1
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 12,5 mg placebo oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks.

Number of subjects in period 1	Melatonin 25 mg	Placebo
Started	126	126
Completed	126	126

Period 2

Period 2 title	Day 14
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The Regional Pharmacy in Region Zealand Denmark handled randomization and allocation concealment. A randomization was produced by applying online software (http://www.randomization.com/) and used a 1:1 allocation in blocks containing six participants (3 melatonin and 3 placebo). To assure allocation concealment during the trial the Regional Pharmacy produced two sets of coded envelopes (an opaque, sealed envelope for each patient, containing the randomization code for each patient).

Arms

Are arms mutually exclusive?	Yes
Arm title	Melatonin 25 mg

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2 x 12,5 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks.

Arm title	Placebo

Arm description:

Placebo tablet (oral) administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PL1
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 12,5 mg placebo oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks.

Number of subjects in period 2	Melatonin 25 mg	Placebo
Started	126	126
Completed	116	121
Not completed	10	5
Consent withdrawn by subject	5	3
Other trial	1	-
Adverse event, non-fatal	3	1
Prolonged hospitalization	1	-
Coronary artery bypass graft	-	1

Period 3

Period 3 title	Day 84
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The Regional Pharmacy in Region Zealand Denmark handled randomization and allocation concealment. A randomization was produced by applying online software (http://www.randomization.com/) and used a 1:1 allocation in blocks containing six participants (3 melatonin and 3 placebo). To assure allocation concealment during the trial the Regional Pharmacy produced two sets of coded envelopes (an opaque, sealed envelope for each patient, containing the randomization code for each patient).

Arms

Are arms mutually exclusive?	Yes
Arm title	Melatonin 25 mg

Arm description:

25 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Arm type	Experimental

Investigational medicinal product name	Bio-Melatonin
Investigational medicinal product code	ATC: NO5CH01
Other name	Marketing authorisation number - OGYI-T-8974/01/02/03, CAS 73-31-4
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 12,5 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks.

Arm title	Placebo

Arm description:

Placebo tablet (oral) administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PL1
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 12,5 mg placebo oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks.

Number of subjects in period 3	Melatonin 25 mg	Placebo
Started	116	121
Completed	107	117
Not completed	9	4
Consent withdrawn by subject	4	2
Adverse event, non-fatal	1	1
Prolonged hospitalization	1	-
Acute myocardial infaction	2	-
Depression	1	-
Acute myocardial infarction	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Melatonin 25 mg
Reporting group description:	
25 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablet (oral) administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.	

Reporting group values	Melatonin 25 mg	Placebo	Total
Number of subjects	126	126	252
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	62.9	62.10	
standard deviation	± 11.32	± 10.81	-
Gender categorical			
Units: Subjects			
Female	31	25	56
Male	95	101	196
Family history of mental disorder			
Units: Subjects			
Yes	22	25	47
No	104	101	205
Cardiac diagnosis			
Type of acute coronary syndrome			
Units: Subjects			
STEMI	53	62	115
NSTEMI	66	58	124
UAP	7	6	13
Percutaneus coronary intervention			
Units: Subjects			
Yes	98	99	197
No	28	27	55
NYHA Class			

Units: Subjects			
NYHA I	86	92	178
NYHA II	34	32	66
NYHA III	6	2	8
Medicine compliance day 14			
Medicine compliance above 75% at day 14			
Units: Subjects			
Above 75%	116	121	237
Below 75%	10	5	15
Medicine compliance day 84			
Medicine compliance above 75% at day 84			
Units: Subjects			
Below 75%	19	13	32
Above 75%	107	113	220

End points

End points reporting groups

Reporting group title	Melatonin 25 mg

Reporting group description:

25 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Reporting group title	Placebo

Reporting group description:

Placebo tablet (oral) administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Reporting group title	Melatonin 25 mg

Reporting group description:

25 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Reporting group title	Placebo

Reporting group description:

Placebo tablet (oral) administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Reporting group title	Melatonin 25 mg

Reporting group description:

25 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Reporting group title	Placebo

Reporting group description:

Placebo tablet (oral) administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Primary: Major Depression Inventory

End point title	Major Depression Inventory

End point description:

The primary outcome of the trial was the Major Depressive Inventory (MDI) and is a self-rating scale consisting of 12 questions covering the ICD-10 criteria of depression. The MDI has a maximum score of 50 points indicating a maximum number of depressive symptoms. Each question supplies between 0 or 5 points; however, for subsets of question 8 and 10 (restlessness/subdued and appetite) only the highest score counts.

End point type	Primary

End point timeframe:

Day 0, Day 14 and Day 84.

End point values	Melatonin 25 mg	Placebo	Melatonin 25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	126	116	121
Units: Points				
arithmetic mean (confidence interval 95%)	6.18 (5.32 to 7.05)	5.98 (5.19 to 6.77)	5.95 (5.02 to 6.87)	5.10 (4.30 to 5.80)

End point values	Melatonin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	117		
Units: Points				
arithmetic mean (confidence interval 95%)	3.54 (2.76 to 4.32)	4.10 (3.23 to 4.97)		

Statistical analyses

Statistical analysis title	Students T-test - unpaired
Statistical analysis description: intergroups comparison at earch period 1-3.	
Comparison groups	Melatonin 25 mg v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Primary: Major depression inventory (Depression Yes/No)

End point title	Major depression inventory (Depression Yes/No)
End point description: Depression (MDI score≥21) during follow-up during the MEDACIS trial on available data	
End point type	Primary
End point timeframe: Day 0, Day 14 and Day 84.	

End point values	Melatonin 25 mg	Placebo	Melatonin 25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	126	121	116
Units: Depression				
Depression	0	0	2	0
No depression	126	126	114	121

End point values	Melatonin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	117		
Units: Depression				
Depression	1	2		
No depression	107	117		

Statistical analyses

Statistical analysis title	Fischers exact test
Statistical analysis description: Fischers exact test at period 1-3	
Comparison groups	Melatonin 25 mg v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Fisher exact
Parameter estimate	number of events

Secondary: Hospital Anxiety and depression scale - Anxiety

End point title	Hospital Anxiety and depression scale - Anxiety
End point description: The Hospital Anxiety and Depression Scale (HADS) was administered in the current trial three times (at baseline, 2 and 12 weeks) (Zigmond and Snaith, 1983). The HADS was developed as a screening tool for anxiety and depression in a hospital setting and supplies a score of 0–21. A cut-off of 8 points or higher on the HADS-D or HADS-A subscales gives a sensitivity and specificity of 0.8, and this cut-off was applied in the current study.	
End point type	Secondary
End point timeframe: Day 0, Day 14 and Day 84	

End point values	Melatonin 25 mg	Placebo	Melatonin 25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	126	116	121
Units: Points				
arithmetic mean (confidence interval 95%)	2.98 (2.50 to 3.46)	2.81 (2.28 to 3.34)	2.53 (2.01 to 3.06)	2.39 (1.86 to 2.93)

End point values	Melatonin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Points				
arithmetic mean (confidence interval 95%)	1.75 (1.19 to 2.03)	2.28 (1.68 to 2.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Anxiety and depression scale - Depression

End point title	Hospital Anxiety and depression scale - Depression

End point description:

The Hospital Anxiety and Depression Scale (HADS) was administered in the current trial three times (at baseline, 2 and 12 weeks) (Zigmond and Snaith, 1983). The HADS was developed as a screening tool for anxiety and depression in a hospital setting and supplies a score of 0–21. A cut-off of 8 points or higher on the HADS-D or HADS-A subscales gives a sensitivity and specificity of 0.8, and this cut-off was applied in the current study.

End point type	Secondary

End point timeframe:

Day 0, Day 14 and Day 84

End point values	Melatonin 25 mg	Placebo	Melatonin 25 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	126	116	121
Units: Point				
arithmetic mean (confidence interval 95%)	1.68 (1.31 to 2.05)	1.35 (1.00 to 1.70)	1.61 (1.19 to 2.03)	1.11 (0.76 to 1.47)

End point values	Melatonin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	117		
Units: Point				
arithmetic mean (confidence interval 95%)	1.19 (0.80 to 1.57)	1.48 (1.09 to 1.88)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported during the conduct of the trial and until 24 hours after intake of last study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Melatonin 25 mg

Reporting group description:

25 mg melatonin oral tablet administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Reporting group title	Placebo

Reporting group description:

Placebo tablet (oral) administered approximately 1 hour before bedtime for a duration of 12 weeks following acute coronary syndrome.

Serious adverse events	Melatonin 25 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 126 (13.49%)	18 / 126 (14.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Cerebral ischaemia	Additional description: Transitory cerebral ischaemia		
subjects affected / exposed	1 / 126 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction	Additional description: NSTEMI during the conduct of the trial		
subjects affected / exposed	2 / 126 (1.59%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 126 (1.59%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anginal equivalent	Additional description: Admission of suspected acute myocardial infarction		

subjects affected / exposed	2 / 126 (1.59%)	6 / 126 (4.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 126 (0.79%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery bypass			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve disease			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	3 / 126 (2.38%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	10 / 126 (7.94%)	15 / 126 (11.90%)	
occurrences causally related to treatment / all	0 / 10	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 126 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Gout			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 126 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Discomfort			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep disorder			
subjects affected / exposed	11 / 126 (8.73%)	9 / 126 (7.14%)	
occurrences causally related to treatment / all	0 / 11	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle discomfort			
subjects affected / exposed	13 / 126 (10.32%)	16 / 126 (12.70%)	
occurrences causally related to treatment / all	0 / 13	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry mouth			
subjects affected / exposed	12 / 126 (9.52%)	7 / 126 (5.56%)	
occurrences causally related to treatment / all	0 / 12	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diverticulitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	15 / 126 (11.90%)	12 / 126 (9.52%)	
occurrences causally related to treatment / all	0 / 27	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	3 / 126 (2.38%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 126 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 126 (0.79%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 126 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 126 (0.00%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Influenza			
subjects affected / exposed	9 / 126 (7.14%)	11 / 126 (8.73%)	
occurrences causally related to treatment / all	0 / 9	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Melatonin 25 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 126 (11.11%)	18 / 126 (14.29%)	
Cardiac disorders			
Orthostatic hypotension			
subjects affected / exposed	5 / 126 (3.97%)	4 / 126 (3.17%)	
occurrences (all)	5	4	
Nervous system disorders			
Sleep deficit			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 126 (1.59%)	0 / 126 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	0 / 126 (0.00%)	1 / 126 (0.79%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	2 / 126 (1.59%)	0 / 126 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	6 / 126 (4.76%)	2 / 126 (1.59%)	
occurrences (all)	6	2	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 126 (0.79%)	0 / 126 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Itching scar			
subjects affected / exposed	1 / 126 (0.79%)	8 / 126 (6.35%)	
occurrences (all)	1	8	
Rash			
subjects affected / exposed	3 / 126 (2.38%)	2 / 126 (1.59%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31586772

http://www.ncbi.nlm.nih.gov/pubmed/31355944

http://www.ncbi.nlm.nih.gov/pubmed/28228148