EU Clinical Trials Register

Clinical trial results:
Diabetic retinopathy: Effects of melatonin treatment on visual functions and circadian rhythm.

Summary

EudraCT number	2015-003955-23
Trial protocol	DK
Global end of trial date	07 July 2021

Results information

Result version number	v1 (current)
This version publication date	20 March 2023
First version publication date	20 March 2023
Summary attachment (see zip file)	Trial summary_Eudract no 2015-003955-23 (Trial summary_Eudract no 2015-003955-23.pdf)

Trial information

Trial identification

Sponsor protocol code	DR2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03478306
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Valdemar Hansens vej 1-13, Glostrup, Denmark, 2600
Public contact	Research laboratory section 37, Dept. of Ophthalmology, Rigshospitalet – Glostrup, +45 31614923, shakoor.ba-ali.04@regionh.dk
Scientific contact	Research laboratory section 37, Dept. of Ophthalmology, Rigshospitalet – Glostrup, +45 31614923, shakoor.ba-ali.04@regionh.dk

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	26 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2021
Global end of trial reached?	Yes
Global end of trial date	07 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effects of melatonin treatment on visual functions and circadian rhythm in diabetic patients with or without diabetic retinopathy.

Protection of trial subjects:

The physical and mental health of each subject was assessed during each visit, i.e. at basline and after treatments. In addition each subject were consulted through phone calls 3 days after the first treatmente date to assess their physical and mental health. Moreover, blood pressure and puls were measured during each visit. Also, blood tests were taken at baseline and at the end of each trial arms to assess red/white blood count, lever and kidney function.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	22
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Diabetic subjects with and without non-proliferative diabetic retinopathy were recruited from march 27th 2018 to april 1st 2021 from Steno Diabetes Center Copenhagen or Department of Ophthalmology Rigshospitalet-Glostrup encompassing the capital region in Denmark

Pre-assignment

Screening details:

Inclusion Criteria:
- Diabetic patients
- Age range 40-75 years
- Participant should be legally competent

Exclusion Criteria:
- Other known eye disease.
- Eye disease manifestation during ocular examination.
- Competing neurologic and systemic conditions affecting retina.
- Use of any drugs influencing

Pre-assignment period milestones

Number of subjects started	31
Number of subjects completed	31

Period 1

Period 1 title	Baseline 1
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 subjects were randomized by a central third party, Glostrup pharmacy.

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline 1 for melatonin

Arm description:

Baseline for melatonin group 1st period

Arm type	Experimental
Investigational medicinal product name	Melatonin
Investigational medicinal product code	SUB11496MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Basline for melatonin group

Arm title	Baseline 1 for placebo

Arm description:

Baseline for placebo group 1st period

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Baseline for placebo group

Number of subjects in period 1	Baseline 1 for melatonin	Baseline 1 for placebo
Started	16	15
Completed	15	14
Not completed	1	1
Consent withdrawn by subject	1	1

Period 2

Period 2 title	Treatment 1
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 participants were randomized into two treatment arms by an independent party, Glostrup pharmacy A/S, and the lists of the randomization were keep in a closed envelope, which was locked in a box. The melatonin- and placebo tablets were manufactured by the Glostrup Pharmacy A/S and was identical in form, taste and color. The subjects received a bottle with tablets for each treatment arm. Neither the investigator nor the subjects were aware of the active ingredients of the tablets.

Arms

Are arms mutually exclusive?	Yes
Arm title	Melatonin 1

Arm description:

Subjects recieved 1 tablet melatonin 4 mg every evening 2 hours before bedtime in 3 weeks.

Arm type	Experimental
Investigational medicinal product name	Melatonin
Investigational medicinal product code	SUB11496MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet melatonin 4 mg every evening 2 hours before bedtime in 3 weeks.

Arm title	Placebo 1

Arm description:

Subjects recieved 1 tablet placebo every evening 2 hours before bedtime in 3 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects recieved 1 tablet placebo every evening 2 hours before bedtime in 3 weeks.

Number of subjects in period 2	Melatonin 1	Placebo 1
Started	15	14
Completed	15	14

Period 3

Period 3 title	Baseline 2
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:

see previous periods

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline 2 for melatonin

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Baseline 2 for placebo

Arm description: -

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

Dosage and administration details:

1 tablet placebo 2 hours before bedtime

Number of subjects in period 3	Baseline 2 for melatonin	Baseline 2 for placebo
Started	14	15
Completed	14	15

Period 4

Period 4 title	Treatment 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo 2

Arm description: -

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

Dosage and administration details:

1 tablet placebo every evening 2 hours prior to bedtime for 3 weeks.

Arm title	Melatonin 2

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Melatonin
Investigational medicinal product code	SUB11496MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet melatonin 4 mg every evening 2 hours prior to bedtime for 3 weeks.

Number of subjects in period 4	Placebo 2	Melatonin 2
Started	15	14
Completed	14	14
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Baseline 1

Reporting group description: -

Reporting group values	Baseline 1	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
Age continuous			
age range 40-74			
Units: years			
arithmetic mean	61		
standard deviation	± 8	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	21	21	
BMI Units: kilogram(s)/square metre			
arithmetic mean	29		
standard deviation	± 5	-	
blood pressure systolic Units: mmHg			
arithmetic mean	138		
standard deviation	± 20	-	
Blood pressure - diastolic Units: mmHg			
arithmetic mean	77		
standard deviation	± 10	-	
Alcohol concumption Units: unit/week			
arithmetic mean	7		
standard deviation	± 6	-	
HbA1c Units: mmol/mol			
arithmetic mean	60		
standard deviation	± 15	-	
Glucose			
Plasma glucose level at the visiting day.			
Units: mmol/L			
arithmetic mean	10		
standard deviation	± 4	-	
Hemoglobin			
plasma hemoglobin level during the visit			
Units: mol/L			
arithmetic mean	11		

standard deviation	± 11	-	
Albumin			
Plasma albumin level prior to treatment start.			
Units: g/dL			
arithmetic mean	44		
standard deviation	± 3	-	
Bilirubin			
Plasma bilirubin level prior to treatment start.			
Units: µmol/l			
arithmetic mean	8		
standard deviation	± 3	-	
ALAT			
Plasma alanintransaminase			
Units: U/L			
arithmetic mean	31		
standard deviation	± 11	-	
Creatinine			
Units: µmol/L			
arithmetic mean	82		
standard deviation	± 27	-	
Cholesterol, total			
Units: mmol/L			
arithmetic mean	4		
standard deviation	± 1	-	
HDL			
High Density Lipoprotein Cholesterol level prior to treamtent start.			
Units: mmol/L			
arithmetic mean	1.5		
standard deviation	± 0.6	-	
LDL			
Low Density Lipoprotein cholesterol measured prior to treatment start			
Units: mmol/L			
arithmetic mean	1.8		
standard deviation	± 1.0	-	
VLDL			
Very Low Density Lipoprotein cholesterol measured prior to treatment start			
Units: mmol/			
arithmetic mean	0.9		
standard deviation	± 0.4	-	
Triclycerides			
Plasma triglycerides measured prior to treatment start			
Units: mmol/L			
arithmetic mean	2.4		
standard deviation	± 1.5	-	
Diabetes duration			
Units: year			
arithmetic mean	31		
standard deviation	± 10	-	
Visual acuity			
Units: ETDRS			
arithmetic mean	85.1		
standard deviation	± 6.8	-	

Intraocular pressure (IOP) Units: mmHg			
arithmetic mean	14.1		
standard deviation	± 3.0	-	

End points

End points reporting groups

Reporting group title	Baseline 1 for melatonin
Reporting group description:	
Baseline for melatonin group 1st period	
Reporting group title	Baseline 1 for placebo
Reporting group description:	
Baseline for placebo group 1st period	
Reporting group title	Melatonin 1
Reporting group description:	
Subjects recieved 1 tablet melatonin 4 mg every evening 2 hours before bedtime in 3 weeks.	
Reporting group title	Placebo 1
Reporting group description:	
Subjects recieved 1 tablet placebo every evening 2 hours before bedtime in 3 weeks.	
Reporting group title	Baseline 2 for melatonin
Reporting group description: -	
Reporting group title	Baseline 2 for placebo
Reporting group description: -	
Reporting group title	Placebo 2
Reporting group description: -	
Reporting group title	Melatonin 2
Reporting group description: -	

Primary: OP1

End point title	OP1
End point description:	
Oscillatory potential 1	
End point type	Primary
End point timeframe:	
Before treatment	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: µV				
arithmetic mean (standard deviation)	19 (± 14)	12 (± 5)	19 (± 10)	11 (± 7)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14

Units: µV				
arithmetic mean (standard deviation)	16 (± 8)	19 (± 13)	19 (± 7)	15 (± 4)

Statistical analyses

Statistical analysis title	Wilcoxon signed-rank test
Comparison groups	Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Primary: OP2

End point title	OP2

End point description:

Oscillatory potential amplitude as measure of the amacrines in retina.

End point type	Primary

End point timeframe:

OP1 measured before (baseline) and after treatment

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: µV				
arithmetic mean (standard deviation)	60 (± 17)	53 (± 26)	55 (± 28)	53 (± 26)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: µV				
arithmetic mean (standard deviation)	50 (± 18)	71 (± 28)	59 (± 18)	51 (± 25)

Statistical analyses

Statistical analysis title	Wilcoxon signed-rank test
Comparison groups	Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Primary: OP3

End point title	OP3

End point description:

Oscillatory potential 2, measured with ff-ERG.

End point type	Primary

End point timeframe:

Befor treatment

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: µV				
arithmetic mean (standard deviation)	19 (± 13)	23 (± 11)	23 (± 16)	20 (± 14)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: µV				
arithmetic mean (standard deviation)	23 (± 12)	24 (± 21)	20 (± 12)	24 (± 8)

Statistical analyses

Statistical analysis title	Wilcoxon signed-rank test
Comparison groups	Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Primary: It1

End point title	It1
End point description:	
Implicit time of the 1st amplitude in ff-ERG	
End point type	Primary
End point timeframe:	
Before and after	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: ms				
arithmetic mean (standard deviation)	20 (± 1)	19 (± 1)	22 (± 5)	19 (± 1)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: ms				
arithmetic mean (standard deviation)	20 (± 4)	20 (± 2)	20 (± 1)	20 (± 1)

Statistical analyses

Statistical analysis title	Wilcoxon signed-rank test
Comparison groups	Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Variability estimate	Standard deviation

Primary: It2

End point title	It2

End point description:

Implicit time of the 1st amplitude in ff-ERG

End point type	Primary

End point timeframe:

Before and after

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: ms				
arithmetic mean (standard deviation)	27 (± 1)	27 (± 1)	29 (± 4)	27 (± 2)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: ms				
arithmetic mean (standard deviation)	27 (± 2)	28 (± 1)	28 (± 1)	27 (± 1)

Statistical analyses

Statistical analysis title	Wilcoxon signed-rank test
Comparison groups	Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Primary: It 3

End point title	It 3
End point description:	
Implicit time of the 1st amplitude in ff-ERG	
End point type	Primary
End point timeframe:	
Before and after	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: ms				
arithmetic mean (standard deviation)	34 (± 2)	33 (± 1)	35 (± 5)	34 (± 3)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: ms				
arithmetic mean (standard deviation)	34 (± 4)	34 (± 1)	34 (± 1)	33 (± 1)

Statistical analyses

Statistical analysis title	Wilcoxon signed-rank test
Comparison groups	Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Secondary: DA0.01 b-wave amplitude

End point title	DA0.01 b-wave amplitude
End point description:	
Dark adapted b-wave amplitdude (rod bipolar cells) measured with ERG.	
End point type	Secondary
End point timeframe:	
Measured before and after treatment	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: µV				
arithmetic mean (standard deviation)	138 (± 57)	171 (± 118)	159 (± 74)	192 (± 80)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: µV				
arithmetic mean (standard deviation)	139 (± 46)	184 (± 92)	163 (± 62)	152 (± 52)

Statistical analyses

No statistical analyses for this end point

Secondary: DA0.01 b-wave implicit time

End point title	DA0.01 b-wave implicit time
End point description:	
Dark adapted b-wave amplitude (rod bipolar cells) measured with ERG (DA0.01 b-wave implicit time)	
End point type	Secondary
End point timeframe:	
Measured before and after treatment	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: ms				
arithmetic mean (standard deviation)	138 (± 57)	94 (± 21)	93 (± 12)	97 (± 8)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: ms				
arithmetic mean (standard deviation)	99 (± 8)	95 (± 13)	94 (± 10)	93 (± 11)

Statistical analyses

No statistical analyses for this end point

Secondary: LA3.0 a-wave amplitude

End point title	LA3.0 a-wave amplitude
End point description:	
Light adapted a-wave amplitude (cone bipolar cells) measured with ERG (LA3.0 a-wave amplitude)	
End point type	Secondary
End point timeframe:	
Measured before and after	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: µV				
arithmetic mean (standard deviation)	24 (± 12)	20 (± 8)	28 (± 16)	22 (± 8)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: µV				
arithmetic mean (standard deviation)	20 (± 6)	24 (± 9)	25 (± 8)	20 (± 8)

Statistical analyses

No statistical analyses for this end point

Secondary: LA3.0 a-wave implicit time

End point title	LA3.0 a-wave implicit time
End point description:	
Light adapted a-wave implicit time measured with ERG.	
End point type	Secondary
End point timeframe:	
Measured before and after	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: ms				
arithmetic mean (standard deviation)	15 (± 1)	15 (± 1)	16 (± 1)	15 (± 1)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: ms				
arithmetic mean (standard deviation)	14 (± 2)	15 (± 1)	15 (± 2)	15 (± 1)

Statistical analyses

No statistical analyses for this end point

Secondary: Pupil size

End point title	Pupil size
End point description:	
Pupillary size (mm) prior to light stimulation, measured with pupillometry.	
End point type	Secondary
End point timeframe:	
measured before and after	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: mm				
arithmetic mean (standard deviation)	5.7 (± 0.8)	5.6 (± 1.0)	5.8 (± 0.9)	5.6 (± 0.9)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: mm				
arithmetic mean (standard deviation)	6.0 (± 1.0)	5.7 (± 0.8)	5.7 (± 0.9)	5.8 (± 1.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal pupillary contraction

End point title	Maximal pupillary contraction

End point description:

Maximal pupillary contraktion in relation to baseline pupillary light size durin glight stimulation. Measured with pupillometer.

End point type	Secondary

End point timeframe:

Measured before and after

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: ratio				
arithmetic mean (standard deviation)	0.6 (± 0.1)	0.6 (± 0.0)	0.6 (± 0.0)	0.6 (± 0.1)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: ratio				

| arithmetic mean (standard deviation) | 0.6 (± 0.1) | 0.6 (± 0.0) | 0.6 (± 0.0) | 0.6 (± 0.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: PIPR_early

End point title	PIPR_early

End point description:

Pupillary contraktion measured 0-10 seconds after termination of blue light stimuli in 20 seconds. Measured with pupillometer.

End point type	Secondary

End point timeframe:

Measured before and after

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: ratio				
arithmetic mean (standard deviation)	0.5 (± 0.1)	0.4 (± 0.1)	0.5 (± 0.1)	0.4 (± 0.1)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: ratio				
arithmetic mean (standard deviation)	0.4 (± 0.1)	0.5 (± 0.1)	0.4 (± 0.1)	0.4 (± 0.1)

Statistical analyses

No statistical analyses for this end point

Secondary: PIPR_late

End point title	PIPR_late

End point description:

Pupillary contraktion measured 10-20 seconds after termination of blue light stimuli in 20 seconds. Measured with pupillometer.

End point type	Secondary

End point timeframe:

Measured before and after treatment

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: ratio				
arithmetic mean (standard deviation)	0.4 (± 0.1)	0.4 (± 0.1)	0.4 (± 0.1)	0.1 (± 0.1)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: ratio				
arithmetic mean (standard deviation)	0.1 (± 0.1)	0.4 (± 0.1)	0.4 (± 0.1)	0.3 (± 0.1)

Statistical analyses

No statistical analyses for this end point

Secondary: PSQI global score

End point title	PSQI global score

End point description:

End point type	Secondary

End point timeframe:

Befor and after treatment

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: Global score				
arithmetic mean (standard deviation)	5.2 (± 3.2)	4.1 (± 3.5)	6.4 (± 3.0)	5.1 (± 3.5)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14

Units: Global score				
arithmetic mean (standard deviation)	3.8 (± 2.6)	6.0 (± 3.6)	4.8 (± 3.1)	4.3 (± 3.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Melatonin at 04:00 AM

End point title	Melatonin at 04:00 AM
End point description:	
Salivary melatonin level measured at 04:00 AM	
End point type	Secondary
End point timeframe:	
Measured at 04:00 AM befor and after treatment.	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: Pg/mL				
arithmetic mean (standard deviation)	35.5 (± 43.5)	10.6 (± 14.7)	7.0 (± 12.8)	4.4 (± 4.2)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: Pg/mL				
arithmetic mean (standard deviation)	5.2 (± 7.4)	11.3 (± 14.7)	7.0 (± 12.7)	26.7 (± 18.6)

Statistical analyses

No statistical analyses for this end point

Secondary: p-Glucose at 04:00 AM

End point title	p-Glucose at 04:00 AM
End point description:	
End point type	Secondary
End point timeframe:	
Capillary glucose level measured at 04:00 AM	

End point values	Melatonin 1	Placebo 1	Baseline 1 for melatonin	Baseline 1 for placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	15
Units: mmol/L				
arithmetic mean (standard deviation)	7.2 (± 1.9)	8.2 (± 3.7)	7.6 (± 2.5)	8.2 (± 2.2)

End point values	Baseline 2 for melatonin	Baseline 2 for placebo	Placebo 2	Melatonin 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	14	14
Units: mmol/L				
arithmetic mean (standard deviation)	9.0 (± 3.9)	7.0 (± 2.4)	7.4 (± 1.5)	9.0 (± 3.2)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:	
No serious adverse events (SAE) or Serious Adverse (Drug) Reaction (SAR) were observed	
Assessment type	Non-systematic

Dictionary used

Dictionary name	Annual report
Dictionary version	1

Frequency threshold for reporting non-serious adverse events: 1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no non-serious adverse events recorded for these results.

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? Yes

Date	Interruption	Restart date
14 November 2019	The recruitment process was interrupted by Danish Medicines Agency due to suspicious laboratory analysis in the process of melatonin production by our external lab-analyse provider. After further investigation the Danish Medicines Agency found that the lab-analysis was conducted properly, and the research was allowed to restart.	09 March 2020

Notes:

Limitations and caveats

None reported