Clinical trial results:
Multicenter, randomized, double-blind, placebo controlled trial of 2 mg melatonin for circadian phase adjustment and improvement of metabolic control in night shift workers

Summary

EudraCT number	2012-005254-30
Trial protocol	DE
Global end of trial date	07 March 2017

Results information

Result version number	v1 (current)
This version publication date	07 September 2022
First version publication date	07 September 2022

Trial information

Trial identification

Sponsor protocol code	EuRhythDiaII

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02108353
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center Hamburg-Eppendorf (UKE)
Sponsor organisation address	Martinistrasse 52, Hamburg, Germany,
Public contact	Prof. Dr. Rainer Boeger , Department of Clinical Pharmacology and Toxicoloy University Medical Center Hamburg-Eppendorf, +49 40741059759, boeger@uke.de
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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	31 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2014
Global end of trial reached?	Yes
Global end of trial date	07 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate in night shift workers the efficacy of melatonin over 12 weeks to a) improve metabolic control and b) regulate expression patterns of genes involved in the regulation of metabolism and circadian rhythm

Protection of trial subjects:

Measures were taken to minimize invasive sampling for all subjects. Patient visits were coordinate study requirements with the working schedules to reduce conflicts with daily working life.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2014
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	Germany: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Individuals were eligible if they were night shift workers on regular night shifts with at least four night shifts per month; if they had been on regular night shifts for at least six months before inclusion into the study; if they were above the age of 18 inclusive.

Pre-assignment

Screening details:

Individuals were excluded if they were pregnant or breast-fedding, had a history of physical or psychiatric illness , known autoimmune disease, evidence of relevant renal insufficiency (GFR < 60 mL/min), liver injury (AST, ALT, GGT, Ap, or bilirubin elevated), intolerance to study products, galactose intolerance, or used melatonin before.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	melatonin

Arm description:

Melatonin sustained release 2 mg tablets (Circadin) once daily 0.5-1 hour before going to bed

Arm type	Experimental
Investigational medicinal product name	Circadin 2 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One table once daily 0.5-1 hour before going to bed.

Arm title	Placebo

Arm description:

One tablet of placebo per day 0.5-1 hour before going to bed

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:

one tablet once daily 0.5-1 hour before going to bed

Number of subjects in period 1	melatonin	Placebo
Started	17	19
Completed	17	18
Not completed	0	1
Adverse event, non-fatal	-	1

Period 2

Period 2 title	Wash-out period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Arm title	No active treatment

Arm description:

All study poarticipants, both ffrom the melatonin and placebo groups during the inervention phase, were allocated to "No active treatment" in the second half of the study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	No active treatment
Started	35
Completed	35

Baseline characteristics

Reporting groups	
Reporting group title	melatonin
Reporting group description:	
Melatonin sustained release 2 mg tablets (Circadin) once daily 0.5-1 hour before going to bed	
Reporting group title	Placebo
Reporting group description:	
One tablet of placebo per day 0.5-1 hour before going to bed	

Reporting group values	melatonin	Placebo	Total
Number of subjects	17	19	36
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	38.3	34.8	
standard deviation	± 11.6	± 11.5	-
Gender categorical Units: Subjects			
Female	12	9	21
Male	5	10	15

End points

End points reporting groups

Reporting group title	melatonin
Reporting group description:	
Melatonin sustained release 2 mg tablets (Circadin) once daily 0.5-1 hour before going to bed	
Reporting group title	Placebo
Reporting group description:	
One tablet of placebo per day 0.5-1 hour before going to bed	
Reporting group title	No active treatment
Reporting group description:	
All study poarticipants, both ffrom the melatonin and placebo groups during the inervention phase, were allocated to "No active treatment" in the second half of the study.	
Subject analysis set title	primary endpoint
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects that completed at least visits 1 (baseline) and 2 (after 12 weeks of intervention).	

Primary: serum glucose during OGTT

End point title	serum glucose during OGTT
End point description:	
AUC of the serum glucose over time during OGTT (0-120 min)	
End point type	Primary
End point timeframe:	
baseline, 12 weeks, 24 weeks	

End point values	melatonin	Placebo	No active treatment	primary endpoint
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	12	23	24
Units: mg/dL*min				
arithmetic mean (standard deviation)	13854 (± 2741)	14924 (± 3181)	13633 (± 2561)	14393 (± 2588)

Attachments (see zip file)	AUC of serum glucose/2022-08-22 - AUC Glucose.tif

Statistical analyses

Statistical analysis title	One-way ANOVA
Comparison groups	melatonin v Placebo v No active treatment v primary endpoint

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 weeks (12 weeks of double-blind intervention, followed by 12 weeks of wash-out)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0
Reporting groups	
Reporting group title	melatonin
Reporting group description: Melatonin sustained release 2 mg tablets (Circadin) once daily 0.5-1 hour before going to bed	
Reporting group title	Placebo
Reporting group description: One tablet of placebo per day 0.5-1 hour before going to bed	

Serious adverse events	melatonin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
tibial plateau fracture			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	melatonin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)	5 / 13 (38.46%)	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vascular disorders			

Vascular test abnormal subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 13 (0.00%) 0	
Cardiac disorders Cardiac disorder subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 5	0 / 13 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	9 / 14 (64.29%) 11	4 / 13 (30.77%) 8	
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	9 / 14 (64.29%) 9	2 / 13 (15.38%) 2	
Musculoskeletal and connective tissue disorders Musculoskeletal disorder subjects affected / exposed occurrences (all)	8 / 14 (57.14%) 8	0 / 13 (0.00%) 0	
Infections and infestations Infection subjects affected / exposed occurrences (all)	8 / 14 (57.14%) 8	3 / 13 (23.08%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2013	Inclusion Criteria.: Number of required night shifts was changed to 4 and "Signed and written in-formed consent" was added. "Pregnancy and breast feeding" was changed in "Pregnancy or breast feeding" as Exclusion Criteria. 72 h blood glucose monitoring" was deleted from the protocol. Total blood amount was adapted. Urine pregnancy test for female subjects was added to the Screening as well as to every ambulato-ry visit. Intrauterine devices were specified without hormonal component and and oral contraceptives were deleted as Concomitant Therapy. The study visit schedule was changed in 3-7 days after the end of the night shift and the in-patient-period was set at 26 hours. 24 h Actigraphy Measurement was prolonged to 72 h. Screening and follow-up were deleted from vital signs.
22 July 2014	Inclusion Criteria: "Evidence of impaired fasting glucose or impaired glucose tolerance at screening (applicable for 50% of the participants)." was deleted. The treatment administration for consecutive night shifts was defined. The determination of FSH levels in female subjects >50 years was deleted, thus an urine pregnancy test to exclude pregnancy is performed in all female subjects. New clinically significant abnormal findings, which occur after the first dosing are captured as AE. An acceptable form of contraception as requirement for all sexually-active females of child-bearing and non-child bearing potential was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The anticipated number of study subjects was not reached.

Notes: