



## Clinical trial results:

### Chronotherapeutic lifestyle intervention for diabetes and obesity to reset the circadian rhythm and improve cardiometabolic risk in the European population

#### Summary

EudraCT number	2012-005255-17
Trial protocol	GB
Global end of trial date	01 November 2017

#### Results information

Result version number	v1 (current)
This version publication date	03 January 2020
First version publication date	03 January 2020
Summary attachment (see zip file)	Eurythdia Final Report (Final Report- Eurythdia Specific information.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	ED14/11124
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##### Additional study identifiers

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

Notes:

##### Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Worsley Building, Leeds, United Kingdom, LS2 9LN
Public contact	Clare Skinner, University of Leeds, 0113 3434897, c.e.skinner@leeds.ac.uk
Scientific contact	Clare Skinner, University of Leeds, 0113 3434897, c.e.skinner@leeds.ac.uk

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	23 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 November 2016
Global end of trial reached?	Yes
Global end of trial date	01 November 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

to investigate the effectiveness of 6 months of randomization to melatonin therapy or placebo as a chronotherapeutic intervention for individuals at high risk of development of T2DM. This will be carried out by analysing the influence of these interventions on glucose regulation, insulin resistance, cardiometabolic function and markers of central and peripheral circadian rhythms, in particular CLOCK mRNA, in healthy first degree relatives of patients with T2DM

Protection of trial subjects:

All information collected during the course of the trial will be kept strictly confidential.

Information will be held securely on paper and electronically at the LIGHT Laboratories, University of Leeds for the duration of the study. Data collection will be performed on paper at each individual participants visit and transcribed to electronic CRFs. The paper copies containing visit data will act as source data.

The investigators will comply with all aspects of the Data Protection Act 1998.

All data obtained in this study should be entered within 7 days of patient contact in the appropriate case report form (eCRF). The investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported in the CRFs and in all required reports. Data reported on the CRF should be consistent with the source documents or the discrepancies should be explained. Paper documentation will be completed in black ink ballpoint pen. Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/ data positioned as close to the original as possible. Any change or correction to should not obscure or eliminate the original entry ("correction fluid" should not be used) and should be dated, initialled and explained (if necessary) by the person making the correction. The investigator has to date and sign off the completed paper documentation including copies of blood results and any other reports. Corrections made after the investigators review and signature of the completed CRF have to be signed and dated by the investigator. If an investigation was not performed, this needs to be indicated with "n.d." (not done).

Prior to start and during the study, when applicable, the investigator will list on the form "Delegation of Tasks" all person to whom he/ she delegated significant trial-related duties.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 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	United Kingdom: 71
Worldwide total number of subjects	71
EEA total number of subjects	71

Notes:

<b>Subjects enrolled per age group</b>	
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)	63
From 65 to 84 years	8
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 4000 patients were screened and 340 relatives of patients could be contacted. A total of 75 patients willing to participate were subsequently randomized in a 1:1 random allocation held by the Leeds Teaching Hospitals Trust pharmacy to either 6 months melatonin therapy or placebo

### Pre-assignment

Screening details:

Inclusion Criteria: Age 18-75, Males, females of non-child bearing potential (post-menopausal or 6 weeks post-sterilisation), females of child-bearing potential,) One or more first degree relative with an established diagnosis of T2DM, Absence of clinical symptoms and signs of infection, Absence of systemic disease.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

Subjects were assigned to a specified treatment according to a random list, which was generated before the beginning of the study. Labelling for the study and blinding according to randomization list will be performed at the UMC-Hamburg Hospital pharmacy; study medication will be shipped from Hamburg to the hospital pharmacy in Leeds for dispensing to study participants.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Melatonin Treatment
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Oral Melatonin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Neurim Pharmaceuticals (Zug, Switzerland [swissinfo@neurim.com](mailto:swissinfo@neurim.com)) will provide 2 mg prolonged-release melatonin tablet: Circadin® 2 mg tablets. Placebo tablets have been developed to match the Circadin® 2 mg tablets in blind clinical studies. They contain the same excipients than those used in the composition of Circadin® 2 mg tablets (Ammonio Methacrylate Copolymer, Type B [Eudragit RSPO®], Calcium Hydrogen Phosphate Dihydrate, Lactose Monohydrate, Silica, Colloidal Anhydrous [Aerosil®], Talcum, Magnesium Stearate), except the ethanol used to dissolve the drug substance and spray it in the dry excipient blend for a partial wet granulation. The tablets (active/placebo) are then obtained by dry-mixing and direct compression. Since the residual ethanol has to be less than 5000 ppm in the final formulation of Circadin® 2 mg tablets, the placebo formulation without ethanol can be considered as equivalent to the Circadin® tablet formulation, except the absence of the drug substance.

<b>Arm title</b>	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

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Dosage and administration details:

Placebo tablets have been developed to match the Circadin® 2 mg tablets in blind clinical studies. They contain the same excipients than those used in the composition of Circadin® 2 mg tablets (Ammonio Methacrylate Copolymer, Type B [Eudragit RSPO®], Calcium Hydrogen Phosphate Dihydrate, Lactose Monohydrate, Silica, Colloidal Anhydrous [Aerosil®], Talcum, Magnesium Stearate), except the ethanol used to dissolve the drug substance and spray it in the dry excipient blend for a partial wet granulation.

<b>Number of subjects in period 1</b>	Melatonin Treatment	Placebo
Started	36	35
Completed	30	30
Not completed	6	5
Consent withdrawn by subject	6	5

## Baseline characteristics

### Reporting groups

Reporting group title	Melatonin Treatment
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Reporting group values	Melatonin Treatment	Placebo	Total
Number of subjects	36	35	71
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	32	31	63
From 65-84 years	4	4	8
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	31	28	59
Male	5	7	12

## End points

### End points reporting groups

Reporting group title	Melatonin Treatment
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

### Primary: The differences in indices of glucose regulation (HbA1c, OGTT, insulin AUC) between intervention and control groups.

End point title	The differences in indices of glucose regulation (HbA1c, OGTT, insulin AUC) between intervention and control groups. <sup>[1]</sup>
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End point description:

End point type	Primary
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End point timeframe:

total study duration will be 26 months, with trial recruitment anticipated to be 12 months. This would leave 14 months for end point analysis.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Please see results paper which has been uploaded and contains details of the statistical analysis.

End point values	Melatonin Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	35		
Units: mmol/mol				
HbA1c	3497	3709		

<b>Attachments (see zip file)</b>	Primary and Secondary outcome tables/primary and secondary
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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

AEs will be collected for all participants and will be evaluated according to the NCRI Common Toxicity Criteria. AEs will be collected for all participants from date of randomisation until 30 days after the last dose of treatment

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

### Reporting groups

Reporting group title	Melatonin Treatment
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

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: No Non-Serious adverts were reported as this was a healthy volunteers trial.

Serious adverse events	Melatonin Treatment	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 36 (8.33%)	0 / 35 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Elective Cholecystectomy			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Appendicitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bilateral Cellulitis	Additional description: Cellulitis in both feet. Treated by GP with oral antibiotics and with IV antibiotics in hospital.		
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Melatonin Treatment	Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2014	Protocol and PIS amended to v3.0 & v2.0
19 June 2015	Participant Information Sheet V4, ,Informed Consent Form V3 Supplementary Protocol added to study
22 June 2015	GP cover letter version 1 dated 22/06/15 Additional info for attaching to letter above, version 1 dated 22nd June 2015
23 June 2015	Protocol updated to version 4.0, dated 18th June 2015

Notes:

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### 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.

None

Notes: