



## Clinical trial results:

### **Prolonged-release melatonin versus placebo for benzodiazepine discontinuation in patients with schizophrenia or bipolar disorder: a randomised, placebo-controlled, blinded trial (the SMART trial)**

#### **Summary**

EudraCT number	2010-024065-46
Trial protocol	DK
Global end of trial date	09 June 2014

#### **Results information**

Result version number	v1 (current)
This version publication date	31 January 2020
First version publication date	31 January 2020
Summary attachment (see zip file)	Summary of results, main paper (SMART main.pdf)

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	2010-379
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01431092
WHO universal trial number (UTN)	-

Notes:

#### **Sponsors**

Sponsor organisation name	Psykiatrisk Center Glostrup
Sponsor organisation address	Nordstjernevej 41, Glostrup, Denmark, 2600
Public contact	Psykiatrisk Center Glostrup, Center for Neuropsykiatrisk Skizofreniforskning, 0045 3864 0840, lone.baandrup@regionh.dk
Scientific contact	Psykiatrisk Center Glostrup, Center for Neuropsykiatrisk Skizofreniforskning, 0045 3864 0840, lone.baandrup@regionh.dk
Sponsor organisation name	Mental Health Center Glostrup
Sponsor organisation address	Ndr. Ringvej 29-67, Glostrup, Denmark, 2600
Public contact	Lone Baandrup, Center for Neuropsychiatric Research, Mental Health Center Glostrup, Ndr. Ringvej 29-67, DK-2600, 20363304 20363304, lone.baandrup@regionh.dk
Scientific contact	Center for Neuropsychiatric Research, Mental Health Center Glostrup, Ndr. Ringvej 29-67, DK-2600, Center for Neuropsychiatric Research, Mental Health Center Glostrup, Ndr. Ringvej 29-67, DK-2600, 20363304 20363304, lone.baandrup@regionh.dk

Notes:

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**Paediatric regulatory details**

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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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	03 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 June 2014
Global end of trial reached?	Yes
Global end of trial date	09 June 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

We assessed if prolonged-release melatonin can facilitate withdrawal of long-term benzodiazepine usage in patients with schizophrenia or bipolar disorder.

Protection of trial subjects:

Frequent follow-up visits and telephone contacts

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Denmark: 86
Worldwide total number of subjects	86
EEA total number of subjects	86

Notes:

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**Subjects enrolled per age group**

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

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	86
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects referred from outpatient mental health care settings

### Pre-assignment

Screening details:

Out of 155 patients screened, 86 were randomised: 42 to PRM versus 44 to placebo. The mean age of the 69 excluded patients was 50.9 years and 40.6% were men. Figure 1 illustrates the flow of participants through the trial (CONSORT diagram). Only one patient was switched to a long-acting benzodiazepine (diazepam) before tapering began.

### 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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Prolonged-release melatonin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	melatonin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule (2 mg) 2 hours before bedtime

<b>Arm title</b>	Placebo
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Arm description: -

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

Dosage and administration details:

1 capsule (2 mg) 2 hours before bedtime

<b>Number of subjects in period 1</b>	Prolonged-release melatonin	Placebo
Started	42	44
Completed	30	32
Not completed	12	12
Adverse event, serious fatal	-	1
Adverse event, non-fatal	2	1
Protocol deviation	10	7
Lack of efficacy	-	3

## Baseline characteristics

### Reporting groups

Reporting group title	Prolonged-release melatonin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Prolonged-release melatonin	Placebo	Total
Number of subjects	42	44	86
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)	42	44	86
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.9	49.4	
standard deviation	± 8.7	± 12.3	-
Gender categorical Units: Subjects			
Female	19	19	38
Male	23	25	48

## End points

### End points reporting groups

Reporting group title	Prolonged-release melatonin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

### Primary: mean daily dosage of benzodiazepines (including benzodiazepine related drugs) at 24 week follow-up

End point title	mean daily dosage of benzodiazepines (including benzodiazepine related drugs) at 24 week follow-up
End point description:	
End point type	Primary
End point timeframe:	
24 weeks follow-up	

End point values	Prolonged-release melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42 <sup>[1]</sup>	44		
Units: mg diazepam equivalents	42	44		

Notes:

[1] - Primary outcome was available for all included subjects

### Statistical analyses

Statistical analysis title	univariate general linear model
Statistical analysis description:	
All analyses were adjusted by the protocol specified stratification variable (baseline diazepam equivalents > 15 mg, yes/no) and the baseline value of the dependent outcome variable. All analyses were intention to treat. Two-sided 5% significance tests were used. We analysed the primary outcome using the univariate general linear model.	
Comparison groups	Prolonged-release melatonin v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Regression, Linear

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 weeks

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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### Reporting groups

Reporting group title	Prolonged-release melatonin
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Prolonged-release melatonin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 42 (28.57%)	10 / 44 (22.73%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Suicidal ideation	Additional description: All reported AEs in the suicidal ideation category were associated with hospitalisation (mostly of brief duration) and were therefore categorised as SAEs.		
subjects affected / exposed	9 / 42 (21.43%)	4 / 44 (9.09%)	
occurrences causally related to treatment / all	0 / 12	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatremia	Additional description: Acute severe hyponatremia with confusion and seizures		
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 12	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Prolonged-release melatonin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 42 (61.90%)	28 / 44 (63.64%)	



Vascular disorders unspecified subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 26	4 / 44 (9.09%) 28	
Nervous system disorders Mood altered subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 26	1 / 44 (2.27%) 28	
Immune system disorders Influenza like illness subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 26	0 / 44 (0.00%) 28	
Gastrointestinal disorders Unspecified subjects affected / exposed occurrences (all)	8 / 42 (19.05%) 26	4 / 44 (9.09%) 28	
Psychiatric disorders somnolence subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 26	2 / 44 (4.55%) 28	
Musculoskeletal and connective tissue disorders Unspecified subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 26	3 / 44 (6.82%) 28	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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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 (see link)
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26086792>