



## Clinical trial results:

**Effects of agomelatine (25 to 50 mg/day) on circadian rhythms in patients with Major Depressive Disorder. An exploratory 6-week open, flexible dose, international multicentre, non comparative study.**

### Summary

EudraCT number	2010-024191-25
Trial protocol	DE AT
Global end of trial date	25 July 2014

### Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	05 August 2015

### Trial information

#### Trial identification

Sponsor protocol code	CL3-20098-080
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	Innovation Therapeutic Pole, Institut de Recherches Internationales Servier, 50 rue Carnot, Suresnes Cedex, France 92284 , +33 1 55 72 43 66, clinicaltrials@servier.com
Scientific contact	Innovation Therapeutic Pole, Institut de Recherches Internationales Servier, 50 rue Carnot, Suresnes Cedex, France 92284 , +33 1 55 72 43 66, clinicaltrials@servier.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	25 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2014
Global end of trial reached?	Yes
Global end of trial date	25 July 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this exploratory study was to assess the effect of agomelatine on the circadian rhythms in Major Depressive Disorder patients by evaluating circadian parameters.

Protection of trial subjects:

The study was performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, Brazil, 2013.

For MDD patients: mandatory withdrawal from the study if hospitalisation for aggravation of depression, high suicide risk or suicide attempt, occurrence of psychotic features, occurrence of pre-defined laboratory criteria and / or signs or symptoms of hepatic dysfunction, pregnancy.  
Other criteria for premature withdrawal from the study: treatment failure, adverse event.

For Healthy Volunteers: withdrawal from the study if serious adverse event or significant alteration in clinical and/or laboratory parameters.

Background therapy: -

Evidence for comparator:

A cohort of Healthy Volunteers was designed to define the circadian parameters in a normal control group without treatment and to allow the comparison of the baseline circadian profile of MDD patients to the circadian profile of non depressed individuals.

Actual start date of recruitment	26 July 2012
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	Poland: 28
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Germany: 132
Worldwide total number of subjects	166
EEA total number of subjects	166

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)	166
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Investigators were psychiatrists.

### Pre-assignment

Screening details:

MDD patients were male or female outpatients fulfilling DSM-IV-TR criteria for MDD, single episode or recurrent (no more than 3), with a current episode of moderate to severe intensity, with HAM-D total score  $\geq 22$ , sum of HAM-D items 5+6  $\geq 3$  and HAD depression score  $\geq 11$ .

Healthy volunteers matched in classes of age and sex to MDD patients.

### Period 1

Period 1 title	Exploratory open period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	MDD patients (agomelatine)

Arm description: -

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

Dosage and administration details:

Agomelatine 25 mg: 1 or 2 tablets daily

<b>Arm title</b>	Healthy Volunteers (no treatment)
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Arm description: -

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	MDD patients (agomelatine)	Healthy Volunteers (no treatment)
Started	123	43
Completed	108	39
Not completed	15	4
Adverse event, non-fatal	2	-
Non-medical reason	8	4
Protocol deviation	4	-
Lack of efficacy	1	-



## Baseline characteristics

### Reporting groups

Reporting group title	MDD patients (agomelatine)
Reporting group description: -	
Reporting group title	Healthy Volunteers (no treatment)
Reporting group description: -	

Reporting group values	MDD patients (agomelatine)	Healthy Volunteers (no treatment)	Total
Number of subjects	123	43	166
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	44.6	41.3	
standard deviation	± 10.6	± 12	-
Gender categorical Units: Subjects			
Female	63	25	88
Male	60	18	78
DLMO			
For comparison at baseline, Dim Light Melatonin Onset (DLMO) was assessed the day before W0 for MDD patients and on D7 for healthy volunteers, by measuring melatonin levels in the saliva. For Healthy Volunteers, DLMO was measured only in the CAS-HV.			
Units: h.min			
arithmetic mean	20.58	0	
standard deviation	± 1.02	± 0	-

### Subject analysis sets

Subject analysis set title	Circadian Analysis Set of MDD patients
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The Circadian Analysis Set of MDD patients (CAS-MDD) was defined as all included patients having taken at least one dose of study medication and having at least one interpretable value at baseline and after baseline for any efficacy criterion related to circadian rhythms.	
Subject analysis set title	Circadian Analysis Set of Healthy Volunteers
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Circadian Analysis Set of Healthy Volunteers (CAS-HV) was defined as all included healthy volunteers having at least one interpretable value for any criterion related to circadian rhythms.

<b>Reporting group values</b>	Circadian Analysis Set of MDD patients	Circadian Analysis Set of Healthy Volunteers	
Number of subjects	117	30	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 44.5 $\pm 10.8$	 41.5 $\pm 12.7$	
Gender categorical Units: Subjects			
Female	59	15	
Male	58	15	
DLMO			
For comparison at baseline, Dim Light Melatonin Onset (DLMO) was assessed the day before W0 for MDD patients and on D7 for healthy volunteers, by measuring melatonin levels in the saliva. For Healthy Volunteers, DLMO was measured only in the CAS-HV.			
Units: h.min arithmetic mean standard deviation	 20.58 $\pm 1.03$	 21.29 $\pm 0.37$	

## End points

### End points reporting groups

Reporting group title	MDD patients (agomelatine)
Reporting group description: -	
Reporting group title	Healthy Volunteers (no treatment)
Reporting group description: -	
Subject analysis set title	Circadian Analysis Set of MDD patients
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The Circadian Analysis Set of MDD patients (CAS-MDD) was defined as all included patients having taken at least one dose of study medication and having at least one interpretable value at baseline and after baseline for any efficacy criterion related to circadian rhythms.	
Subject analysis set title	Circadian Analysis Set of Healthy Volunteers
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The Circadian Analysis Set of Healthy Volunteers (CAS-HV) was defined as all included healthy volunteers having at least one interpretable value for any criterion related to circadian rhythms.	

### Primary: no primary criterion

End point title	no primary criterion <sup>[1]</sup>
End point description:	

End point type	Primary
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End point timeframe:

As the study was an exploratory study, no primary criterion was defined.

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: As the study was an exploratory study, no primary criterion was defined

End point values	Circadian Analysis Set of MDD patients			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: not available	0			

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported all over the study.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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### Reporting groups

Reporting group title	MDD patients (agomelatine)
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Reporting group description: -

Reporting group title	Healthy Volunteers (no treatment)
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Reporting group description: -

Serious adverse events	MDD patients (agomelatine)	Healthy Volunteers (no treatment)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 122 (0.82%)	0 / 43 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 122 (0.82%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 122 (0.82%)	0 / 43 (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: 0.5 %

<b>Non-serious adverse events</b>	<b>MDD patients (agomelatine)</b>	<b>Healthy Volunteers (no treatment)</b>	
Total subjects affected by non-serious adverse events subjects affected / exposed	40 / 122 (32.79%)	3 / 43 (6.98%)	
Vascular disorders Lymphoedema subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1  1 / 122 (0.82%) 1	0 / 43 (0.00%) 0  0 / 43 (0.00%) 0	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)  Polycystic ovaries subjects affected / exposed occurrences (all)	2 / 122 (1.64%) 2  1 / 122 (0.82%) 1	0 / 43 (0.00%) 0  0 / 43 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)  Weight increased subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1  1 / 122 (0.82%) 1	1 / 43 (2.33%) 1  0 / 43 (0.00%) 0	

Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 122 (0.00%) 0	1 / 43 (2.33%) 1	
Cardiac disorders Bradyarrhythmia subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	13 / 122 (10.66%) 16	2 / 43 (4.65%) 2	
Paraesthesia subjects affected / exposed occurrences (all)	3 / 122 (2.46%) 3	0 / 43 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	2 / 122 (1.64%) 2	0 / 43 (0.00%) 0	
Cubital tunnel syndrome subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Dizziness postural subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Dysguesia subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Orthostatic intolerance subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Sedation subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Somnolence subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Tension headache			

subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	3 / 122 (2.46%) 3	0 / 43 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Gastrointestinal motility disorder subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Gastrointestinal tract irritation subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Haemorrhoidal haemorrhage subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	

Myalgia subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 122 (5.74%) 7	0 / 43 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Influenza subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Metabolism and nutrition disorders			
Increased appetite subjects affected / exposed occurrences (all)	2 / 122 (1.64%) 2	0 / 43 (0.00%) 0	
Fluid retention subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	
Myositis subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1	0 / 43 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2012	<ul style="list-style-type: none"><li>-Concerned all countries:<ul style="list-style-type: none"><li>Modification required by the Austria's Ethics Committees, which was to add the withdrawal criterion "CGI item 2 (global improvement) score <math>\geq 5</math> at W4".</li><li>-Addition of a new precaution for saliva sampling (patients should not brush their teeth during salivary sampling), as recommended in literature.</li><li>-Update of non-pre-selection criteria, miscellaneous conditions and method and measurement times, notably regarding the conditions for use of the pill (new contra indications and wearing of a MRI warning wrist band) and the wearing of the belt (for 1 instead 2 days, because recording time lasted for about 21 hours).</li><li>-A footnote of the investigational schedule table was modified to get the liver function tests results before the W4 visit.</li><li>-Administrative changes.</li><li>-Update of the study drug storage conditions, according to the agomelatine SmPC.</li></ul></li></ul>
08 October 2012	<ul style="list-style-type: none"><li>Concerned all countries:<ul style="list-style-type: none"><li>-Inclusion of the centralised analysis of body temperature, heart rate and DLMO, to further minimise bias.</li><li>-Addition of an example "patients not having fully cooperated with baseline examinations" in the non-inclusion criteria.</li><li>-Update of the methods and measurement times, circadian parameters and minimal core body temperature by:<ul style="list-style-type: none"><li>Adding a possible contact between investigator and the patient in order to help him to put and activate the core body temperature and heart rate kit.</li><li>Specifying the procedure for telemetric pill excretion.</li></ul></li><li>Administrative changes.</li></ul></li></ul>
20 December 2013	<ul style="list-style-type: none"><li>-Concerned all sites in Germany:<ul style="list-style-type: none"><li>Addition of efficacy measurements (maximum of core body temperature, mid-range crossing of core body temperature, maximum of heart rate and mid-range crossing of heart rate) for circadian parameters analysis.</li><li>-Update of the protocol in order to include the cohort of healthy volunteers in the main technical protocol, instead of the initially planned sub-study protocol dedicated to the description of healthy volunteers.</li><li>-Adaption of the safety measurements' description in accordance with international guidance.</li><li>-Modification of statistical methodology following the addition of healthy volunteers and the upgrade process for adverse events. The analysis of circadian rhythms in patients of the FAS was also deleted.</li><li>-Administrative changes.</li></ul></li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported