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

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, occurence 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 >=22, sum of HAM-D items 5+6 >= 3 and HAD depression score >= 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
Arm title	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

Arm title	Healthy Volunteers (no treatment)

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.

Reporting group values	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	44.5	41.5	
standard deviation	± 10.8	± 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	20.58	21.29	
standard deviation	± 1.03	± 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[1]

End point description:

End point type	Primary

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2012	-Concerned all countries: Modification required by the Austria's Ethics Committees, which was to add the withdrawal criterion "CGI item 2 (global improvement) score ≥ 5 at W4". -Addition of a new precaution for saliva sampling (patients should not brush their teeth during salivary sampling), as recommended in literature. -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). -A footnote of the investigational schedule table was modified to get the liver function tests results before the W4 visit. -Administrative changes. -Update of the study drug storage conditions, according to the agomelatine SmPC.
08 October 2012	Concerned all countries: -Inclusion of the centralised analysis of body temperature, heart rate and DLMO, to further minimise bias. -Addition of an example "patients not having fully cooperated with baseline examinations" in the non-inclusion criteria. -Update of the methods and measurement times, circadian parameters and minimal core body temperature by: 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. Specifying the procedure for telemetric pill excretion. Administrative changes.
20 December 2013	-Concerned all sites in Germany: 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. -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. -Adaption of the safety measurements' description in accordance with international guidance. -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. -Administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported