Clinical trial results:
Effects of agomelatine versus escitalopram on emotional experiences in outpatients suffering from Major Depressive Disorder. An exploratory, randomised, double-blind, international, multicentre study with parallel groups: agomelatine (25 to 50 mg/day) versus escitalopram (10 to 20 mg/day) over a 6- month period.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-005320-17
Trial protocol	GB
Global end of trial date	03 October 2014

Results information

Result version number	v1 (current)
This version publication date	17 March 2016
First version publication date	17 March 2016

Trial information

Trial identification

Sponsor protocol code	CL3-20098-060

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, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, 33 1 55 72 43 66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, 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	03 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2014
Global end of trial reached?	Yes
Global end of trial date	03 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this exploratory study is to differentiate the effect of two antidepressants, agomelatine versus escitalopram, on the emotional experiences in outpatients suffering from Major Depressive Disorder.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, as revised in Seoul, 2008 and Fortaleza, 2013.

Mandatory withdrawal of the trial if withdrawal of consent by the patient, hospitalisation for aggravation of depression, high suicidal risks or suicide attempt, occurrence of psychotic features, occurrence of pre-defined laboratory criteria and / or signs or symptoms of hepatic dysfunction, signs of cardiac arrhytmia, pregnancy

Other criteria for premature withdrawal from the study: treatment failure, adverse event, any event or circumstances related or unrelated to the treatment justifying the discontinuation of the treatment in the investigator's opinion

In order to avoid abrupt discontinuation of escitalopram and according to the investigator's opinion and the reason for withdrawal, a tapering treatment could be dispensed to the patient at the withdrawal visit for a period of 7 days.

Background therapy: -

Evidence for comparator:

escitalopram

Actual start date of recruitment	11 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	Australia: 25
Country: Number of subjects enrolled	Brazil: 73
Country: Number of subjects enrolled	Canada: 97
Country: Number of subjects enrolled	South Africa: 104
Country: Number of subjects enrolled	United Kingdom: 99
Worldwide total number of subjects	398
EEA total number of subjects	99

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)	394
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Investigators were psychiatrists or general practitioners.

Pre-assignment

Screening details:

Study population was male or female outpatients with Major Depressive Disorder. At selection, Hamilton Depression Rating Scale 17 items was to be ≥ 22, Clinical Global Impression severity of illness ≥ 4, Hospital Anxiety and Depression scale with Depression score ≥ 11 and Depression score > Anxiety score.

Period 1

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

Blinding implementation details:

Treatment randomisation and allocation centralized (interactive response system).
Study products of identical appearance
The double-blind treatment period with all subjects receiving either experimental treatment (agomelatine) or active comparator (escitalopram) is described in the document.

Arms

Are arms mutually exclusive?	Yes
Arm title	agomelatine

Arm description: -

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

Dosage and administration details:

1 capsule daily: 25 or 50 mg agomelatine

Arm title	escitalopram

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	escitalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1 capsule daily: 10 or 20 mg escitalopram

Number of subjects in period 1	agomelatine	escitalopram
Started	199	199
Completed	140	135
Not completed	59	64
recovery-improvement	-	1
non-medical reason	22	26
Adverse event, non-fatal	14	26
Protocol deviation	6	6
Lack of efficacy	17	5

Baseline characteristics

Reporting groups	
Reporting group title	agomelatine
Reporting group description: -	
Reporting group title	escitalopram
Reporting group description: -	

Reporting group values	agomelatine	escitalopram	Total
Number of subjects	199	199	398
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	41.4	40.8	
standard deviation	± 12	± 12.7	-
Gender categorical Units: Subjects			
Female	133	133	266
Male	66	66	132

End points

End points reporting groups

Reporting group title	agomelatine
Reporting group description: -	
Reporting group title	escitalopram
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients of the Randomized Set having taken at least one dose of study medication and having a value at baseline and at least one post-baseline efficacy assessment

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	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	[2]			
Units: not available	0			

Notes:

[2] - As the study was an exploratory study, no primary criterion was defined.

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 . Adverse events reported during the period W0 -W24 are presented here as it was the only period of the study when patients received agomelatine.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	agomelatine
Reporting group description: -	
Reporting group title	escitalopram

Reporting group description: -

Serious adverse events	agomelatine	escitalopram	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 199 (4.52%)	17 / 198 (8.59%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 199 (0.00%)	2 / 198 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Suicidal ideation			
subjects affected / exposed	1 / 199 (0.50%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional self-injury			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressive symptom			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, auditory			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep disorder			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
joint dislocation			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal compression fracture			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
accident			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sedation			
subjects affected / exposed	0 / 199 (0.00%)	2 / 198 (1.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
somnolence			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

syncope			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restless legs syndrome			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
inguinal hernia			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis alcoholic			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Localised infection			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sinusitis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
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: 5 %

Non-serious adverse events	agomelatine	escitalopram	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	132 / 199 (66.33%)	142 / 198 (71.72%)	

Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	 31 / 199 (15.58%) 43 11 / 199 (5.53%) 11	 34 / 198 (17.17%) 40 8 / 198 (4.04%) 9	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 14 / 199 (7.04%) 14	 34 / 198 (17.17%) 36	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 5 / 199 (2.51%) 5	 16 / 198 (8.08%) 18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2012	Update of the phase of the study from Phase III to Phase II for all Brazilians sites, in the context of an exploratory study
11 May 2012	Following the update of the SmPC of escitalopram from postmarketing experience, the following points were added: A non-selection criteria for patients with known QT interval prolongation or congenital long QT syndrome. A mandatory withdrawal criteria for patients with signs of cardiac arrhythmia. Clarification on forbidden treatments before and during the study for treatments known to prolong QT interval.
08 June 2012	Concerned all sites in UK: change of national coordinator (considered in UK as substantial amendment)
29 October 2012	According to this updated SmPC, a liver function test at W8 visit had been added so that when the dose was increased at the W2 visit, the liver function tests were performed at the same frequency as when initiating treatment. In addition, the follow-up of the patient in case of withdrawal from the study had been clarified: the patient was asked to come back for a follow-up visit 7 days after the withdrawal visit instead of 14 days after the study discontinuation visit.
13 June 2013	The follow-up / assessments to be performed and visits to be completed for prematurely withdrawn patients had been clarified in order to avoid any misunderstanding. The criterion on drug screening had been clarified in order to be consistent with authorised codeine intake. The recruitment period had been extended as the recruitment rate is slower than expected. Fasting conditions were required only in case of lipid parameters and blood glucose assessment.
15 November 2013	The recruitment period had been extended as the recruitment rate was slower than expected. The non-selection criteria and the treatments authorised with restriction before and during the study had been updated according to the last version of Summary of Product Characteristics (SmPC) of Escitalopram. The withdrawal criterion "Jaundice or any other symptom suggesting hepatic dysfunction" had been updated in order to be consistent with the information reported in the SmPC of Agomelatine. In case of any AST and/or ALT increase > 3 ULN, an adverse event had to be immediately reported without waiting for the liver function retest results in order to ensure an accurate follow-up of the event. The new version of the Declaration of Helsinki had been integrated in this new amendment following its review at the last WMA meeting (Fortaleza, October 2013).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported