Clinical trial results:
Pharmacokinetics and safety of agomelatine in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) with Depressive or Anxiety Disorder.
An open-labelled, multicenter, three-dose level, non-comparative study.

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	2012-003404-12
Trial protocol	FI SE HU EE RO PL
Global end of trial date	14 March 2015

Results information

Result version number	v1 (current)
This version publication date	21 February 2016
First version publication date	21 February 2016

Trial information

Trial identification

Sponsor protocol code	CL2-20098-075

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 Cedex
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001181-PIP01-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2015
Global end of trial reached?	Yes
Global end of trial date	14 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate pharmacokinetics of 3 doses (5, 10 and 25 mg) of agomelatine in patients from 7 to less than 18 years suffering from Depressive or Anxiety Disorder.

Protection of trial subjects:

This open-labelled PK and safety study was done before placebo-controlled studies are conducted, in order to provide information on agomelatine PK and preliminary safety data in children and adolescents.
--Based on the PK characteristics of agomelatine, a single administration was considered sufficient to assess the PK parameters, as steady state is reached from the first day of administration. Due to the rapid elimination of agomelatine, an interval of 24 hours was considered sufficient between doses.
The oral film-coated tablet formulation was used, as agomelatine tablet shape and size was acceptable for this age-range and this formulation offers the best profile in terms of expected palatability, safety, compliance and efficacy.
Saliva samples were collected for evaluating the agomelatine PK, as this was a non-invasive procedure. Only one PK blood sample was drawn, in order to check the correlation between plasma and saliva agomelatine concentrations. The total of blood collected was not superior to maximum tolerated volume.
In addition to standard study withdrawal criteria, the following led to a mandatory withdrawal from the study:
-Hospitalisation of the patient for aggravation of depression/psychiatric disorder
-Worsening of Major Depressive Episode/psychiatric disorder, according to investigator’s clinical judgment.
-High suicidal risk, according to investigator’s judgement.
-Any suicide attempt during the study, whatever its severity.
-Occurrence of psychotic features.
-AST and/or ALT > 3 x ULN, confirmed at re-test.
-Any symptoms or signs of potential liver injury.
-Pregnancy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 August 2013
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	Romania: 18
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	Hungary: 26

Worldwide total number of subjects	51
EEA total number of subjects	51

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)	24
Adolescents (12-17 years)	27
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There was a screening period of 3 to 7 days between the selection and inclusion (Day 0) visits: this period, without IMP administration, was to be as short as possible. It allowed investigators to perform electrocardiogram (ECG) and laboratory examinations. The results of the examinations had to be available at the inclusion visit.

Period 1

Period 1 title	Treatment Period (Day 1)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Agomelatine 5 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Agomelatine
Investigational medicinal product code	S 20098
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One oral film-coated tablet of agomelatine 5 mg on Day 1 between 6.00 p.m. and 7.00 p.m.

Number of subjects in period 1	Agomelatine 5 mg
Started	51
Completed	51

Period 2

Period 2 title	Treatment Period (Day 2)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Agomelatine 10 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Agomelatine
Investigational medicinal product code	S 20098
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One oral film-coated tablet of agomelatine 10 mg on Day 2 between 6.00 p.m. and 7.00 p.m.

Number of subjects in period 2	Agomelatine 10 mg
Started	51
Completed	49
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Period 3

Period 3 title	Treatment Period (Day 3)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Agomelatine 25 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Agomelatine
Investigational medicinal product code	S 20098
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One oral film-coated tablet of agomelatine 25 mg on Day 3 between 6.00 p.m. and 7.00 p.m.

Number of subjects in period 3	Agomelatine 25 mg
Started	49
Completed	49

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period (Day 1)
Reporting group description: -	

Reporting group values	Treatment Period (Day 1)	Total	
Number of subjects	51	51	
Age categorical Units: Subjects			
Children (2-11 years)	24	24	
Adolescents (12-17 years)	27	27	
Age continuous Units: years			
arithmetic mean	12.4		
standard deviation	± 3	-	
Gender categorical Units: Subjects			
Female	25	25	
Male	26	26	

Subject analysis sets	
Subject analysis set title	Adolescents
Subject analysis set type	Full analysis
Subject analysis set description: Participants from 12 to less than 18 years of age	
Subject analysis set title	Children
Subject analysis set type	Full analysis
Subject analysis set description: Participants from 7 to less than 12 years of age	

Reporting group values	Adolescents	Children	
Number of subjects	27	24	
Age categorical Units: Subjects			
Children (2-11 years)			
Adolescents (12-17 years)			
Age continuous Units: years			
arithmetic mean	14.8	9.8	
standard deviation	± 1.8	± 1	
Gender categorical Units: Subjects			
Female	15	10	
Male	12	14	

End points

End points reporting groups

Reporting group title	Agomelatine 5 mg
Reporting group description: -	
Reporting group title	Agomelatine 10 mg
Reporting group description: -	
Reporting group title	Agomelatine 25 mg
Reporting group description: -	
Subject analysis set title	Adolescents
Subject analysis set type	Full analysis
Subject analysis set description: Participants from 12 to less than 18 years of age	
Subject analysis set title	Children
Subject analysis set type	Full analysis
Subject analysis set description: Participants from 7 to less than 12 years of age	

Primary: AUC

End point title	AUC[1]
End point description:	
End point type	Primary
End point timeframe: D1, D2 and D3	

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: Descriptive statistical analysis was planned in the protocol.

End point values	Agomelatine 5 mg	Agomelatine 10 mg	Agomelatine 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	51	49	
Units: ng.h/mL				
median (confidence interval 90%)	4.18 (1.97 to 19.1)	7.09 (3.9 to 41.7)	19 (7.76 to 147)	

Statistical analyses

No statistical analyses for this end point

Primary: Cmax

End point title	Cmax[2]
End point description:	
End point type	Primary
End point timeframe: D1, D2 and D3	

Notes:

[2] - 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: Descriptive statistical analysis was planned in the protocol.

End point values	Agomelatine 5 mg	Agomelatine 10 mg	Agomelatine 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	51	49	
Units: ng/mL				
median (confidence interval 90%)	1.63 (0.766 to 10.8)	2.69 (1.1 to 19.4)	9.68 (1.97 to 87.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Between screening and the last visit (run-out)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Overall: all patients
Reporting group description:	
All AEs in all patients throughout the study	
Reporting group title	Overall: adolescents
Reporting group description:	
All AEs in all adolescent patients throughout the study	
Reporting group title	Overall: children
Reporting group description:	
All AEs in all children patients throughout the study	
Reporting group title	Agomelatine 5 mg: all patients
Reporting group description:	
AEs associated with the 5 mg dose intake (Day 1) in all patients	
Reporting group title	Agomelatine 5 mg: adolescents
Reporting group description:	
AEs associated with the 5 mg dose intake (Day 1) in adolescent patients	
Reporting group title	Agomelatine 5 mg: children
Reporting group description:	
AEs associated with the 5 mg dose intake (Day 1) in children patients	
Reporting group title	Agomelatine 10 mg: all patients
Reporting group description:	
AEs associated with the 10 mg dose intake (Day 2) in all patients	
Reporting group title	Agomelatine 10 mg: adolescents
Reporting group description:	
AEs associated with the 10 mg dose intake (Day 2) in adolescent patients	
Reporting group title	Agomelatine 10 mg: children
Reporting group description:	
AEs associated with the 10 mg dose intake (Day 2) in children patients	
Reporting group title	Agomelatine 25 mg: all patients
Reporting group description:	
AEs associated with the 25 mg dose intake (Day 3) in all patients	
Reporting group title	Agomelatine 25 mg: adolescents
Reporting group description:	
AEs associated with the 25 mg dose intake (Day 3) in adolescent patients	
Reporting group title	Agomelatine 25 mg: children
Reporting group description:	
AEs associated with the 25 mg dose intake (Day 3) in children patients	

Serious adverse events	Overall: all patients	Overall: adolescents	Overall: children
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Agomelatine 5 mg: all patients	Agomelatine 5 mg: adolescents	Agomelatine 5 mg: children
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Agomelatine 10 mg: all patients	Agomelatine 10 mg: adolescents	Agomelatine 10 mg: children
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Agomelatine 25 mg: all patients	Agomelatine 25 mg: adolescents	Agomelatine 25 mg: children
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall: all patients	Overall: adolescents	Overall: children
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 51 (33.33%)	10 / 27 (37.04%)	7 / 24 (29.17%)
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Blood prolactin increased			

subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Nervous system disorders			
Hypersomnia			
subjects affected / exposed	5 / 51 (9.80%)	4 / 27 (14.81%)	1 / 24 (4.17%)
occurrences (all)	6	5	1
Somnolence			
subjects affected / exposed	3 / 51 (5.88%)	2 / 27 (7.41%)	1 / 24 (4.17%)
occurrences (all)	5	4	1
Disturbance in attention			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	3 / 51 (5.88%)	1 / 27 (3.70%)	2 / 24 (8.33%)
occurrences (all)	4	2	2
Dyskinesia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 51 (7.84%)	3 / 27 (11.11%)	1 / 24 (4.17%)
occurrences (all)	5	3	2
Hunger			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	3	1	2
Injection site pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Thirst			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Vessel puncture site reaction			

subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Neutropenia			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Lymphocytosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	3 / 51 (5.88%)	2 / 27 (7.41%)	1 / 24 (4.17%)
occurrences (all)	3	2	1
Mouth haemorrhage			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Diarrhoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Breast disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Sexual dysfunction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Anxiety			

subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Depressed mood			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	3	1	2
Emotional disorder			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Mood swings			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Disorientation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Conjunctivitis bacterial			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Influenza			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1

Non-serious adverse events	Agomelatine 5 mg: all patients	Agomelatine 5 mg: adolescents	Agomelatine 5 mg: children
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 51 (19.61%)	6 / 27 (22.22%)	4 / 24 (16.67%)
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Blood prolactin increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Hypersomnia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Somnolence			
subjects affected / exposed	2 / 51 (3.92%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	2	2	0
Disturbance in attention			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Dyskinesia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Hunger			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Injection site pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Thirst			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Vessel puncture site reaction			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			

Leukopenia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lymphocytosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Mouth haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Breast disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Sexual dysfunction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Depressed mood			

subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Emotional disorder			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Disorientation			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Conjunctivitis bacterial			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Influenza			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Agomelatine 10 mg: all patients	Agomelatine 10 mg: adolescents	Agomelatine 10 mg: children
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 51 (15.69%)	5 / 27 (18.52%)	3 / 24 (12.50%)
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Blood prolactin increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Hypersomnia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Somnolence			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Disturbance in attention			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	3	2	1
Dyskinesia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Hunger			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Injection site pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site reaction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Neutropenia			

subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lymphocytosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Mouth haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast disorder			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Sexual dysfunction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Depressed mood			
subjects affected / exposed	2 / 51 (3.92%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	1	1
Emotional disorder			
subjects affected / exposed	1 / 51 (1.96%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	1	1	0

Mood swings			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Disorientation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 51 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 51 (1.96%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1

Non-serious adverse events	Agomelatine 25 mg: all patients	Agomelatine 25 mg: adolescents	Agomelatine 25 mg: children
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 49 (22.45%)	8 / 27 (29.63%)	3 / 22 (13.64%)
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Blood prolactin increased			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	1 / 22 (4.55%)
occurrences (all)	2	1	1
Nervous system disorders			
Hypersomnia			
subjects affected / exposed	4 / 49 (8.16%)	3 / 27 (11.11%)	1 / 22 (4.55%)
occurrences (all)	4	3	1
Somnolence			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	1 / 22 (4.55%)
occurrences (all)	2	1	1

Disturbance in attention			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dyskinesia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Hunger			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site reaction			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	1 / 22 (4.55%)
occurrences (all)	2	1	1
Neutropenia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	1 / 22 (4.55%)
occurrences (all)	2	1	1
Lymphocytosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Gastrointestinal disorders			

Dry mouth			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Mouth haemorrhage			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Sexual dysfunction			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Emotional disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Disorientation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2013	-Addition of Estonia, Hungary, Poland and Romania. -Removal of Sweden; no longer part of the study. -Since January 2011, the National Institute for Health and Welfare recommendation on the usage of vitamin D in children and adolescents has been taken into consideration by the Ministry of Health in Finland. Accordingly, vitamin D administration is recommended in the prophylaxis of vitamin D-deficiency from 2 to 18 years old. Therefore, the administration of vitamin D as concomitant treatment during the study was authorised up to 1.000 IU per day. -The Total Reaction Time was removed from the evaluation criteria since the 2 other criteria obtained from the Choice Reaction Time (Recognition Reaction Time and Motor Reaction Time) are the most relevant criteria to be analysed in order to assess the vigilance/sedation. -The description of safety analysis relative to Adverse Events was adapted in accordance with international guidance. -The Declaration of Helsinki was reviewed at the last WMA meeting (Fortaleza, Brazil, October 2013).
08 July 2014	-Extension of the recruitment period until March 2015. -Change in selection and inclusion criteria. -Deletion of criteria of moderate or severe intensity for Major Depressive Episode, addition of Dysthymic Disorder, Generalized Anxiety Disorder, Separation Anxiety Disorder, Social Phobia and Specific Phobia. -Harmonisation of the inclusion- and non-inclusion criteria regarding the levels of liver enzymes and serum total bilirubin tests results with studies in adult population. -Minor clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported