Clinical trial results:
Efficacy and safety of 2 doses of agomelatine (10mg, 25mg) given orally in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) with moderate to severe Major Depressive Disorder. A 12-week, randomized, double-blind, active (fluoxetine 10 mg/day with potential adjustment to 20 mg/day) and placebo-controlled, parallel groups, international, multicentre study followed by an optional open-labelled 21-month safety extension period.

Summary

EudraCT number	2015-002181-23
Trial protocol	FI HU DE BG PL
Global end of trial date	

Results information

Result version number	v1
This version publication date	24 July 2020
First version publication date	24 July 2020

Trial information

Trial identification

Sponsor protocol code	CL3-20098-076

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 Recherche International Servier, 33 155724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherche International Servier, 33 155724366, 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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	14 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate the antidepressant short-term efficacy of at least one of the two doses of agomelatine compared to placebo after 12 weeks of treatment in children (from 7 to less than 12 years of age) and adolescents (from 12 to less than 18 years of age) suffering from moderate to severe Major Depressive Disorder using Children Depression Rating Scale – Revised (CDRS-R).

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	21 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Ukraine: 72
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	Hungary: 74
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Romania: 61
Country: Number of subjects enrolled	Russian Federation: 120
Country: Number of subjects enrolled	Serbia: 10
Worldwide total number of subjects	400
EEA total number of subjects	181

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)	80
Adolescents (12-17 years)	320
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:

Male or female, in-or-out patients: children (from 7 to less than 12 years old) and adolescents (from 12 to less than 18 years old). Primary diagnosis of Major Depressive Disorder (MDD), single or recurrent episode, of moderate to severe intensity, fulfilling DSM-IV-TR, CDRS-R Raw score > or = 45, CGI-S score > or = 4.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Agomelatine 10 mg - Total population

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:

From W0 to W2: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 10 mg in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator’s clinical judgement, the volume of oral solution could double: 5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 10 mg in the evening at bedtime.

Arm title	Agomelatine 25 mg - Total population

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:

From W0 to W2: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 25 mg in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator’s clinical judgement, the volume of oral solution could double: 5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 25 mg in the evening at bedtime.

Arm title	Placebo - Total population

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Oral solution
Routes of administration	Oral use

Dosage and administration details:

From W0 to W2: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator's clinical judgement, the volume of oral solution could double: 5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.

Arm title	Fluoxetine - Total population

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Fluoxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

From W0 to W2: 2.5 mL (10 mg) of oral solution of fluoxetine in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator's clinical judgement, the volume of oral solution could double leading to an increased dose: 5 mL (20 mg) of oral solution of fluoxetine in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.

Number of subjects in period 1	Agomelatine 10 mg - Total population	Agomelatine 25 mg - Total population	Placebo - Total population
Started	102	95	103
Completed	94	84	87
Not completed	8	11	16
Non medical reason	3	7	12
Adverse event, non-fatal	2	3	2
Lack of efficacy	3	1	2
Protocol deviation	-	-	-

Number of subjects in period 1	Fluoxetine - Total population
Started	100
Completed	87
Not completed	13
Non medical reason	9
Adverse event, non-fatal	3
Lack of efficacy	-
Protocol deviation	1

Period 2

Period 2 title	Double-blind period - Adolescents
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Agomelatine 10 mg - Adolescents

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:

From W0 to W2: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 10 mg in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator's clinical judgement, the volume of oral solution could double: 5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 10 mg in the evening at bedtime.

Arm title	Agomelatine 25 mg - Adolescents

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:

From W0 to W2: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 25 mg in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator's clinical judgement, the volume of oral solution could double: 5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 25 mg in the evening at bedtime.

Arm title	Placebo - Adolescents

Arm description: -

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

Dosage and administration details:

From W0 to W2: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.

From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator's clinical judgement, the volume of oral solution could double: 5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.

Arm title	Fluoxetine - Adolescents
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Fluoxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

From W0 to W2: 2.5 mL (10 mg) of oral solution of fluoxetine in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator's clinical judgement, the volume of oral solution could double leading to an increased dose: 5 mL (20 mg) of oral solution of fluoxetine in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.

Number of subjects in period 2[1]	Agomelatine 10 mg - Adolescents	Agomelatine 25 mg - Adolescents	Placebo - Adolescents
Started	81	76	82
Completed	73	68	71
Not completed	8	8	11
Non medical reason	3	5	8
Adverse event, non-fatal	2	2	1
Lack of efficacy	3	1	2
Protocol deviation	-	-	-

Number of subjects in period 2[1]	Fluoxetine - Adolescents
Started	81
Completed	71
Not completed	10
Non medical reason	6
Adverse event, non-fatal	3
Lack of efficacy	-
Protocol deviation	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Period 2 described the adolescents population which is a subgroup of the total population rather than a period of time following the period 1.

Period 3

Period 3 title	Double-blind period - Children
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Agomelatine 10 mg - Children

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:

From W0 to W2: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 10 mg in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator’s clinical judgement, the volume of oral solution could double: 5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 10 mg in the evening at bedtime.

Arm title	Agomelatine 25 mg - Children

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:

From W0 to W2: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 25 mg in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator’s clinical judgement, the volume of oral solution could double: 5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 25 mg in the evening at bedtime.

Arm title	Placebo - Children

Arm description: -

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

Dosage and administration details:

From W0 to W2: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator’s clinical judgement, the volume of oral solution could double: 5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.

Arm title	Fluoxetine - Children

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Fluoxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

From W0 to W2: 2.5 mL (10 mg) of oral solution of fluoxetine in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.
From W2 to W12, patients with a sufficient improvement remained on the initial dose. In case of insufficient improvement according to the investigator's clinical judgement, the volume of oral solution could double leading to an increased dose: 5 mL (20 mg) of oral solution of fluoxetine in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.

Number of subjects in period 3[2]	Agomelatine 10 mg - Children	Agomelatine 25 mg - Children	Placebo - Children
Started	21	19	21
Completed	21	16	16
Not completed	0	3	5
Non medical reason	-	2	4
Adverse event, non-fatal	-	1	1

Number of subjects in period 3[2]	Fluoxetine - Children
Started	19
Completed	16
Not completed	3
Non medical reason	3
Adverse event, non-fatal	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Period 3 described the children population which is a subgroup of the total population rather than a period of time following the period 1.

Baseline characteristics

Reporting groups	
Reporting group title	Agomelatine 10 mg - Total population
Reporting group description: -	
Reporting group title	Agomelatine 25 mg - Total population
Reporting group description: -	
Reporting group title	Placebo - Total population
Reporting group description: -	
Reporting group title	Fluoxetine - Total population
Reporting group description: -	

Reporting group values	Agomelatine 10 mg - Total population	Agomelatine 25 mg - Total population	Placebo - Total population
Number of subjects	102	95	103
Age categorical Units: Subjects			
Children (2-11 years)	21	19	21
Adolescents (12-17 years)	81	76	82
Age continuous Units: years			
arithmetic mean	13.6	13.4	13.8
standard deviation	± 2.9	± 2.7	± 2.6
Gender categorical Units: Subjects			
Female	68	61	64
Male	34	34	39

Reporting group values	Fluoxetine - Total population	Total	
Number of subjects	100	400	
Age categorical Units: Subjects			
Children (2-11 years)	19	80	
Adolescents (12-17 years)	81	320	
Age continuous Units: years			
arithmetic mean	13.8		
standard deviation	± 2.7	-	
Gender categorical Units: Subjects			
Female	57	250	
Male	43	150	

Subject analysis sets	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

In accordance with the intention-to-treat principle and the section 5.2.1 of ICH E9 guideline, all patients

of the Modified Randomised Set (MRS) having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value for the primary efficacy endpoint.
MRS: All included and randomised patients (i.e. all included patients to whom a therapeutic unit was randomly assigned using IRS).

Subject analysis set title	Adolescents of the Full Analysis Set (FAS_ADO)
Subject analysis set type	Full analysis

Subject analysis set description:

In accordance with the intention-to-treat principle and the section 5.2.1 of ICH E9 guideline, all adolescents patients of the MRS having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value for the primary efficacy endpoint.

Subject analysis set title	Children of the Full Analysis Set (FAS_CHILD)
Subject analysis set type	Full analysis

Subject analysis set description:

In accordance with the intention-to-treat principle and the section 5.2.1 of ICH E9 guideline, all children patients of the MRS having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value for the primary efficacy endpoint.

Reporting group values	Full Analysis Set (FAS)	Adolescents of the Full Analysis Set (FAS_ADO)	Children of the Full Analysis Set (FAS_CHILD)
Number of subjects	396	317	79
Age categorical Units: Subjects			
Children (2-11 years)	79		
Adolescents (12-17 years)	317		
Age continuous Units: years			
arithmetic mean	13.7	14.8	9.2
standard deviation	± 2.7	± 1.6	± 1.3
Gender categorical Units: Subjects			
Female	247	216	31
Male	149	101	48

End points

End points reporting groups

Reporting group title	Agomelatine 10 mg - Total population
Reporting group description: -	
Reporting group title	Agomelatine 25 mg - Total population
Reporting group description: -	
Reporting group title	Placebo - Total population
Reporting group description: -	
Reporting group title	Fluoxetine - Total population
Reporting group description: -	
Reporting group title	Agomelatine 10 mg - Adolescents
Reporting group description: -	
Reporting group title	Agomelatine 25 mg - Adolescents
Reporting group description: -	
Reporting group title	Placebo - Adolescents
Reporting group description: -	
Reporting group title	Fluoxetine - Adolescents
Reporting group description: -	
Reporting group title	Agomelatine 10 mg - Children
Reporting group description: -	
Reporting group title	Agomelatine 25 mg - Children
Reporting group description: -	
Reporting group title	Placebo - Children
Reporting group description: -	
Reporting group title	Fluoxetine - Children
Reporting group description: -	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

In accordance with the intention-to-treat principle and the section 5.2.1 of ICH E9 guideline, all patients of the Modified Randomised Set (MRS) having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value for the primary efficacy endpoint.
MRS: All included and randomised patients (i.e. all included patients to whom a therapeutic unit was randomly assigned using IRS).

Subject analysis set title	Adolescents of the Full Analysis Set (FAS_ADO)
Subject analysis set type	Full analysis

Subject analysis set description:

In accordance with the intention-to-treat principle and the section 5.2.1 of ICH E9 guideline, all adolescents patients of the MRS having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value for the primary efficacy endpoint.

Subject analysis set title	Children of the Full Analysis Set (FAS_CHILD)
Subject analysis set type	Full analysis

Subject analysis set description:

In accordance with the intention-to-treat principle and the section 5.2.1 of ICH E9 guideline, all children patients of the MRS having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value for the primary efficacy endpoint.

Primary: CDRS-R raw total score: change from baseline to W12 (Total population of the FAS)

End point title	CDRS-R raw total score: change from baseline to W12 (Total population of the FAS)

End point description:

The superiority of each agomelatine dose as compared to placebo on antidepressant efficacy after a 12-week treatment period was assessed, from the CDRS-R raw total score expressed in terms of change from baseline to W12.
The CDRS-R was used to assess the diagnosis and severity of the current depressed episode in children and adolescents. This is a 17-item clinician rated instrument integrating multiple-source information. Each of them can be rated within the ranges of 1-5 or 1-7. The total score ranges from 17 (normal) to 113 (severe depression).
The rater has to:
- complete the rating scale during 2 separate interviews: 1 with the patient and 1 with the parent(s)/legally authorized representative(s).
- fill in the rating comments for each item, from both sources.
- evaluate the symptoms rating from both sources and provide/define the "best description of the child".
- enter in the e-CRF the final rated values of each item corresponding to the "best description of the child" an

End point type	Primary

End point timeframe:

The Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski & Mokros, 1996) was assessed by the investigator at each visit from the selection visit to W12.

End point values	Agomelatine 10 mg - Total population	Agomelatine 25 mg - Total population	Placebo - Total population	Fluoxetine - Total population
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	94	101	99
Units: No unit				
arithmetic mean (standard deviation)	-20.9 (± 14.0)	-22.5 (± 15.2)	-19.7 (± 14.4)	-21.7 (± 14.1)

Statistical analyses

Statistical analysis title	Placebo minus agomelatine 10 mg

Statistical analysis description:

The superiority of agomelatine 10 mg as compared to placebo on antidepressant efficacy after a 12-week treatment period was assessed, from the CDRS-R raw total score expressed in terms of change from baseline to W12. A three-way analysis of covariance (ANCOVA) model was used.
Analysis included the fixed, categorical effects of treatment, age subgroup and country, and the continuous, fixed covariate of baseline. Missing data were imputed with the Last Observation Carried Forward (LOCF) approach.

Comparison groups	Placebo - Total population v Agomelatine 10 mg - Total population
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079 [1]
Method	ANCOVA
Parameter estimate	Estimate of the adjusted difference
Point estimate	3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	6.73

Variability estimate	Standard error of the mean
Dispersion value	1.81

Notes:

[1] - Dunnett-adjusted p-value

Statistical analysis title	Placebo minus agomelatine 25 mg

Statistical analysis description:

The superiority of agomelatine 25 mg as compared to placebo on antidepressant efficacy after a 12-week treatment period was assessed, from the CDRS-R raw total score expressed in terms of change from baseline to W12. A three-way analysis of covariance (ANCOVA) model was used.
Analysis included the fixed, categorical effects of treatment, age subgroup and country, and the continuous, fixed covariate of baseline. Missing data were imputed with the Last Observation Carried Forward (LOCF) approach.

Comparison groups	Agomelatine 25 mg - Total population v Placebo - Total population
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [2]
Method	ANCOVA
Parameter estimate	Estimate of the adjusted difference
Point estimate	4.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	7.82
Variability estimate	Standard error of the mean
Dispersion value	1.83

Notes:

[2] - Dunnett-adjusted p-value

Statistical analysis title	Placebo minus fluoxetine

Statistical analysis description:

An assay sensitivity was studied with a three-way analysis of covariance (ANCOVA) model using the comparison of fluoxetine to placebo. Analysis included the fixed, categorical effects of treatment, age subgroup and country, and the continuous, fixed covariate of baseline. Missing data were imputed with the Last Observation Carried Forward (LOCF) approach.

Comparison groups	Placebo - Total population v Fluoxetine - Total population
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	ANCOVA
Parameter estimate	Estimate of the difference
Point estimate	3.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	7.3
Variability estimate	Standard error of the mean
Dispersion value	1.81

Primary: CDRS-R raw total score: change from baseline to W12 (Adolescents of the FAS)

End point title	CDRS-R raw total score: change from baseline to W12 (Adolescents of the FAS)

End point description:

The superiority of each agomelatine dose as compared to placebo on antidepressant efficacy after a 12-week treatment period was assessed, from the CDRS-R raw total score expressed in terms of change from baseline to W12.
The CDRS-R was used to assess the diagnosis and severity of the current depressed episode in children and adolescents. This is a 17-item clinician rated instrument integrating multiple-source information. Each of them can be rated within the ranges of 1-5 or 1-7. The total score ranges from 17 (normal) to 113 (severe depression).
The rater has to:
- complete the rating scale during 2 separate interviews: 1 with the patient and 1 with the parent(s)/legally authorized representative(s).
- fill in the rating comments for each item, from both sources.
- evaluate the symptoms rating from both sources and provide/define the "best description of the child".
- enter in the e-CRF the final rated values of each item corresponding to the "best description of the child"

End point type	Primary

End point timeframe:

The Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski & Mokros, 1996) was assessed by the investigator at each visit from the selection visit to W12.

End point values	Agomelatine 10 mg - Adolescents	Agomelatine 25 mg - Adolescents	Placebo - Adolescents	Fluoxetine - Adolescents
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	75	81	80
Units: No unit				
arithmetic mean (standard error)	-21.1 (± 14.1)	-23.8 (± 15.4)	-19.8 (± 13.4)	-22.0 (± 14.2)

Statistical analyses

Statistical analysis title	Placebo minus agomelatine 10 mg

Statistical analysis description:

The superiority of agomelatine 10 mg as compared to placebo on antidepressant efficacy after a 12-week treatment period was assessed, from the CDRS-R raw total score expressed in terms of change from baseline to W12. A three-way analysis of covariance (ANCOVA) model was used. Analysis included the fixed, categorical effects of treatment, age subgroup and country, and the continuous, fixed covariate of baseline. Missing data were imputed with the Last Observation Carried Forward (LOCF) approach.

Comparison groups	Placebo - Adolescents v Agomelatine 10 mg - Adolescents

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132 [3]
Method	ANCOVA
Parameter estimate	Estimate of the adjusted difference
Point estimate	3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	7.32
Variability estimate	Standard error of the mean
Dispersion value	2.11

Notes:

[3] - Dunnett-adjusted p-value

Statistical analysis title	Placebo minus agomelatine 25 mg

Statistical analysis description:

The superiority of agomelatine 25 mg as compared to placebo on antidepressant efficacy after a 12-week treatment period was assessed, from the CDRS-R raw total score expressed in terms of change from baseline to W12. A three-way analysis of covariance (ANCOVA) model was used. Analysis included the fixed, categorical effects of treatment, age subgroup and country, and the continuous, fixed covariate of baseline. Missing data were imputed with the Last Observation Carried Forward (LOCF) approach.

Comparison groups	Placebo - Adolescents v Agomelatine 25 mg - Adolescents
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028 [4]
Method	ANCOVA
Parameter estimate	Estimate of the adjusted difference
Point estimate	5.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	9.4
Variability estimate	Standard error of the mean
Dispersion value	2.13

Notes:

[4] - Dunnett-adjusted p-value

Statistical analysis title	Placebo minus fluoxetine

Statistical analysis description:

An assay sensitivity was studied with a three-way analysis of covariance (ANCOVA) model using the comparison of fluoxetine to placebo. Analysis included the fixed, categorical effects of treatment, age subgroup and country, and the continuous, fixed covariate of baseline. Missing data were imputed with the Last Observation Carried Forward (LOCF) approach.

Comparison groups	Placebo - Adolescents v Fluoxetine - Adolescents

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	ANCOVA
Parameter estimate	Estimate of the difference
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	7.84
Variability estimate	Standard error of the mean
Dispersion value	2.1

Primary: CDRS-R raw total score: change from baseline to W12 (Children of the FAS)

End point title	CDRS-R raw total score: change from baseline to W12 (Children of the FAS)[5]

End point description:

The CDRS-R was used to assess the diagnosis and severity of the current depressed episode in children and adolescents. This is a 17-item clinician rated instrument integrating multiple-source information. Each of them can be rated within the ranges of 1-5 or 1-7. The total score ranges from 17 (normal) to 113 (severe depression).
The rater has to:
- complete the rating scale during 2 separate interviews: 1 with the patient and 1 with the parent(s)/legally authorized representative(s).
- fill in the rating comments for each item, from both sources.
- evaluate the symptoms rating from both sources and provide/define the "best description of the child".
- enter in the e-CRF the final rated values of each item corresponding to the "best description of the child" and the corresponding Raw summary score.

End point type	Primary

End point timeframe:

The Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski & Mokros, 1996) was assessed by the investigator at each visit from the selection visit to W12.

Notes:

[5] - 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: Comparison tests were computed in total population and adolescents group, the children group was too small to perform test.

End point values	Agomelatine 10 mg - Children	Agomelatine 25 mg - Children	Placebo - Children	Fluoxetine - Children
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	19	20	19
Units: No unit				
arithmetic mean (standard deviation)	-20.0 (± 13.9)	-17.1 (± 13.3)	-19.0 (± 18.3)	-20.7 (± 14.4)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events which occurred or worsen or became serious according to the investigator, or upgraded by the Sponsor, between the first IMP intake date (included) and the last IMP intake date + 1 day (included).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Agomelatine 10 mg - Total population
Reporting group description: -	
Reporting group title	Agomelatine 25 mg - Total population
Reporting group description: -	
Reporting group title	Placebo - Total population
Reporting group description: -	
Reporting group title	Agomelatine 10 mg - Adolescents
Reporting group description: -	
Reporting group title	Fluoxetine - Total population
Reporting group description: -	
Reporting group title	Agomelatine 25 mg - Adolescents
Reporting group description: -	
Reporting group title	Placebo - Adolescents
Reporting group description: -	
Reporting group title	Fluoxetine - Adolescents
Reporting group description: -	
Reporting group title	Agomelatine 10 mg - Children
Reporting group description: -	
Reporting group title	Agomelatine 25 mg - Children
Reporting group description: -	
Reporting group title	Placebo - Children
Reporting group description: -	
Reporting group title	Fluoxetine - Children

Reporting group description: -

Serious adverse events	Agomelatine 10 mg - Total population	Agomelatine 25 mg - Total population	Placebo - Total population
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 102 (5.88%)	3 / 94 (3.19%)	0 / 103 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 102 (0.98%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haemorrhagic vasculitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 102 (0.98%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anorexia nervosa			
subjects affected / exposed	1 / 102 (0.98%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	1 / 102 (0.98%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			

subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Measles			
subjects affected / exposed	1 / 102 (0.98%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Agomelatine 10 mg - Adolescents	Fluoxetine - Total population	Agomelatine 25 mg - Adolescents
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 81 (6.17%)	7 / 100 (7.00%)	2 / 75 (2.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 81 (1.23%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haemorrhagic vasculitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 81 (1.23%)	2 / 100 (2.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Anorexia nervosa			
subjects affected / exposed	1 / 81 (1.23%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	1 / 81 (1.23%)	1 / 100 (1.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Measles			

subjects affected / exposed	1 / 81 (1.23%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo - Adolescents	Fluoxetine - Adolescents	Agomelatine 10 mg - Children
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 82 (0.00%)	7 / 81 (8.64%)	1 / 21 (4.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			

subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haemorrhagic vasculitis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 82 (0.00%)	2 / 81 (2.47%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anorexia nervosa			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Suicidal ideation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Measles			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Agomelatine 25 mg - Children	Placebo - Children	Fluoxetine - Children
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haemorrhagic vasculitis			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anorexia nervosa			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypothyroidism			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Measles			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Agomelatine 10 mg - Total population	Agomelatine 25 mg - Total population	Placebo - Total population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 102 (59.80%)	59 / 94 (62.77%)	63 / 103 (61.17%)
General disorders and administration site conditions			
Drug interaction			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	5 / 102 (4.90%)	6 / 94 (6.38%)	7 / 103 (6.80%)
occurrences (all)	5	6	9
Thirst			
subjects affected / exposed	16 / 102 (15.69%)	13 / 94 (13.83%)	10 / 103 (9.71%)
occurrences (all)	16	15	10
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	1 / 103 (0.97%)
occurrences (all)	0	1	1
Anxiety			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	2 / 103 (1.94%)
occurrences (all)	0	1	2
Impulsive behaviour			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Learning disability			
subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 102 (0.98%)	2 / 94 (2.13%)	2 / 103 (1.94%)
occurrences (all)	1	2	2
Electrocardiogram PR shortened			

subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	1 / 102 (0.98%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	1	1	0
Weight increased			
subjects affected / exposed	6 / 102 (5.88%)	5 / 94 (5.32%)	0 / 103 (0.00%)
occurrences (all)	6	5	0
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	2 / 103 (1.94%)
occurrences (all)	0	1	2
Dizziness postural			
subjects affected / exposed	2 / 102 (1.96%)	5 / 94 (5.32%)	1 / 103 (0.97%)
occurrences (all)	2	5	1
Headache			
subjects affected / exposed	16 / 102 (15.69%)	11 / 94 (11.70%)	14 / 103 (13.59%)
occurrences (all)	21	15	14
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 102 (7.84%)	7 / 94 (7.45%)	7 / 103 (6.80%)
occurrences (all)	9	8	10
Diarrhoea			
subjects affected / exposed	6 / 102 (5.88%)	4 / 94 (4.26%)	6 / 103 (5.83%)
occurrences (all)	6	5	7
Dry mouth			
subjects affected / exposed	21 / 102 (20.59%)	13 / 94 (13.83%)	11 / 103 (10.68%)
occurrences (all)	21	14	12

Nausea			
subjects affected / exposed	10 / 102 (9.80%)	12 / 94 (12.77%)	14 / 103 (13.59%)
occurrences (all)	11	14	17
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 102 (2.94%)	4 / 94 (4.26%)	2 / 103 (1.94%)
occurrences (all)	4	4	2
Dermatitis allergic			
subjects affected / exposed	0 / 102 (0.00%)	2 / 94 (2.13%)	0 / 103 (0.00%)
occurrences (all)	0	2	0
Endocrine disorders			
Hyperprolactinaemia			
subjects affected / exposed	2 / 102 (1.96%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	2 / 102 (1.96%)	3 / 94 (3.19%)	6 / 103 (5.83%)
occurrences (all)	2	3	6
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	1 / 103 (0.97%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	2 / 102 (1.96%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal infection			
subjects affected / exposed	1 / 102 (0.98%)	0 / 94 (0.00%)	1 / 103 (0.97%)
occurrences (all)	1	0	1
Gastrointestinal viral infection			
subjects affected / exposed	1 / 102 (0.98%)	1 / 94 (1.06%)	4 / 103 (3.88%)
occurrences (all)	1	1	4
Nasopharyngitis			
subjects affected / exposed	3 / 102 (2.94%)	5 / 94 (5.32%)	3 / 103 (2.91%)
occurrences (all)	3	5	3
Pharyngitis bacterial			

subjects affected / exposed	0 / 102 (0.00%)	0 / 94 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	1 / 102 (0.98%)	1 / 94 (1.06%)	3 / 103 (2.91%)
occurrences (all)	2	1	3
Upper respiratory tract infection			
subjects affected / exposed	1 / 102 (0.98%)	0 / 94 (0.00%)	1 / 103 (0.97%)
occurrences (all)	1	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 102 (0.98%)	1 / 94 (1.06%)	2 / 103 (1.94%)
occurrences (all)	1	2	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 102 (2.94%)	5 / 94 (5.32%)	7 / 103 (6.80%)
occurrences (all)	3	5	7
Food intolerance			
subjects affected / exposed	0 / 102 (0.00%)	1 / 94 (1.06%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	7 / 102 (6.86%)	6 / 94 (6.38%)	0 / 103 (0.00%)
occurrences (all)	7	6	0

Non-serious adverse events	Agomelatine 10 mg - Adolescents	Fluoxetine - Total population	Agomelatine 25 mg - Adolescents
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 81 (61.73%)	55 / 100 (55.00%)	47 / 75 (62.67%)
General disorders and administration site conditions			
Drug interaction			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	4 / 81 (4.94%)	2 / 100 (2.00%)	6 / 75 (8.00%)
occurrences (all)	4	2	6
Thirst			
subjects affected / exposed	15 / 81 (18.52%)	15 / 100 (15.00%)	11 / 75 (14.67%)
occurrences (all)	15	15	13
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 81 (0.00%)	5 / 100 (5.00%)	1 / 75 (1.33%)
occurrences (all)	0	5	1
Anxiety			
subjects affected / exposed	0 / 81 (0.00%)	3 / 100 (3.00%)	1 / 75 (1.33%)
occurrences (all)	0	3	1
Impulsive behaviour			
subjects affected / exposed	0 / 81 (0.00%)	2 / 100 (2.00%)	1 / 75 (1.33%)
occurrences (all)	0	2	1
Learning disability			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 81 (0.00%)	2 / 100 (2.00%)	1 / 75 (1.33%)
occurrences (all)	0	2	1
Blood glucose increased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 81 (0.00%)	2 / 100 (2.00%)	2 / 75 (2.67%)
occurrences (all)	0	2	2
Electrocardiogram PR shortened			

subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	4 / 81 (4.94%)	2 / 100 (2.00%)	4 / 75 (5.33%)
occurrences (all)	4	2	4
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	1 / 75 (1.33%)
occurrences (all)	0	1	1
Dizziness postural			
subjects affected / exposed	2 / 81 (2.47%)	2 / 100 (2.00%)	5 / 75 (6.67%)
occurrences (all)	2	2	5
Headache			
subjects affected / exposed	13 / 81 (16.05%)	11 / 100 (11.00%)	7 / 75 (9.33%)
occurrences (all)	17	11	9
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 81 (6.17%)	4 / 100 (4.00%)	5 / 75 (6.67%)
occurrences (all)	6	4	5
Diarrhoea			
subjects affected / exposed	5 / 81 (6.17%)	8 / 100 (8.00%)	3 / 75 (4.00%)
occurrences (all)	5	9	4
Dry mouth			
subjects affected / exposed	18 / 81 (22.22%)	13 / 100 (13.00%)	10 / 75 (13.33%)
occurrences (all)	18	13	11

Nausea			
subjects affected / exposed	9 / 81 (11.11%)	9 / 100 (9.00%)	10 / 75 (13.33%)
occurrences (all)	10	9	12
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 81 (2.47%)	2 / 100 (2.00%)	4 / 75 (5.33%)
occurrences (all)	3	2	4
Dermatitis allergic			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	1 / 75 (1.33%)
occurrences (all)	0	1	1
Endocrine disorders			
Hyperprolactinaemia			
subjects affected / exposed	1 / 81 (1.23%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 81 (1.23%)	1 / 100 (1.00%)	3 / 75 (4.00%)
occurrences (all)	1	1	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 81 (0.00%)	2 / 100 (2.00%)	0 / 75 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal infection			
subjects affected / exposed	1 / 81 (1.23%)	2 / 100 (2.00%)	0 / 75 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal viral infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 100 (1.00%)	4 / 75 (5.33%)
occurrences (all)	1	1	4
Pharyngitis bacterial			

subjects affected / exposed	0 / 81 (0.00%)	2 / 100 (2.00%)	0 / 75 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection viral			
subjects affected / exposed	1 / 81 (1.23%)	2 / 100 (2.00%)	0 / 75 (0.00%)
occurrences (all)	2	2	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 81 (1.23%)	1 / 100 (1.00%)	0 / 75 (0.00%)
occurrences (all)	1	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 81 (1.23%)	5 / 100 (5.00%)	4 / 75 (5.33%)
occurrences (all)	1	5	4
Food intolerance			
subjects affected / exposed	0 / 81 (0.00%)	0 / 100 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	5 / 81 (6.17%)	3 / 100 (3.00%)	6 / 75 (8.00%)
occurrences (all)	5	3	6

Non-serious adverse events	Placebo - Adolescents	Fluoxetine - Adolescents	Agomelatine 10 mg - Children
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 82 (59.76%)	45 / 81 (55.56%)	11 / 21 (52.38%)
General disorders and administration site conditions			
Drug interaction			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	4 / 82 (4.88%)	2 / 81 (2.47%)	1 / 21 (4.76%)
occurrences (all)	6	2	1
Thirst			
subjects affected / exposed	9 / 82 (10.98%)	13 / 81 (16.05%)	1 / 21 (4.76%)
occurrences (all)	9	13	1
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 82 (0.00%)	3 / 81 (3.70%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Anxiety			
subjects affected / exposed	2 / 82 (2.44%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Impulsive behaviour			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Learning disability			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 82 (2.44%)	1 / 81 (1.23%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Electrocardiogram PR shortened			

subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 82 (1.22%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dizziness postural			
subjects affected / exposed	1 / 82 (1.22%)	2 / 81 (2.47%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Headache			
subjects affected / exposed	12 / 82 (14.63%)	9 / 81 (11.11%)	3 / 21 (14.29%)
occurrences (all)	12	9	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 82 (7.32%)	3 / 81 (3.70%)	3 / 21 (14.29%)
occurrences (all)	8	3	3
Diarrhoea			
subjects affected / exposed	5 / 82 (6.10%)	8 / 81 (9.88%)	1 / 21 (4.76%)
occurrences (all)	6	9	1
Dry mouth			
subjects affected / exposed	10 / 82 (12.20%)	11 / 81 (13.58%)	3 / 21 (14.29%)
occurrences (all)	11	11	3

Nausea			
subjects affected / exposed	12 / 82 (14.63%)	8 / 81 (9.88%)	1 / 21 (4.76%)
occurrences (all)	15	8	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 82 (2.44%)	2 / 81 (2.47%)	1 / 21 (4.76%)
occurrences (all)	2	2	1
Dermatitis allergic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hyperprolactinaemia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	5 / 82 (6.10%)	1 / 81 (1.23%)	1 / 21 (4.76%)
occurrences (all)	5	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 82 (1.22%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Gastrointestinal infection			
subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal viral infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 82 (3.66%)	1 / 81 (1.23%)	2 / 21 (9.52%)
occurrences (all)	3	1	2
Pharyngitis bacterial			

subjects affected / exposed	0 / 82 (0.00%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	2 / 82 (2.44%)	1 / 81 (1.23%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 82 (2.44%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 82 (4.88%)	4 / 81 (4.94%)	2 / 21 (9.52%)
occurrences (all)	4	4	2
Food intolerance			
subjects affected / exposed	0 / 82 (0.00%)	0 / 81 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 82 (0.00%)	3 / 81 (3.70%)	2 / 21 (9.52%)
occurrences (all)	0	3	2

Non-serious adverse events	Agomelatine 25 mg - Children	Placebo - Children	Fluoxetine - Children
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 19 (63.16%)	14 / 21 (66.67%)	10 / 19 (52.63%)
General disorders and administration site conditions			
Drug interaction			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 19 (0.00%)	3 / 21 (14.29%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Thirst			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	2 / 19 (10.53%)
occurrences (all)	2	1	2
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Anxiety			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Impulsive behaviour			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Learning disability			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood glucose increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Electrocardiogram PR shortened			

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Dizziness postural			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	4 / 19 (21.05%)	2 / 21 (9.52%)	2 / 19 (10.53%)
occurrences (all)	6	2	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	1 / 19 (5.26%)
occurrences (all)	3	2	1
Diarrhoea			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Dry mouth			
subjects affected / exposed	3 / 19 (15.79%)	1 / 21 (4.76%)	2 / 19 (10.53%)
occurrences (all)	3	1	2

Nausea			
subjects affected / exposed	2 / 19 (10.53%)	2 / 21 (9.52%)	1 / 19 (5.26%)
occurrences (all)	2	2	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperprolactinaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Gastrointestinal viral infection			
subjects affected / exposed	1 / 19 (5.26%)	3 / 21 (14.29%)	0 / 19 (0.00%)
occurrences (all)	1	3	0
Nasopharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pharyngitis bacterial			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory tract infection viral			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 19 (5.26%)	3 / 21 (14.29%)	1 / 19 (5.26%)
occurrences (all)	1	3	1
Food intolerance			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Increased appetite			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 19 (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
19 September 2016	It mainly concerned: - Supplementary non-inclusion criteria for liver function: *Free bilirubin > 2 ULN (criterion n°63), to exclude patients with Gilbert-syndrome who could present unpredictable timing and level of free bilirubin levels. *ALP and GGT > 1 ULN (criterion n°65), to exclude patients in normal growth but with potential hepatic enzyme alterations. *In the inclusion criteria (n°56): the selection criteria on scales scores which had to be still fulfilled were specified in the text. - Measures concerning liver function tests: *Liver function tests (AST, ALT, total bilirubin, free bilirubin, conjugated bilirubin, ALP, GGT) were added during double-blind period (W004) and during open label extension period (W014, W048 and W068). *Close monitoring through blood samplings re-tests in case of abnormalities observed on ALT/AST, bilirubin, ALP or GGT was defined as a monitoring every two weeks. *In case of ALT/AST > 2ULN under study treatment, a monitoring was organized every two weeks until values return to normal/baseline values. *Additional investigations which were to be performed in case of AST and/or ALT > 3 ULN were described in detail. - PAERS scale was added as individual safety assessment in addition to AEs. - Data of the PAERS scale (clinician part) were to be reported in the e-CRF and adverse events from the PAERS were to be reported in the AE form of the e-CRF. - Period of time i.e. "in the morning" was defined to perform biological sampling required in the seven days after the selection visit. - ECG recording was to be done under the supervision of the qualified specialist.
13 December 2019	It mainly concerned: - Integration of agreed modifications on the Paediatric Investigation Plan by EMA: decreased sample size (at least 390 patients instead of 484) and adapted statistical analysis including the modifications of subgroup analyses of primary endpoint and the update of statistical patient sets (at least 312 adolescents, with no requirement on children population). - Update of the total number of centres (63 instead of 67) and the list of participating countries (deletion of Germany and addition of Serbia). - Modifications of centres' downloads of participants' data from the e-CRF for archiving.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported