



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 | 27 October 2021 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 11 May 2022 |
| First version publication date | 24 July 2020 |
| Version creation reason | • New data added to full data set Final results |

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 |
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Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001181-PIP01-11 |
| Does article 45 of REGULATION (EC) No | No |

| | |
|--|-----|
| 1901/2006 apply to this trial? | |
| 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 | 27 October 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 October 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 October 2021 |
| Was the trial ended prematurely? | 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 | Safety, Efficacy |
| 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 | Subject, Investigator |

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? | No |
| 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 | 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 | Fluoxetine - Adolescents |
|---------------------------------------|-----------------------------|
| Started | 81 |
| Completed | 71 |
| Not completed | 10 |
| Non medical reason | 6 |
| Adverse event, non-fatal | 3 |
| Lack of efficacy | - |
| Protocol deviation | 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? | No |
|------------------------------|----|

| | |
|------------------|------------------------------|
| 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 | 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 | Fluoxetine - Children |
|---------------------------------------|-----------------------|
| Started | 19 |
| Completed | 16 |
| Not completed | 3 |
| Non medical reason | 3 |
| Adverse event, non-fatal | - |

Period 4

| | |
|------------------------------|--------------------------------------|
| Period 4 title | Open-label Period - Total population |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | No |
| Arm title | Agomelatine 10 or 25 mg / 10-25 mg - W012-W104 period |
| 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 W12 to W14, patients took 1 tablet of agomelatine 10 mg in the evening at bedtime.

From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient.

During the double-blind period (W0-W12), those patients were in the agomelatine 10 mg or agomelatine 25 mg groups.

| | |
|------------------|---|
| Arm title | Placebo / Agomelatine 10-25 mg - W012-W104 period |
|------------------|---|

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 W12 to W14, all patients took 1 tablet of agomelatine 10 mg in the evening at bedtime.

From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient.

During the double-blind period (W0-W12), those patients were on placebo.

| | |
|------------------|---|
| Arm title | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - W012-W104 period |
|------------------|---|

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 W12 to W14, all patients took 1 tablet of agomelatine 10 mg in the evening at bedtime.

From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient.

During the double-blind period (W0-W12), those patients were in the fluoxetine group (10 mg or 20 mg from W2 depending on the improvement of the patient).

| | |
|------------------|------------------------|
| Arm title | All - W012-W104 period |
|------------------|------------------------|

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 W12 to W14, all patients took 1 tablet of agomelatine 10 mg in the evening at bedtime.

From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient.

During the double-blind period (W0-W12), those patients were in agomelatine, fluoxetine or placebo groups.

| Number of subjects in period 4 | Agomelatine 10 or 25 mg / 10-25 mg - W012-W104 period | Placebo / Agomelatine 10-25 mg - W012-W104 period | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - W012-W104 period |
|--------------------------------|---|---|---|
| | | | |
| Started | 170 | 85 | 84 |
| Completed | 93 | 48 | 46 |
| Not completed | 77 | 37 | 38 |
| Recovery | 40 | 14 | 15 |
| Non medical reason | 25 | 12 | 17 |
| Adverse event, non-fatal | 6 | 5 | 3 |
| Lost to follow-up | 1 | 1 | - |
| Lack of efficacy | 4 | 2 | 2 |
| Protocol deviation | 1 | 3 | 1 |

| Number of subjects in period 4 | All - W012-W104 period |
|--------------------------------|------------------------|
| Started | 339 |
| Completed | 187 |
| Not completed | 152 |
| Recovery | 69 |
| Non medical reason | 54 |
| Adverse event, non-fatal | 14 |
| Lost to follow-up | 2 |
| Lack of efficacy | 8 |
| Protocol deviation | 5 |

Period 5

| | |
|------------------------------|---------------------------------|
| Period 5 title | Open-label Period - Adolescents |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|--|--|
| Are arms mutually exclusive? | No |
| Arm title | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W012-W104 |
| 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 W12 to W14, adolescent patients took 1 tablet of agomelatine 10 mg in the evening at bedtime.

From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient. During the double-blind period (W0-W12), those patients were in the agomelatine 10 mg or agomelatine 25 mg groups.

| | |
|--|--|
| Arm title | Placebo / Agomelatine 10-25 mg - Ado - W012-W104 |
| 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 W12 to W14, adolescents took 1 tablet of agomelatine 10 mg in the evening at bedtime. From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient. During the double-blind period (W0-W12), those patients were on placebo.

| | |
|--|--|
| Arm title | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - Ado - W012-W104 |
| 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 W12 to W14, adolescents took 1 tablet of agomelatine 10 mg in the evening at bedtime. From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient. During the double-blind period (W0-W12), those patients were in the fluoxetine group (10 mg or 20 mg from W2 depending on the improvement of the patient).

| | |
|--|-------------------------------|
| Arm title | All - Adolescents - W012-W104 |
| 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 W12 to W14, adolescents took 1 tablet of agomelatine 10 mg in the evening at bedtime. From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient. During the double-blind period (W0-W12), those patients were in agomelatine, fluoxetine or placebo groups.

| Number of subjects in period 5 | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W012-W104 | Placebo / Agomelatine 10-25 mg - Ado - W012-W104 | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - Ado - W012-W104 |
|--------------------------------|--|--|--|
| | | | |
| Started | 134 | 69 | 68 |
| Completed | 71 | 38 | 36 |
| Not completed | 63 | 31 | 32 |
| Recovery | 31 | 11 | 13 |
| Non medical reason | 23 | 9 | 14 |
| Adverse event, non-fatal | 3 | 5 | 3 |
| Lost to follow-up | 1 | 1 | - |
| Lack of efficacy | 4 | 2 | 1 |
| Protocol deviation | 1 | 3 | 1 |

| Number of subjects in period 5 | All - Adolescents - W012-W104 |
|--------------------------------|-------------------------------|
| Started | 271 |
| Completed | 145 |
| Not completed | 126 |
| Recovery | 55 |
| Non medical reason | 46 |
| Adverse event, non-fatal | 11 |
| Lost to follow-up | 2 |
| Lack of efficacy | 7 |
| Protocol deviation | 5 |

Period 6

| | |
|------------------------------|-----------------------------|
| Period 6 title | Study period W000-W104 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|--|---|
| Are arms mutually exclusive? | No |
| Arm title | Agomelatine 10 or 25 mg / 10-25 mg - W000-W104 period |
| 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 or 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 10 mg or agomelatine 25 mg in the evening at bedtime.

From W12 to W14, patients took 1 tablet of agomelatine 10 mg in the evening at bedtime.

From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient.

| | |
|--|--|
| Arm title | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W000-W104 |
| 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 or 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 10 mg or agomelatine 25 mg in the evening at bedtime.

From W12 to W14, adolescents took 1 tablet of agomelatine 10 mg in the evening at bedtime.

From W14 to W104, the dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit by investigator based on the clinical picture of patient.

| Number of subjects in period 6 | Agomelatine 10 or 25 mg / 10-25 mg - W000-W104 period | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W000-W104 |
|---------------------------------------|---|--|
| Started | 170 | 134 |
| Completed | 93 | 71 |
| Not completed | 77 | 63 |
| Recovery | 40 | 31 |
| Non medical reason | 25 | 23 |
| Adverse event, non-fatal | 6 | 3 |
| Lost to follow-up | 1 | 1 |
| Lack of efficacy | 4 | 4 |
| Protocol deviation | 1 | 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: - | |
| Reporting group title | Agomelatine 10 or 25 mg / 10-25 mg - W012-W104 period |
| Reporting group description: - | |
| Reporting group title | Placebo / Agomelatine 10-25 mg - W012-W104 period |
| Reporting group description: - | |
| Reporting group title | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - W012-W104 period |
| Reporting group description: - | |
| Reporting group title | All - W012-W104 period |
| Reporting group description: - | |
| Reporting group title | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W012-W104 |
| Reporting group description: - | |
| Reporting group title | Placebo / Agomelatine 10-25 mg - Ado - W012-W104 |
| Reporting group description: - | |
| Reporting group title | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - Ado - W012-W104 |
| Reporting group description: - | |
| Reporting group title | All - Adolescents - W012-W104 |
| Reporting group description: - | |
| Reporting group title | Agomelatine 10 or 25 mg / 10-25 mg - W000-W104 period |
| Reporting group description: - | |
| Reporting group title | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W000-W104 |
| 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 | Agomelatine 10 mg - Total population v Placebo - 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: <ul style="list-style-type: none">- 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: No statistical inferences for children

| 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 | 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: - | |
| Reporting group title | Agomelatine 10 or 25 mg / 10-25 mg - W012-W104 period |
| Reporting group description: - | |
| Reporting group title | Placebo / Agomelatine 10-25 mg - W012-W104 period |
| Reporting group description: - | |
| Reporting group title | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - W012-W104 period |
| Reporting group description: - | |
| Reporting group title | All - W012-W104 period |
| Reporting group description: - | |
| Reporting group title | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W012-W104 |
| Reporting group description: - | |
| Reporting group title | Placebo / Agomelatine 10-25 mg - Ado - W012-W104 |
| Reporting group description: - | |
| Reporting group title | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - Ado - W012-W104 |

Reporting group description: -

| | |
|-----------------------|-------------------------------|
| Reporting group title | All - Adolescents - W012-W104 |
|-----------------------|-------------------------------|

Reporting group description: -

| | |
|-----------------------|---|
| Reporting group title | Agomelatine 10 or 25 mg / 10-25 mg - W000-W104 period |
|-----------------------|---|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W000-W104 |
|-----------------------|--|

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 |
| Platelet count decreased | | | |
| 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 |
| Ankle fracture | | | |
| 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 |
| Humerus fracture | | | |
| 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 |
| Liver contusion | | | |
| 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 |
| Meniscus injury | | | |
| 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 |
| Pulmonary contusion | | | |
| 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 |
| Rib fracture | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| 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 |
| Road traffic accident | | | |
| 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 |
| Cerebral cyst | | | |
| 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 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| 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 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| 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 |
| Abdominal pain | | | |
| 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 |
| Gastritis | | | |
| 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 |
| 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 |
| Depression | | | |
| 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 |
| Adjustment disorder | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| 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 |
| anger | | | |
| 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 |
| drug abuse | | | |
| 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 |
| Emotional disorder of childhood | | | |
| 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 |
| Irritability | | | |
| 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 |
| Mood swings | | | |
| 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 |
| self-injurious 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 |
| Suicidal behaviour | | | |
| 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 |
| 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 |
| Pneumonia | | | |
| 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 |
| Respiratory tract infection | | | |
| 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 |
| Tonsillitis bacterial | | | |
| 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 |
| Tracheitis | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| 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 |
| Metabolism and nutrition disorders | | | |
| Latent tetany | | | |
| 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 |
| Dehydration | | | |
| 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 |

| Serious adverse events | Fluoxetine - Total population | Agomelatine 10 mg - Adolescents | Agomelatine 25 mg - Adolescents |
|---|-------------------------------|---------------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 100 (7.00%) | 5 / 81 (6.17%) | 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 | 1 / 100 (1.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 | 1 / 100 (1.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 81 (1.23%) | 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 |
| Intentional overdose | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 | 1 / 100 (1.00%) | 0 / 81 (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 |
| Concussion | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 81 (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 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Liver contusion | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Meniscus injury | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Pulmonary contusion | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Vascular disorders | | | |
| Haemorrhagic vasculitis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 / 100 (0.00%) | 0 / 81 (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 | 2 / 100 (2.00%) | 1 / 81 (1.23%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral cyst | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-----------------|----------------|----------------|
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Psychiatric disorders | | | |
| Anorexia nervosa | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 81 (1.23%) | 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 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 | 1 / 100 (1.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intentional self-injury | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 1 / 81 (1.23%) | 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 |

| | | | |
|---|-----------------|----------------|----------------|
| Depression | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Adjustment disorder | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| anger | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| drug abuse | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Emotional disorder of childhood | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Irritability | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Mood swings | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| self-injurious ideation | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Suicidal behaviour | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 / 100 (0.00%) | 0 / 81 (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 | 1 / 100 (1.00%) | 0 / 81 (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 |
| Measles | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 81 (1.23%) | 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 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Tonsillitis bacterial | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Metabolism and nutrition disorders | | | |
| Latent tetany | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (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 |
| Platelet 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 |
| 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 |
| Ankle fracture | | | |
| 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 |
| Humerus fracture | | | |
| 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 |
| Liver contusion | | | |

| | | | |
|---|----------------|----------------|----------------|
| 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 |
| Meniscus injury | | | |
| 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 |
| Pulmonary contusion | | | |
| 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 |
| Rib fracture | | | |
| 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 |
| Road traffic accident | | | |
| 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 |
| 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 |
| Cerebral cyst | | | |

| | | | |
|---|----------------|----------------|----------------|
| 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 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| 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 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| 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 |
| Abdominal pain | | | |
| 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 |
| Gastritis | | | |
| 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 |
| 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 |
| Depression | | | |
| 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 |
| Adjustment disorder | | | |
| 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 |
| anger | | | |
| 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 |
| drug abuse | | | |
| 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 |
| Emotional disorder of childhood | | | |
| 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 |
| Irritability | | | |
| 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 |
| Mood swings | | | |
| 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 |
| self-injurious ideation | | | |

| | | | |
|---|----------------|----------------|----------------|
| 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 behaviour | | | |
| 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 |
| 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 |
| Pneumonia | | | |
| 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 |
| Respiratory tract infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| 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 |
| Tonsillitis bacterial | | | |
| 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 |
| Tracheitis | | | |
| 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 |
| Metabolism and nutrition disorders | | | |
| Latent tetany | | | |
| 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 |
| Dehydration | | | |
| 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 |

| 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 |
| Platelet count decreased | | | |
| 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 |
| Ankle fracture | | | |
| 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 |
| Humerus fracture | | | |
| 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 |

| | | | |
|---|----------------|----------------|----------------|
| Liver contusion | | | |
| 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 |
| Meniscus 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 |
| Pulmonary contusion | | | |
| 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 |
| Rib fracture | | | |
| 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 |
| Road traffic accident | | | |
| 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 |

| | | | |
|---|----------------|----------------|----------------|
| Cerebral cyst | | | |
| 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 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| 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 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| 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 |
| Abdominal pain | | | |
| 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 |
| Gastritis | | | |
| 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 |
| Depression | | | |
| 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 |
| Adjustment disorder | | | |
| 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 |
| anger | | | |
| 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 |
| drug abuse | | | |
| 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 |
| Emotional disorder of childhood | | | |
| 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 |
| Irritability | | | |
| 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 |
| Mood swings | | | |

| | | | |
|---|----------------|----------------|----------------|
| 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 |
| self-injurious 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 |
| Suicidal behaviour | | | |
| 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 |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|----------------|
| 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 |
| Respiratory tract infection | | | |
| 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 |
| Tonsillitis bacterial | | | |
| 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 |
| Tracheitis | | | |
| 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 |
| Metabolism and nutrition disorders | | | |
| Latent tetany | | | |
| 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 |
| Dehydration | | | |
| 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 |

| Serious adverse events | Agomelatine 10 or 25 mg / 10-25 mg - W012-W104 period | Placebo / Agomelatine 10-25 mg - W012-W104 period | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - W012-W104 period |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 170 (4.71%) | 12 / 85 (14.12%) | 9 / 84 (10.71%) |
| 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 / 170 (0.00%) | 2 / 85 (2.35%) | 0 / 84 (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 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 / 170 (0.00%) | 1 / 85 (1.18%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 / 170 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| 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 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Ankle fracture | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Liver contusion | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Pulmonary contusion | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral cyst | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Psychiatric disorders | | | |
| Anorexia nervosa | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 / 170 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| 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 / 170 (0.00%) | 1 / 85 (1.18%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intentional self-injury | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Depression | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 3 / 85 (3.53%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adjustment disorder | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| anger | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| drug abuse | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Emotional disorder of childhood | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Irritability | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| Mood swings | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |
| self-injurious ideation | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 behaviour | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Tonsillitis bacterial | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Latent tetany | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 0 / 84 (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 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (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 |

| | | | |
|-------------------------------|-----------------|-------------------|-----------|
| Serious adverse events | All - W012-W104 | Agomelatine 10 or | Placebo / |
|-------------------------------|-----------------|-------------------|-----------|

| | period | 25 mg / 10-25 mg - Ado - W012-W104 | Agomelatine 10-25 mg - Ado - W012- W104 |
|--|------------------|---------------------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 339 (8.55%) | 7 / 134 (5.22%) | 11 / 69 (15.94%) |
| 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 | 2 / 339 (0.59%) | 0 / 134 (0.00%) | 2 / 69 (2.90%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 | 2 / 339 (0.59%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 339 (0.59%) | 1 / 134 (0.75%) | 0 / 69 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 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 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Fall | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 1 / 134 (0.75%) | 0 / 69 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Liver contusion | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary contusion | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Road traffic accident | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Vascular disorders | | | |
| Haemorrhagic vasculitis | | | |
| subjects affected / exposed | 0 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 | 2 / 339 (0.59%) | 1 / 134 (0.75%) | 0 / 69 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral cyst | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 1 / 134 (0.75%) | 0 / 69 (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 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 1 / 134 (0.75%) | 0 / 69 (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 |
| Abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anorexia nervosa | | | |
| subjects affected / exposed | 0 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Suicidal ideation | | | |
| subjects affected / exposed | 2 / 339 (0.59%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intentional self-injury | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 4 / 339 (1.18%) | 0 / 134 (0.00%) | 3 / 69 (4.35%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adjustment disorder | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| anger | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| drug abuse | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Emotional disorder of childhood | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Irritability | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mood swings | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| self-injurious ideation | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal behaviour | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Measles | | | |
| subjects affected / exposed | 0 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 / 339 (0.00%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 339 (0.59%) | 1 / 134 (0.75%) | 0 / 69 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 1 / 134 (0.75%) | 0 / 69 (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 |
| Tonsillitis bacterial | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (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 |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Latent tetany | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 1 / 134 (0.75%) | 0 / 69 (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 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - Ado - W012-W104 | All - Adolescents - W012-W104 | Agomelatine 10 or 25 mg / 10-25 mg - W000-W104 period |
|---|--|-------------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 68 (11.76%) | 26 / 271 (9.59%) | 11 / 170 (6.47%) |
| 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 / 68 (0.00%) | 2 / 271 (0.74%) | 0 / 170 (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 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 2 / 271 (0.74%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 | 1 / 68 (1.47%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 |
| Liver contusion | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Pulmonary contusion | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 / 68 (0.00%) | 0 / 271 (0.00%) | 1 / 170 (0.59%) |
| 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 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 | 1 / 68 (1.47%) | 2 / 271 (0.74%) | 2 / 170 (1.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral cyst | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Psychiatric disorders | | | |
| Anorexia nervosa | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 | 1 / 68 (1.47%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 2 / 271 (0.74%) | 0 / 170 (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 |
| Intentional self-injury | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Depression | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 4 / 271 (1.48%) | 0 / 170 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Adjustment disorder | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| anger | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| drug abuse | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Emotional disorder of childhood | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Irritability | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Mood swings | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| self-injurious ideation | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 behaviour | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (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 / 68 (0.00%) | 0 / 271 (0.00%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 2 / 271 (0.74%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis bacterial | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Tracheitis | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 68 (1.47%) | 1 / 271 (0.37%) | 0 / 170 (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 |
| Metabolism and nutrition disorders | | | |
| Latent tetany | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 1 / 170 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 0 / 170 (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 |

| | | | |
|---|--|--|--|
| Serious adverse events | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W000-W104 | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 134 (5.97%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelet count decreased | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intentional overdose | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Liver contusion | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meniscus injury | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary contusion | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Haemorrhagic vasculitis | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 2 / 134 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral cyst | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-----------------|--|--|
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anorexia nervosa | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intentional self-injury | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Depression | | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Adjustment disorder | | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| anger | | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| drug abuse | | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Emotional disorder of childhood | | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Irritability | | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mood swings | | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| self-injurious ideation | | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Suicidal behaviour | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Measles | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tonsillitis bacterial | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Latent tetany | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 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 occurrences (all) | 0 / 102 (0.00%) 0 | 1 / 94 (1.06%) 1 | 0 / 103 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) | 0 / 102 (0.00%) 0 0 / 102 (0.00%) 0 | 0 / 94 (0.00%) 0 1 / 94 (1.06%) 1 | 0 / 103 (0.00%) 0 0 / 103 (0.00%) 0 |
| Psychiatric disorders Aggression subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all) Impulsive behaviour subjects affected / exposed occurrences (all) Learning disability subjects affected / exposed occurrences (all) | 0 / 102 (0.00%) 0 0 / 102 (0.00%) 0 0 / 102 (0.00%) 0 0 / 102 (0.00%) 0 | 1 / 94 (1.06%) 1 1 / 94 (1.06%) 1 1 / 94 (1.06%) 1 0 / 94 (0.00%) 0 | 1 / 103 (0.97%) 1 2 / 103 (1.94%) 2 0 / 103 (0.00%) 0 0 / 103 (0.00%) 0 |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood glucose increased subjects affected / exposed occurrences (all) Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all) Electrocardiogram PR shortened | 0 / 102 (0.00%) 0 0 / 102 (0.00%) 0 1 / 102 (0.98%) 1 0 / 102 (0.00%) 0 | 1 / 94 (1.06%) 1 1 / 94 (1.06%) 1 2 / 94 (2.13%) 2 0 / 94 (0.00%) 0 | 0 / 103 (0.00%) 0 0 / 103 (0.00%) 0 2 / 103 (1.94%) 2 0 / 103 (0.00%) 0 |

| | | | |
|---|-------------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 0 / 102 (0.00%) 0 | 1 / 94 (1.06%) 1 | 0 / 103 (0.00%) 0 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 1 / 102 (0.98%) 1 | 1 / 94 (1.06%) 1 | 0 / 103 (0.00%) 0 |
| Weight increased subjects affected / exposed occurrences (all) | 6 / 102 (5.88%) 6 | 5 / 94 (5.32%) 5 | 0 / 103 (0.00%) 0 |
| Blood prolactin increased subjects affected / exposed occurrences (all) | 4 / 102 (3.92%) 4 | 1 / 94 (1.06%) 1 | 1 / 103 (0.97%) 1 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 3 / 102 (2.94%) 3 | 2 / 94 (2.13%) 2 | 1 / 103 (0.97%) 1 |
| Injury, poisoning and procedural complications Limb injury subjects affected / exposed occurrences (all) | 0 / 102 (0.00%) 0 | 0 / 94 (0.00%) 0 | 0 / 103 (0.00%) 0 |
| Cardiac disorders Bundle branch block right subjects affected / exposed occurrences (all) | 0 / 102 (0.00%) 0 | 1 / 94 (1.06%) 1 | 0 / 103 (0.00%) 0 |
| Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all) | 0 / 102 (0.00%) 0 | 1 / 94 (1.06%) 1 | 2 / 103 (1.94%) 2 |
| Dizziness postural subjects affected / exposed occurrences (all) | 2 / 102 (1.96%) 2 | 5 / 94 (5.32%) 5 | 1 / 103 (0.97%) 1 |
| Headache subjects affected / exposed occurrences (all) | 16 / 102 (15.69%) 21 | 11 / 94 (11.70%) 15 | 14 / 103 (13.59%) 14 |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 102 (3.92%) 5 | 3 / 94 (3.19%) 3 | 4 / 103 (3.88%) 4 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-------------------------|------------------------|-------------------------|
| Abdominal pain subjects affected / exposed occurrences (all) | 8 / 102 (7.84%) 9 | 7 / 94 (7.45%) 8 | 7 / 103 (6.80%) 10 |
| Diarrhoea subjects affected / exposed occurrences (all) | 6 / 102 (5.88%) 6 | 4 / 94 (4.26%) 5 | 6 / 103 (5.83%) 7 |
| Dry mouth subjects affected / exposed occurrences (all) | 21 / 102 (20.59%) 21 | 13 / 94 (13.83%) 14 | 11 / 103 (10.68%) 12 |
| Nausea subjects affected / exposed occurrences (all) | 10 / 102 (9.80%) 11 | 12 / 94 (12.77%) 14 | 14 / 103 (13.59%) 17 |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 3 / 102 (2.94%) 4 | 4 / 94 (4.26%) 4 | 2 / 103 (1.94%) 2 |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 0 / 102 (0.00%) 0 | 2 / 94 (2.13%) 2 | 0 / 103 (0.00%) 0 |
| Endocrine disorders | | | |
| Hyperprolactinaemia subjects affected / exposed occurrences (all) | 2 / 102 (1.96%) 2 | 0 / 94 (0.00%) 0 | 0 / 103 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness subjects affected / exposed occurrences (all) | 2 / 102 (1.96%) 2 | 3 / 94 (3.19%) 3 | 6 / 103 (5.83%) 6 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 102 (0.00%) 0 | 0 / 94 (0.00%) 0 | 1 / 103 (0.97%) 1 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 2 / 102 (1.96%) 2 | 0 / 94 (0.00%) 0 | 0 / 103 (0.00%) 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 | Fluoxetine - Total population | Agomelatine 10 mg - Adolescents | Agomelatine 25 mg - Adolescents |
|---|-------------------------------|---------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 55 / 100 (55.00%) | 50 / 81 (61.73%) | 47 / 75 (62.67%) |
| General disorders and administration site conditions | | | |

| | | | |
|--|-------------------------|------------------------|------------------------|
| Drug interaction subjects affected / exposed occurrences (all) | 0 / 100 (0.00%) 0 | 0 / 81 (0.00%) 0 | 0 / 75 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 2 / 100 (2.00%) 2 | 4 / 81 (4.94%) 4 | 6 / 75 (8.00%) 6 |
| Thirst subjects affected / exposed occurrences (all) | 15 / 100 (15.00%) 15 | 15 / 81 (18.52%) 15 | 11 / 75 (14.67%) 13 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 0 / 81 (0.00%) 0 | 0 / 75 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 0 / 81 (0.00%) 0 | 0 / 75 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 100 (0.00%) 0 | 0 / 81 (0.00%) 0 | 0 / 75 (0.00%) 0 |
| Psychiatric disorders Aggression subjects affected / exposed occurrences (all) | 5 / 100 (5.00%) 5 | 0 / 81 (0.00%) 0 | 1 / 75 (1.33%) 1 |
| Anxiety subjects affected / exposed occurrences (all) | 3 / 100 (3.00%) 3 | 0 / 81 (0.00%) 0 | 1 / 75 (1.33%) 1 |
| Impulsive behaviour subjects affected / exposed occurrences (all) | 2 / 100 (2.00%) 2 | 0 / 81 (0.00%) 0 | 1 / 75 (1.33%) 1 |
| Learning disability subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 0 / 81 (0.00%) 0 | 0 / 75 (0.00%) 0 |
| Investigations Aspartate aminotransferase increased | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 100 (2.00%) | 0 / 81 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 0 / 81 (0.00%) | 2 / 75 (2.67%) |
| occurrences (all) | 2 | 0 | 2 |
| Electrocardiogram PR shortened | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 81 (1.23%) | 0 / 75 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 4 / 81 (4.94%) | 4 / 75 (5.33%) |
| occurrences (all) | 2 | 4 | 4 |
| Blood prolactin increased | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 3 / 81 (3.70%) | 1 / 75 (1.33%) |
| occurrences (all) | 0 | 3 | 1 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 3 / 81 (3.70%) | 2 / 75 (2.67%) |
| occurrences (all) | 0 | 3 | 2 |
| Injury, poisoning and procedural complications | | | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Bundle branch block right | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 81 (0.00%) | 1 / 75 (1.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Dizziness postural | | | |

| | | | |
|--|-------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 2 / 100 (2.00%) 2 | 2 / 81 (2.47%) 2 | 5 / 75 (6.67%) 5 |
| Headache subjects affected / exposed occurrences (all) | 11 / 100 (11.00%) 11 | 13 / 81 (16.05%) 17 | 7 / 75 (9.33%) 9 |
| Dizziness subjects affected / exposed occurrences (all) | 3 / 100 (3.00%) 3 | 4 / 81 (4.94%) 5 | 3 / 75 (4.00%) 3 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 4 / 100 (4.00%) 4 | 5 / 81 (6.17%) 6 | 5 / 75 (6.67%) 5 |
| Diarrhoea subjects affected / exposed occurrences (all) | 8 / 100 (8.00%) 9 | 5 / 81 (6.17%) 5 | 3 / 75 (4.00%) 4 |
| Dry mouth subjects affected / exposed occurrences (all) | 13 / 100 (13.00%) 13 | 18 / 81 (22.22%) 18 | 10 / 75 (13.33%) 11 |
| Nausea subjects affected / exposed occurrences (all) | 9 / 100 (9.00%) 9 | 9 / 81 (11.11%) 10 | 10 / 75 (13.33%) 12 |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 2 / 100 (2.00%) 2 | 2 / 81 (2.47%) 3 | 4 / 75 (5.33%) 4 |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 0 / 81 (0.00%) 0 | 1 / 75 (1.33%) 1 |
| Endocrine disorders Hyperprolactinaemia subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 1 / 81 (1.23%) 1 | 0 / 75 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 1 / 81 (1.23%) 1 | 3 / 75 (4.00%) 3 |

| | | | |
|---|-----------------|----------------|----------------|
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 1 / 81 (1.23%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 81 (1.23%) | 0 / 75 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 1 / 81 (1.23%) | 4 / 75 (5.33%) |
| occurrences (all) | 1 | 1 | 4 |
| Pharyngitis bacterial | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 1 / 81 (1.23%) | 0 / 75 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 1 / 81 (1.23%) | 0 / 75 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 81 (1.23%) | 0 / 75 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 100 (5.00%) | 1 / 81 (1.23%) | 4 / 75 (5.33%) |
| occurrences (all) | 5 | 1 | 4 |
| Food intolerance | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 81 (0.00%) | 0 / 75 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Increased appetite | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 100 (3.00%) | 5 / 81 (6.17%) | 6 / 75 (8.00%) |
| occurrences (all) | 3 | 5 | 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 |
| Blood prolactin increased | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 81 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 81 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| 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 occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 81 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Nervous system disorders | | | |
| Disturbance in attention subjects affected / exposed occurrences (all) | 1 / 82 (1.22%) 1 | 0 / 81 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Dizziness postural subjects affected / exposed occurrences (all) | 1 / 82 (1.22%) 1 | 2 / 81 (2.47%) 2 | 0 / 21 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 12 / 82 (14.63%) 12 | 9 / 81 (11.11%) 9 | 3 / 21 (14.29%) 4 |
| Dizziness subjects affected / exposed occurrences (all) | 3 / 82 (3.66%) 3 | 3 / 81 (3.70%) 3 | 0 / 21 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 6 / 82 (7.32%) 8 | 3 / 81 (3.70%) 3 | 3 / 21 (14.29%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 5 / 82 (6.10%) 6 | 8 / 81 (9.88%) 9 | 1 / 21 (4.76%) 1 |
| Dry mouth subjects affected / exposed occurrences (all) | 10 / 82 (12.20%) 11 | 11 / 81 (13.58%) 11 | 3 / 21 (14.29%) 3 |
| Nausea subjects affected / exposed occurrences (all) | 12 / 82 (14.63%) 15 | 8 / 81 (9.88%) 8 | 1 / 21 (4.76%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 2 / 82 (2.44%) 2 | 2 / 81 (2.47%) 2 | 1 / 21 (4.76%) 1 |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 1 / 81 (1.23%) 1 | 0 / 21 (0.00%) 0 |
| Endocrine disorders | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Hyperprolactinaemia subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 81 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness subjects affected / exposed occurrences (all) | 5 / 82 (6.10%) 5 | 1 / 81 (1.23%) 1 | 1 / 21 (4.76%) 1 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 82 (1.22%) 1 | 1 / 81 (1.23%) 1 | 0 / 21 (0.00%) 0 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 1 / 81 (1.23%) 1 | 2 / 21 (9.52%) 2 |
| Gastrointestinal infection subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 1 / 81 (1.23%) 1 | 0 / 21 (0.00%) 0 |
| Gastrointestinal viral infection subjects affected / exposed occurrences (all) | 1 / 82 (1.22%) 1 | 0 / 81 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 82 (3.66%) 3 | 1 / 81 (1.23%) 1 | 2 / 21 (9.52%) 2 |
| Pharyngitis bacterial subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 1 / 81 (1.23%) 1 | 0 / 21 (0.00%) 0 |
| Respiratory tract infection viral subjects affected / exposed occurrences (all) | 2 / 82 (2.44%) 2 | 1 / 81 (1.23%) 1 | 0 / 21 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 82 (1.22%) 1 | 0 / 81 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 82 (2.44%) 2 | 0 / 81 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Decreased appetite subjects affected / exposed occurrences (all) | 4 / 82 (4.88%) 4 | 4 / 81 (4.94%) 4 | 2 / 21 (9.52%) 2 |
| Food intolerance subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 0 / 81 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Increased appetite subjects affected / exposed occurrences (all) | 0 / 82 (0.00%) 0 | 3 / 81 (3.70%) 3 | 2 / 21 (9.52%) 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 occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 19 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 3 / 21 (14.29%) 3 | 0 / 19 (0.00%) 0 |
| Thirst subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | 1 / 21 (4.76%) 1 | 2 / 19 (10.53%) 2 |
| Immune system disorders | | | |
| Drug hypersensitivity subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 19 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 19 (0.00%) 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 |
| Blood prolactin increased | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 0 / 21 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood bilirubin increased | | | |

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

| | | | |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 21 (4.76%) 1 | 1 / 19 (5.26%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 2 | 0 / 21 (0.00%) 0 | 0 / 19 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 3 / 21 (14.29%) 3 | 1 / 19 (5.26%) 1 |
| Food intolerance subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 19 (0.00%) 0 |
| Increased appetite subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 19 (0.00%) 0 |

| Non-serious adverse events | Agomelatine 10 or 25 mg / 10-25 mg - W012-W104 period | Placebo / Agomelatine 10-25 mg - W012-W104 period | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - W012-W104 period |
|--|---|---|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 102 / 170 (60.00%) | 51 / 85 (60.00%) | 49 / 84 (58.33%) |
| General disorders and administration site conditions | | | |
| Drug interaction subjects affected / exposed occurrences (all) | 0 / 170 (0.00%) 0 | 0 / 85 (0.00%) 0 | 0 / 84 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 6 / 170 (3.53%) 6 | 4 / 85 (4.71%) 4 | 2 / 84 (2.38%) 4 |
| Thirst subjects affected / exposed occurrences (all) | 7 / 170 (4.12%) 8 | 3 / 85 (3.53%) 3 | 2 / 84 (2.38%) 2 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 170 (0.00%) 0 | 0 / 85 (0.00%) 0 | 0 / 84 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences (all) | 1 | 0 | 1 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 1 / 84 (1.19%) |
| occurrences (all) | 2 | 0 | 1 |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 3 / 170 (1.76%) | 1 / 85 (1.18%) | 2 / 84 (2.38%) |
| occurrences (all) | 3 | 1 | 2 |
| Impulsive behaviour | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Learning disability | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 170 (2.35%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 170 (0.00%) | 1 / 85 (1.18%) | 0 / 84 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 3 / 170 (1.76%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Electrocardiogram PR shortened | | | |
| subjects affected / exposed | 1 / 170 (0.59%) | 0 / 85 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|-------------------------|------------------------|-----------------------|
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 1 / 170 (0.59%) 1 | 1 / 85 (1.18%) 1 | 2 / 84 (2.38%) 2 |
| Weight increased subjects affected / exposed occurrences (all) | 8 / 170 (4.71%) 8 | 4 / 85 (4.71%) 4 | 1 / 84 (1.19%) 1 |
| Blood prolactin increased subjects affected / exposed occurrences (all) | 8 / 170 (4.71%) 8 | 1 / 85 (1.18%) 1 | 3 / 84 (3.57%) 3 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 2 / 170 (1.18%) 2 | 1 / 85 (1.18%) 1 | 0 / 84 (0.00%) 0 |
| Injury, poisoning and procedural complications Limb injury subjects affected / exposed occurrences (all) | 0 / 170 (0.00%) 0 | 1 / 85 (1.18%) 1 | 0 / 84 (0.00%) 0 |
| Cardiac disorders Bundle branch block right subjects affected / exposed occurrences (all) | 1 / 170 (0.59%) 1 | 0 / 85 (0.00%) 0 | 0 / 84 (0.00%) 0 |
| Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all) | 1 / 170 (0.59%) 1 | 1 / 85 (1.18%) 1 | 0 / 84 (0.00%) 0 |
| Dizziness postural subjects affected / exposed occurrences (all) | 3 / 170 (1.76%) 3 | 0 / 85 (0.00%) 0 | 2 / 84 (2.38%) 2 |
| Headache subjects affected / exposed occurrences (all) | 21 / 170 (12.35%) 32 | 10 / 85 (11.76%) 11 | 9 / 84 (10.71%) 11 |
| Dizziness subjects affected / exposed occurrences (all) | 5 / 170 (2.94%) 6 | 2 / 85 (2.35%) 2 | 4 / 84 (4.76%) 4 |
| Gastrointestinal disorders Abdominal pain | | | |

| | | | |
|--|----------------------|-----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 5 / 170 (2.94%) 5 | 5 / 85 (5.88%) 7 | 1 / 84 (1.19%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 170 (1.18%) 2 | 4 / 85 (4.71%) 5 | 2 / 84 (2.38%) 4 |
| Dry mouth subjects affected / exposed occurrences (all) | 7 / 170 (4.12%) 7 | 0 / 85 (0.00%) 0 | 2 / 84 (2.38%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 5 / 170 (2.94%) 5 | 9 / 85 (10.59%) 12 | 4 / 84 (4.76%) 5 |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 4 / 170 (2.35%) 4 | 2 / 85 (2.35%) 2 | 0 / 84 (0.00%) 0 |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 0 / 170 (0.00%) 0 | 0 / 85 (0.00%) 0 | 0 / 84 (0.00%) 0 |
| Endocrine disorders Hyperprolactinaemia subjects affected / exposed occurrences (all) | 2 / 170 (1.18%) 2 | 1 / 85 (1.18%) 2 | 3 / 84 (3.57%) 3 |
| Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all) | 0 / 170 (0.00%) 0 | 1 / 85 (1.18%) 2 | 0 / 84 (0.00%) 0 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 3 / 170 (1.76%) 3 | 0 / 85 (0.00%) 0 | 0 / 84 (0.00%) 0 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 170 (0.00%) 0 | 0 / 85 (0.00%) 0 | 1 / 84 (1.19%) 1 |
| Gastrointestinal infection subjects affected / exposed occurrences (all) | 1 / 170 (0.59%) 2 | 0 / 85 (0.00%) 0 | 0 / 84 (0.00%) 0 |

| | | | |
|---|------------------------|-----------------------|---------------------|
| Gastrointestinal viral infection subjects affected / exposed occurrences (all) | 1 / 170 (0.59%) 1 | 0 / 85 (0.00%) 0 | 0 / 84 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 11 / 170 (6.47%) 15 | 9 / 85 (10.59%) 11 | 4 / 84 (4.76%) 4 |
| Pharyngitis bacterial subjects affected / exposed occurrences (all) | 1 / 170 (0.59%) 1 | 1 / 85 (1.18%) 1 | 0 / 84 (0.00%) 0 |
| Respiratory tract infection viral subjects affected / exposed occurrences (all) | 6 / 170 (3.53%) 7 | 2 / 85 (2.35%) 2 | 1 / 84 (1.19%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 170 (2.35%) 6 | 2 / 85 (2.35%) 3 | 3 / 84 (3.57%) 4 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 6 / 170 (3.53%) 7 | 2 / 85 (2.35%) 2 | 0 / 84 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 8 / 170 (4.71%) 8 | 2 / 85 (2.35%) 2 | 3 / 84 (3.57%) 3 |
| Food intolerance subjects affected / exposed occurrences (all) | 0 / 170 (0.00%) 0 | 1 / 85 (1.18%) 1 | 0 / 84 (0.00%) 0 |
| Increased appetite subjects affected / exposed occurrences (all) | 5 / 170 (2.94%) 5 | 0 / 85 (0.00%) 0 | 0 / 84 (0.00%) 0 |

| Non-serious adverse events | All - W012-W104 period | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W012-W104 | Placebo / Agomelatine 10-25 mg - Ado - W012- W104 |
|---|---------------------------|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 202 / 339 (59.59%) | 77 / 134 (57.46%) | 43 / 69 (62.32%) |
| General disorders and administration site conditions Drug interaction | | | |

| | | | |
|--|------------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 339 (0.00%) 0 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 12 / 339 (3.54%) 14 | 5 / 134 (3.73%) 5 | 4 / 69 (5.80%) 4 |
| Thirst subjects affected / exposed occurrences (all) | 12 / 339 (3.54%) 13 | 5 / 134 (3.73%) 6 | 3 / 69 (4.35%) 3 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 339 (0.00%) 0 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 339 (0.59%) 2 | 1 / 134 (0.75%) 1 | 0 / 69 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 2 / 339 (0.59%) 3 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Psychiatric disorders Aggression subjects affected / exposed occurrences (all) | 0 / 339 (0.00%) 0 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Anxiety subjects affected / exposed occurrences (all) | 6 / 339 (1.77%) 6 | 2 / 134 (1.49%) 2 | 1 / 69 (1.45%) 1 |
| Impulsive behaviour subjects affected / exposed occurrences (all) | 0 / 339 (0.00%) 0 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Learning disability subjects affected / exposed occurrences (all) | 0 / 339 (0.00%) 0 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 5 / 339 (1.47%) 5 | 4 / 134 (2.99%) 4 | 1 / 69 (1.45%) 1 |

| | | | |
|---|------------------------|----------------------|---------------------|
| Blood glucose increased subjects affected / exposed occurrences (all) | 1 / 339 (0.29%) 1 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all) | 3 / 339 (0.88%) 3 | 3 / 134 (2.24%) 3 | 0 / 69 (0.00%) 0 |
| Electrocardiogram PR shortened subjects affected / exposed occurrences (all) | 1 / 339 (0.29%) 1 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 4 / 339 (1.18%) 4 | 1 / 134 (0.75%) 1 | 1 / 69 (1.45%) 1 |
| Weight increased subjects affected / exposed occurrences (all) | 13 / 339 (3.83%) 13 | 7 / 134 (5.22%) 7 | 3 / 69 (4.35%) 3 |
| Blood prolactin increased subjects affected / exposed occurrences (all) | 12 / 339 (3.54%) 12 | 4 / 134 (2.99%) 4 | 1 / 69 (1.45%) 1 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 3 / 339 (0.88%) 3 | 2 / 134 (1.49%) 2 | 1 / 69 (1.45%) 1 |
| Injury, poisoning and procedural complications Limb injury subjects affected / exposed occurrences (all) | 1 / 339 (0.29%) 1 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Cardiac disorders Bundle branch block right subjects affected / exposed occurrences (all) | 1 / 339 (0.29%) 1 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all) | 2 / 339 (0.59%) 2 | 1 / 134 (0.75%) 1 | 1 / 69 (1.45%) 1 |
| Dizziness postural subjects affected / exposed occurrences (all) | 5 / 339 (1.47%) 5 | 5 / 134 (3.73%) 5 | 0 / 69 (0.00%) 0 |

| | | | |
|---|-------------------------|-------------------------|-----------------------|
| Headache subjects affected / exposed occurrences (all) | 40 / 339 (11.80%) 54 | 19 / 134 (14.18%) 30 | 9 / 69 (13.04%) 10 |
| Dizziness subjects affected / exposed occurrences (all) | 11 / 339 (3.24%) 12 | 5 / 134 (3.73%) 6 | 2 / 69 (2.90%) 2 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 11 / 339 (3.24%) 13 | 4 / 134 (2.99%) 4 | 3 / 69 (4.35%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 8 / 339 (2.36%) 11 | 2 / 134 (1.49%) 2 | 4 / 69 (5.80%) 5 |
| Dry mouth subjects affected / exposed occurrences (all) | 9 / 339 (2.65%) 9 | 5 / 134 (3.73%) 5 | 0 / 69 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 18 / 339 (5.31%) 22 | 3 / 134 (2.24%) 3 | 8 / 69 (11.59%) 9 |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 6 / 339 (1.77%) 6 | 2 / 134 (1.49%) 2 | 1 / 69 (1.45%) 1 |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 0 / 339 (0.00%) 0 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Endocrine disorders | | | |
| Hyperprolactinaemia subjects affected / exposed occurrences (all) | 6 / 339 (1.77%) 7 | 1 / 134 (0.75%) 1 | 1 / 69 (1.45%) 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness subjects affected / exposed occurrences (all) | 1 / 339 (0.29%) 2 | 0 / 134 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Infections and infestations | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| Bronchitis | | | |
| subjects affected / exposed | 3 / 339 (0.88%) | 2 / 134 (1.49%) | 0 / 69 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 0 / 69 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 1 / 134 (0.75%) | 0 / 69 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 1 / 134 (0.75%) | 0 / 69 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 24 / 339 (7.08%) | 8 / 134 (5.97%) | 7 / 69 (10.14%) |
| occurrences (all) | 30 | 12 | 8 |
| Pharyngitis bacterial | | | |
| subjects affected / exposed | 2 / 339 (0.59%) | 1 / 134 (0.75%) | 1 / 69 (1.45%) |
| occurrences (all) | 2 | 1 | 1 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 9 / 339 (2.65%) | 2 / 134 (1.49%) | 1 / 69 (1.45%) |
| occurrences (all) | 10 | 2 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 339 (2.65%) | 2 / 134 (1.49%) | 2 / 69 (2.90%) |
| occurrences (all) | 13 | 3 | 3 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 8 / 339 (2.36%) | 3 / 134 (2.24%) | 2 / 69 (2.90%) |
| occurrences (all) | 9 | 3 | 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 13 / 339 (3.83%) | 8 / 134 (5.97%) | 1 / 69 (1.45%) |
| occurrences (all) | 13 | 8 | 1 |
| Food intolerance | | | |
| subjects affected / exposed | 1 / 339 (0.29%) | 0 / 134 (0.00%) | 1 / 69 (1.45%) |
| occurrences (all) | 1 | 0 | 1 |
| Increased appetite | | | |

| | | | |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 5 / 339 (1.47%) | 4 / 134 (2.99%) | 0 / 69 (0.00%) |
| occurrences (all) | 5 | 4 | 0 |

| Non-serious adverse events | Fluoxetine 10-20 mg / Agomelatine 10-25 mg - Ado - W012-W104 | All - Adolescents - W012-W104 | Agomelatine 10 or 25 mg / 10-25 mg - W000-W104 period |
|---|--|-------------------------------|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 68 (57.35%) | 159 / 271 (58.67%) | 136 / 170 (80.00%) |
| General disorders and administration site conditions | | | |
| Drug interaction | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 10 / 271 (3.69%) | 14 / 170 (8.24%) |
| occurrences (all) | 1 | 10 | 14 |
| Thirst | | | |
| subjects affected / exposed | 2 / 68 (2.94%) | 10 / 271 (3.69%) | 26 / 170 (15.29%) |
| occurrences (all) | 2 | 11 | 31 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 0 / 170 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 271 (0.37%) | 1 / 170 (0.59%) |
| occurrences (all) | 0 | 0 | 1 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 1 / 271 (0.37%) | 1 / 170 (0.59%) |
| occurrences (all) | 1 | 1 | 3 |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 271 (0.00%) | 1 / 170 (0.59%) |
| occurrences (all) | 0 | 0 | 1 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 4 / 271 (1.48%) | 4 / 170 (2.35%) |
| occurrences (all) | 1 | 4 | 4 |
| Impulsive behaviour | | | |

| | | | |
|---|---------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 0 / 271 (0.00%) 0 | 1 / 170 (0.59%) 1 |
| Learning disability subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 0 / 271 (0.00%) 0 | 0 / 170 (0.00%) 0 |
| Investigations | | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 5 / 271 (1.85%) 5 | 4 / 170 (2.35%) 4 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 0 / 271 (0.00%) 0 | 1 / 170 (0.59%) 1 |
| Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 3 / 271 (1.11%) 3 | 6 / 170 (3.53%) 6 |
| Electrocardiogram PR shortened subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 0 / 271 (0.00%) 0 | 1 / 170 (0.59%) 1 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 2 / 68 (2.94%) 2 | 4 / 271 (1.48%) 4 | 2 / 170 (1.18%) 3 |
| Weight increased subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 10 / 271 (3.69%) 10 | 15 / 170 (8.82%) 16 |
| Blood prolactin increased subjects affected / exposed occurrences (all) | 2 / 68 (2.94%) 2 | 7 / 271 (2.58%) 7 | 11 / 170 (6.47%) 12 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 3 / 271 (1.11%) 3 | 7 / 170 (4.12%) 7 |
| Injury, poisoning and procedural complications | | | |
| Limb injury subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 0 / 271 (0.00%) 0 | 0 / 170 (0.00%) 0 |
| Cardiac disorders | | | |

| | | | |
|---|-----------------------|-------------------------|-------------------------|
| Bundle branch block right subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 0 / 271 (0.00%) 0 | 1 / 170 (0.59%) 1 |
| Nervous system disorders | | | |
| Disturbance in attention subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 2 / 271 (0.74%) 2 | 1 / 170 (0.59%) 1 |
| Dizziness postural subjects affected / exposed occurrences (all) | 2 / 68 (2.94%) 2 | 5 / 271 (1.85%) 5 | 9 / 170 (5.29%) 9 |
| Headache subjects affected / exposed occurrences (all) | 9 / 68 (13.24%) 11 | 37 / 271 (13.65%) 51 | 40 / 170 (23.53%) 65 |
| Dizziness subjects affected / exposed occurrences (all) | 3 / 68 (4.41%) 3 | 10 / 271 (3.69%) 11 | 10 / 170 (5.88%) 13 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 68 (1.47%) 1 | 8 / 271 (2.95%) 8 | 17 / 170 (10.00%) 21 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 68 (1.47%) 2 | 7 / 271 (2.58%) 9 | 11 / 170 (6.47%) 13 |
| Dry mouth subjects affected / exposed occurrences (all) | 2 / 68 (2.94%) 2 | 7 / 271 (2.58%) 7 | 31 / 170 (18.24%) 37 |
| Nausea subjects affected / exposed occurrences (all) | 4 / 68 (5.88%) 5 | 15 / 271 (5.54%) 17 | 24 / 170 (14.12%) 28 |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 3 / 271 (1.11%) 3 | 9 / 170 (5.29%) 10 |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 0 / 271 (0.00%) 0 | 1 / 170 (0.59%) 1 |
| Endocrine disorders | | | |

| | | | |
|---|---------------------|------------------------|-------------------------|
| Hyperprolactinaemia subjects affected / exposed occurrences (all) | 2 / 68 (2.94%) 2 | 4 / 271 (1.48%) 5 | 2 / 170 (1.18%) 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 0 / 271 (0.00%) 0 | 5 / 170 (2.94%) 5 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 2 / 271 (0.74%) 2 | 3 / 170 (1.76%) 3 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 1 / 68 (1.47%) 1 | 1 / 271 (0.37%) 1 | 1 / 170 (0.59%) 1 |
| Gastrointestinal infection subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 1 / 271 (0.37%) 2 | 2 / 170 (1.18%) 3 |
| Gastrointestinal viral infection subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 1 / 271 (0.37%) 1 | 2 / 170 (1.18%) 2 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 68 (2.94%) 2 | 17 / 271 (6.27%) 22 | 19 / 170 (11.18%) 23 |
| Pharyngitis bacterial subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 2 / 271 (0.74%) 2 | 1 / 170 (0.59%) 1 |
| Respiratory tract infection viral subjects affected / exposed occurrences (all) | 1 / 68 (1.47%) 1 | 4 / 271 (1.48%) 4 | 7 / 170 (4.12%) 9 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 68 (2.94%) 2 | 6 / 271 (2.21%) 8 | 5 / 170 (2.94%) 7 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 5 / 271 (1.85%) 5 | 8 / 170 (4.71%) 10 |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|------------------------|------------------------|
| Decreased appetite subjects affected / exposed occurrences (all) | 3 / 68 (4.41%) 3 | 12 / 271 (4.43%) 12 | 15 / 170 (8.82%) 16 |
| Food intolerance subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 1 / 271 (0.37%) 1 | 1 / 170 (0.59%) 1 |
| Increased appetite subjects affected / exposed occurrences (all) | 0 / 68 (0.00%) 0 | 4 / 271 (1.48%) 4 | 13 / 170 (7.65%) 15 |

| | | | |
|---|--|--|--|
| Non-serious adverse events | Agomelatine 10 or 25 mg / 10-25 mg - Ado - W000-W104 | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 106 / 134 (79.10%) | | |
| General disorders and administration site conditions Drug interaction subjects affected / exposed occurrences (all) | 0 / 134 (0.00%) 0 | | |
| Fatigue subjects affected / exposed occurrences (all) | 12 / 134 (8.96%) 12 | | |
| Thirst subjects affected / exposed occurrences (all) | 21 / 134 (15.67%) 26 | | |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 134 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 134 (0.75%) 1 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 134 (0.00%) 0 | | |
| Psychiatric disorders | | | |

| | | | |
|---|------------------|--|--|
| Aggression | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences (all) | 1 | | |
| Anxiety | | | |
| subjects affected / exposed | 3 / 134 (2.24%) | | |
| occurrences (all) | 3 | | |
| Impulsive behaviour | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences (all) | 1 | | |
| Learning disability | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 134 (2.99%) | | |
| occurrences (all) | 4 | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 5 / 134 (3.73%) | | |
| occurrences (all) | 5 | | |
| Electrocardiogram PR shortened | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | | |
| occurrences (all) | 2 | | |
| Weight increased | | | |
| subjects affected / exposed | 12 / 134 (8.96%) | | |
| occurrences (all) | 13 | | |
| Blood prolactin increased | | | |
| subjects affected / exposed | 6 / 134 (4.48%) | | |
| occurrences (all) | 7 | | |
| Blood bilirubin increased | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 7 / 134 (5.22%) 7 | | |
| Injury, poisoning and procedural complications Limb injury subjects affected / exposed occurrences (all) | 0 / 134 (0.00%) 0 | | |
| Cardiac disorders Bundle branch block right subjects affected / exposed occurrences (all) | 0 / 134 (0.00%) 0 | | |
| Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all) Dizziness postural subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) | 1 / 134 (0.75%) 1 9 / 134 (6.72%) 9 32 / 134 (23.88%) 54 10 / 134 (7.46%) 13 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 11 / 134 (8.21%) 14 9 / 134 (6.72%) 11 24 / 134 (17.91%) 29 19 / 134 (14.18%) 23 | | |

| | | | |
|--|--|--|--|
| <p>Skin and subcutaneous tissue disorders</p> <p>Acne</p> <p>subjects affected / exposed</p> <p>6 / 134 (4.48%)</p> <p>occurrences (all)</p> <p>7</p> <p>Dermatitis allergic</p> <p>subjects affected / exposed</p> <p>1 / 134 (0.75%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Endocrine disorders</p> <p>Hyperprolactinaemia</p> <p>subjects affected / exposed</p> <p>1 / 134 (0.75%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Muscular weakness</p> <p>subjects affected / exposed</p> <p>4 / 134 (2.99%)</p> <p>occurrences (all)</p> <p>4</p> | | | |
| <p>Infections and infestations</p> <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>2 / 134 (1.49%)</p> <p>occurrences (all)</p> <p>2</p> <p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>0 / 134 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Gastrointestinal infection</p> <p>subjects affected / exposed</p> <p>2 / 134 (1.49%)</p> <p>occurrences (all)</p> <p>3</p> <p>Gastrointestinal viral infection</p> <p>subjects affected / exposed</p> <p>1 / 134 (0.75%)</p> <p>occurrences (all)</p> <p>1</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>13 / 134 (9.70%)</p> <p>occurrences (all)</p> <p>17</p> <p>Pharyngitis bacterial</p> <p>subjects affected / exposed</p> <p>1 / 134 (0.75%)</p> <p>occurrences (all)</p> <p>1</p> <p>Respiratory tract infection viral</p> | | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 134 (2.24%) 4 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 134 (2.24%) 4 | | |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 134 (2.99%) 4 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 12 / 134 (8.96%) 13 | | |
| Food intolerance subjects affected / exposed occurrences (all) | 0 / 134 (0.00%) 0 | | |
| Increased appetite subjects affected / exposed occurrences (all) | 11 / 134 (8.21%) 12 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 19 September 2016 | <p>It mainly concerned:</p> <ul style="list-style-type: none">- Supplementary non-inclusion criteria for liver function:<ul style="list-style-type: none">*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:<ul style="list-style-type: none">*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 | <p>It mainly concerned:</p> <ul style="list-style-type: none">- 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