2. SYNOPSIS

Name of Sponsors: **I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France** **L.L.S., 50 rue Carnot - 92284 Suresnes Cedex - France**		*(For National Authority Use only)*
Test drug **Name of Finished Product:** NA **Name of Active Ingredient:** Agomelatine - S20098		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Efficacy and safety of 2 doses of agomelatine (10 mg, 25 mg) 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.*** Protocol No.: CL3-20098-076 EudraCT No.: 2015-002181-23 The description of the study protocol given hereafter includes the modifications of the two substantial amendments to the protocol (No. 1 and No. 2) and the two non-substantial amendments.		
Main investigator: NA. Nine national coordinators supervised this study.		
Study countries: 46 centres in 9 countries included 400 patients: - 120 patients in Russia (8 centres). - 74 patients in Hungary (5 centres). - 72 patients in Ukraine (10 centres). - 61 patients in Romania (6 centres). - 31 patients in Poland (4 centres). - 17 patients in South Africa (4 centres). - 10 patients in Serbia (4 centres). - 9 patients in Bulgaria (3 centres). - 6 patients in Finland (2 centres).		
Publication (reference): NA		
Studied period: Initiation date: 23 February 2016. Completion date (of the 12-week double-blind period): 14 January 2020	**Phase of development of the study:** Phase III	
Objectives: The purpose of this study was to assess the short-term efficacy and the short-term safety of two doses of agomelatine in children and adolescents patients with Moderate to Severe Major Depressive Disorder (MDD). The primary objective was 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's Depression Rating Scale – Revised (CDRS-R). The secondary objectives were: - to assess the short-term and long-term safety of agomelatine (10 mg, 25 mg). - to evaluate the long-term efficacy of agomelatine (10 mg, 25 mg). - to explore efficacy and safety in children and adolescents separately. **This report concerns only the results of the 12-week double-blind period.**		

Methodology:
This study was a 12-week, randomized, double-blind, two-dose level, active and placebo-controlled, parallel groups, international, multicentre phase III study conducted in children from 7 to less than 12 years of age and adolescents from 12 to less than 18 years of age suffering from MDD.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 390 patients included in the study of which at least 312 patients from 12 to less than 18 years of age.
Included: 400 patients including 320 adolescents (from 12 to less than 18 years of age) and 80 children (from 7 to less than 12 years of age), were randomised as follows:

- 102 patients in the agomelatine 10 mg group.
- 95 in the agomelatine 25 mg group.
- 103 in the placebo group.
- 100 in the fluoxetine group.

Diagnosis and main criteria for inclusion:

- Male or female, aged from 7 to less than 12 or from 12 to less than 18 years of age;
- Primary diagnosis of MDD, single or recurrent episode, of moderate to severe intensity, as per Diagnostic Criteria for Major Depressive Episode, 4th edition, Text Revision (DSM-IV-TR).
- CDRS-R Raw score ≥ 45.
- Clinical Global Impression - Severity (CGI-S) rating score ≥ 4.
- Patients considered as non-responder to Manualized Psychosocial Counselling during the run-in period.
- Absence of hepatic impairment.
- Absence of high suicidal risk.
- Absence of any severe, uncontrolled, chronic condition incompatible with study treatment or likely to interfere with the conduct of the study.

Test drug:
Agomelatine: 10 mg and 25 mg, one film-coated tablet taken once a day, orally, in the evening at bedtime.

Comparator (Reference product and placebo):
Fluoxetine: 10 mg (2.5 mL) with a possible increase to 20 mg (5 mL) at week 2, oral solution taken once a day, in the morning at wake-up.
Placebo: one film-coated tablet taken once a day, orally, in the evening at bedtime or oral solution taken once a day, in the morning at wake-up.

Duration of treatment:
Run-in period: 3 weeks.
Double-blind treatment period: 12 weeks.
Optional open-label extension period: 21 months.
Follow-up period: 5 to 7 days after the last investigational medicinal product (IMP) intake.

Criteria for evaluation:
Efficacy measurements:
Primary efficacy endpoint:
CDRS-R Raw total score, expressed mainly in terms of change from baseline to W12.
Secondary expressions were:

- Value at baseline and at each post-baseline visit.
- Change from baseline to each post-baseline visit (other than W12).
- Remission at W12, defined as a CDRS-R Raw total score ≤ 28.

Secondary efficacy endpoints:

- CGI-S and CGI - Global Improvement (CGI-I) scores.
- Response to treatment based on CGI-I score 1 or 2.
- Children's Global Assessment Scale (CGAS) total score.
- Adolescent Depression Rating Scale (ADRS) total score (only for adolescents).

Safety measurements:

- Adverse events.
- Laboratory tests: biochemistry including liver function tests, haematology, hormonal parameters.
- Columbia Suicide Severity Rating Scale Children's version (C-SSRS-C).
- Continuous Performance Task (CPT) (Selective attention and Vigilance Tests).
- Paediatric Adverse Event Rating Scale (PAERS).
- Tanner stage.
- Physical examination: blood pressure (BP), heart rate (HR), body weight, height.
- Electrocardiogram (ECG).

Pharmacokinetic (PK) measurements:
See the separate PK report.

Other measurements:
Tablet acceptability.

Statistical methods:

Analysis sets and subgroups:

- *Modified Randomised Set (MRS):*

All included and randomised patients (*i.e.* all included patients to whom a therapeutic unit was randomly assigned using IRS).

- *Full Analysis Set (FAS):*

All 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.

- *Safety Set for double blind period (SS):*

All patients having taken at least one dose of IMP.

In order to explore the homogeneity of treatment effect among age subgroups on antidepressant efficacy, the following *subgroups* were planned for this study:

- children (from 7 to less than 12 at selection).
- adolescents (from 12 to less than 18 at selection).

Efficacy analysis:

All efficacy analyses were carried out in the FAS. The Last Observation Carried Forward (LOCF) approach was used to handle missing data.

Primary endpoint: Change from baseline to W012 in CDRS-R Raw score
Primary analysis: superiority of at least one dose of agomelatine as compared to placebo on antidepressant efficacy after a 12-week treatment period, from the CDRS-R raw total score expressed in terms of change from baseline to W012 using a three-way analysis of covariance (ANCOVA) model.
This model included the fixed, categorical effects of treatment (including the four treatment groups), age subgroup and country, as well as the continuous, fixed covariate of baseline. Missing data were imputed with the LOCF approach. The step-down Dunnett procedure was used to control the familywise error rate, since 2 doses of agomelatine were compared to placebo. The estimate of the difference between adjusted treatment group means, associated standard error, two-sided 95% confidence interval and Dunnett-adjusted p-value were provided.

Assay sensitivity: same analysis using the comparison of fluoxetine to placebo.

Sensitivity analyses: to assess the robustness of the primary analysis results to the missing data handling method, the following analyses were performed:

- using a mixed-effects model for repeated measures (MMRM) including the fixed, categorical effects of treatment, age subgroup, country, visit, treatment-by-visit and baseline-by-visit interaction as well as the continuous, fixed covariate of baseline. The baseline-by-visit interaction was added in the model after unblinding as it fitted better to study data.
- using the same ANCOVA model as for the primary analysis but with complete cases at W012.
- using a multiple imputation approach (unplanned).

The same procedure for multiplicity and the same statistical elements to estimate the treatment effect as for primary analysis were used.

Supplementary analysis: on remission derived from CDRS-R raw total score at W012 using a Chi-Square test.

In addition, descriptive statistics at baseline and at each post-baseline visit as well as change from baseline to each post-baseline visit by treatment group were provided for all analytical approaches of the primary efficacy endpoint on the W000-W012 period.

Secondary endpoints:

- *CGI-S and CGI-I scores*: difference between placebo and each active treatment group on the value of these scores at W012 (with the LOCF approach) using a two-sided Student's t-test for independent samples and a Mann-Whitney test.
- *Response to treatment based on CGI-I score*: difference between placebo and each active treatment group of proportion of patients with response to treatment at W012 (with the LOCF approach) using a Chi-Square test.
- *CGAS:* expressed as value at baseline and at each post-baseline visit as well as change from baseline to each post-baseline visit.
- *ADRS total score (only for adolescents):* difference between placebo and each active treatment group on the value of this score at W012 using a two-sided Student's t-test for independent samples and a Mann-Whitney test (with the LOCF approach).

Of note, description at baseline and at each post-baseline visit as well as change from baseline to each post-baseline visit were provided for all secondary efficacy endpoints.

Subgroup analyses:
The following analyses were performed in adolescents [12-17 years old] of the FAS, using the LOCF approach and the same models as for the total population of the FAS:

- CDRS-R raw total score expressed in terms of change from baseline to W012 (primary analysis, planned and sensitivity analyses, unplanned) and of remission (unplanned analysis).
- CGI-S score expressed as value at W012 (unplanned analysis).
- CGI-I score expressed in terms of value at W012 and of response to treatment (unplanned analysis).
- ADRS total score: see above.

Due to the small sample size in children, no statistical comparison test was performed in this subgroup, only descriptive statistics were provided.

Study outcome analysis:
Depending on the criterion, descriptive statistics were provided in the total population, adolescents and children of the MRS and the FAS.

Safety analysis:
Descriptive statistics were provided in the total population, adolescents and children of the Safety Set.

Pharmacokinetic analysis:
See the separate PK report.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

As planned in the protocol, a total of 400 patients were included in the CL3-20098-076 study, and randomly assigned to one of the 4 groups with a balanced ratio. Among them, 320 (80.0%) were adolescents and 80 (20.0%) were children.

The following table gives the disposition of included patients by group. During the study, 48 patients (12.0%) were withdrawn, with the lowest frequency in the agomelatine 10 mg group (7.8%) and the highest frequency in the placebo group (15.5%). The most frequent reasons for premature study withdrawals in the 4 treatment groups were non-medical reasons (7.8% of patients), with a lower frequency in the agomelatine 10 mg group (2.9% of patients) as compared to the other 3 groups (between 7.4% and 11.7%, according to treatment group). More than a third of withdrawn patients (19/48 patients) was withdrawn from the study at W008, mainly in the agomelatine 10 mg group (6/8 withdrawn patients) and placebo group (7/16 withdrawn patients). Most of the patients (88.0%) completed the study with the highest frequency in the agomelatine 10 mg group (92.2%) and the lowest frequency in the placebo group (84.5%). Overall, 88.4% of the adolescents completed the study without relevant difference between groups.

Disposition of included patients by treatment group - Overall patients

		Agomelatine 10 mg	Agomelatine 25 mg	Placebo	Fluoxetine	ALL
Included	**n**	**102**	**95**	**103**	**100**	**400**
Withdrawn due to	**n (%)[a]**	**8 (7.8)**	**11 (11.6)**	**16 (15.5)**	**13 (13.0)**	**48 (12.0)**
- non-medical reason	n (%)[a]	3 (2.9)	7 (7.4)	12 (11.7)	9 (9.0)	31 (7.8)
- adverse event	n (%)[a]	2 (2.0)	3 (3.2)	2 (1.9)	3 (3.0)	10 (2.5)
- lack of efficacy	n (%)[a]	3 (2.9)	1 (1.1)	2 (1.9)	-	6 (1.5)
- protocol deviation	n (%)[a]	-	-	-	1 (1.0)	1 (0.3)
Completed	**n (%)[a]**	**94 (92.2)**	**84 (88.4)**	**87 (84.5)**	**87 (87.0)**	**352 (88.0)**
Modified Randomised Set	**n (%)**	**102 (25.5)[b]**	**95 (23.8)[b]**	**103 (25.8)[b]**	**100 (25.0)[b]**	**400**
Full Analysis Set	**n (%)**	**102 (25.8)[b]**	**94 (23.7)[b]**	**101 (25.5)[b]**	**99 (25.0)[b]**	**396 (99.0)[c]**
Safety set	**n (%)**	**102 (25.6)[b]**	**94 (23.6)[b]**	**103 (25.8)[b]**	**100 (25.1)[b]**	**399 (99.8)[c]**

[a] *% calculated as % of the included patients.*
[b] *% based on ALL of the corresponding set.*
[c] *% calculated as % of the Modified Randomised Set.*

BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics fulfilled with the selection/inclusion criteria defined in the protocol.

In the total population of the MRS (N = 400), the mean age was of 13.7 ± 2.7 years. The mean age of the children (from 7 to 11 years old) was 9.2 ± 1.3 years and that of the adolescents (from 12 to 17 years old) was 14.8 ± 1.6 years. As observed in the adult population, almost 2 thirds of overall patients (62.5%) were girls without relevant difference between groups except a lower rate of girls in the fluoxetine group (57.0%); this trend was the same in the adolescents but not in the children for whom boys (60%) were more numerous than girls which is in line with what is usually observed in the younger population.

According to DSM-IV-TR criteria, 71.5% of the patients of the total population were in their first episode of MDD with a higher rate in the agomelatine 10 and 25 mg groups (78.4% and 74.7%, respectively) than in the placebo (64.1%) and fluoxetine (69.0%) groups. Major depressive episode (MDE) was diagnosed as moderate in most of the patients (61.8%) and as severe without psychotic features in 38.3% of the patients with a lower rate in the agomelatine 10 mg group (27.5%) compared to the other 3 groups (between 41.0% and 43.7%). Overall, 18.3% of the patients had melancholic features without relevant difference between groups.
No relevant difference between groups was observed regarding the other DSM-IV criteria.

Patients of the MRS had this current MDE for 143.4 ± 153.2 days on average (ranging from 29 to 1463 days). This mean duration was higher in the agomelatine 10 mg group (181.2 ± 210.0 days) compared to the other 3 groups (125.2 ± 109.2 to 137.0 ± 130.5 days), mainly due to a maximum equal to 1463 days (~4 years). Overall, 28.5% of the patients already had a history of previous MDE, with a lower rate in the agomelatine 10 mg and 25 mg (21.6% and 25.3%, respectively) groups than in the placebo (35.9%) and fluoxetine (31.0%) groups.

According to Columbia-suicide severity rating scale, 23.0% of the patients had suicidal ideation in their lifetime, without relevant difference between groups. Overall, 3.5% had suicidal behaviour in their lifetime with a higher rate in the agomelatine 25 mg (6.3%) than in the placebo (1.9%) groups, including 3.3% of patients having done actual suicide attempt (higher rate in the agomelatine 25 mg (5.3%) than in the placebo (1.9%) groups) and 1.8% of patients having done preparatory actions toward imminent suicidal behaviour (higher rate in the agomelatine 25 mg group (4.2%) than in the 3 other groups (1.0%, each)). Overall, 11.3% of patients had self-injurious behaviour without suicidal intent in their lifetime with the highest rate in the fluoxetine (14.0%) group (11.8% and 9.5%, respectively, in the agomelatine 10 mg and 25 mg groups and 9.7% in the placebo group).

Most of the patients (62.0%) reported at least one medical history besides MDD with a higher rate in the agomelatine 10 mg group (70.6%) compared to the 3 other groups (56.8% to 61.0% according to the group).

As required in the selection criteria, all patients had CDRS-R raw total score ≥ 45 with a mean of 65.5 ± 8.4 and CGI-S score ≥ 4 with a mean of 4.9 ± 0.6. The mean CGAS score was 46.5 ± 8.2. No relevant difference between groups was observed for these parameters.

No relevant difference between groups was observed for vital signs, at baseline, in the MRS. The mean sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 112.9 ± 10.5 mmHg and 70.0 ± 8.7 mmHg, respectively. The mean heart rate was 75.9 ± 11.1 bpm. The patients weighted on average 53.1 ± 15.5 kg at baseline. Regarding body mass index (BMI), 4.5% of patients were considered underweight, 16.5% overweight and 7.5% obese.
As regards ECG parameters, 6 patients (1.5%) had at least one clinically significant ECG abnormality at baseline.

Concerning the pubertal status, in the Modified Randomised female subgroup, 71.2% of the girls had a Tanner stage IV or V for pubic hair development and for breast development. In the Modified Randomised male subgroup, the distribution between the different stages was more dispersed.
Overall, 84% of the girls had already had their first menstruations without relevant difference between groups.

Regarding the adolescent subgroup in the MRS, 68.1% of adolescents were girls with a higher rate in the agomelatine 10 mg group (77.8%) compared to the 3 other groups (60.5% to 68.3%). Criteria on the characteristics and history of MDD and on the vital signs were close to those presented in the total population. As expected, the weight was higher in the adolescent subgroup compared to the total population with a mean of 58.0 ± 12.8 kg at baseline of the study. The mean score of ADRS at baseline, scale specific to adolescents, was 33.1 ± 6.0 without relevant difference between groups.
Concerning pubertal status, more than 80% of the female adolescents had Tanner stage IV or V for pubic hair development and for breast development. In male adolescents, the distribution between the different stages was more dispersed: they had mainly Tanner stage IV for pubic hair development (37.3%) and for genitalia development (40.2%).

Regarding the children subgroup, as expected in this population, there were more males (60.0%) than females (40.0%): 42.1% to 76.2% of males depending on treatment groups. According to DSM-IV-TR criteria, the MDE was diagnosed as moderate in most of the children (75.0%) and as severe without psychotic features in 25.0% of children with a lower rate in the agomelatine 10 mg (14.3%) than in the placebo (33.3%) groups. MDE presented melancholic features in 7.5%.
According to Columbia-suicide severity rating scale, 15.0% of patients had suicidal ideation in their life. No child had suicidal behaviour or actual suicide attempt in their life. A history of previous MDE was present in 11.3%. The differences between groups regarding MDD history were mainly due to small sample sizes, thus these differences cannot be considered relevant.
Concerning the pubertal status, most of children had Tanner stage I for pubic hair development, for breast development, and for genitalia development (more than 60% for each criteria).

EXTENT OF EXPOSURE (W000-W012 study period)
In the Safety Set (N = 399), the treatment duration ranged between 6 and 97 days with a mean of 80.2 ± 16.0 days. A large majority of patients (82.1%) were treated between 80 and 88 days. The tablet compliance and the oral solution compliance were good (95.7 ± 10.6% and 96.4 ± 13.8%, respectively). No relevant difference between groups was noted for these parameters. Similar results were observed in both age subgroups.

EFFICACY RESULTS

- **Primary efficacy endpoint: CDRS-R raw total score**

The primary efficacy endpoint was defined as the change from baseline to W012 in the CDRS-R raw total score. This score decreased between baseline and the last post-baseline value in the four treatment groups.

The *main analysis* which consisted in the estimation of difference in change from baseline between placebo and each agomelatine dose regimen, in the FAS, using an ANCOVA model with the LOCF approach for the missing data handling showed the superiority of agomelatine 25 mg compared to placebo with a statistically significant difference between groups (E (SE) = 4.22 (1.83); 95% CI [0.63 ; 7.82]; Step-Down Dunnett adjusted p-value = 0.04). The result with agomelatine 10 mg showed an estimated difference (SE) of 3.18 (1.81) without statistical significance (95% CI [-0.37; 6.73]; Step-Down Dunnett adjusted p-value = 0.079).

The assay sensitivity was positive with a difference between placebo and fluoxetine groups statistically significant in favour of fluoxetine.

The superiority of agomelatine 25 mg compared to the placebo was confirmed by the *3 sensitivity analyses* carried out in the FAS to assess the robustness of the primary analysis results to the method of handling missing data (LOCF). Assay sensitivity was confirmed only with the MMRM model and the ANCOVA using a multiple imputation approach to handle missing data (unplanned).

Main results on the primary efficacy endpoint in the FAS are summarised in the following table.

CDRS-R raw total score - Main analysis: change from baseline to last post-baseline - FAS (N = 396)

		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 101)	Fluoxetine (N = 99)
Baseline	n	102	94	101	99
	Mean ± SD	64.3 ± 8.3	65.5 ± 8.3	67.5 ± 8.6	65.0 ± 8.0
	Median	63.5	65.0	67.0	65.0
	Min ; Max	46 ; 87	52 ; 90	49 ; 93	47 ; 89
Last post baseline	n	102	94	101	99
	Mean ± SD	43.4 ± 14.2	43.0 ± 13.4	47.9 ± 15.4	43.3 ± 12.6
	Median	43.0	44.5	48.0	43.0
	Min ; Max	17 ; 87	17 ; 83	17 ; 90	19 ; 76
Last post baseline - Baseline	n	102	94	101	99
	Mean ± SD	-20.9 ± 14.0	-22.5 ± 15.2	-19.7 ± 14.4	-21.7 ± 14.1
	Median	-21.5	-21.0	-20.0	-21.0
	Min ; Max	-59 ; 15	-66 ; 2	-52 ; 20	-53 ; 5
Statistical analyses					
Primary statistical analysis	E (SE) (1a)	3.18 (1.81)	4.22 (1.83)		
	95% CI (2)	[-0.37 ; 6.73]	[0.63 ; 7.82]		
	p-value (3)	0.079	0.040		
Assay sensitivity analysis	E (SE) (1b)				3.74 (1.81)
	95% CI (2)				[0.18 ; 7.30]
	p-value (3)				0.039

(1a) Estimate (Standard Error) of the adjusted difference from baseline to last post baseline value between treatment group means: Placebo minus each Agomelatine dose regimen using an ANCOVA including the fixed, categorical effects of treatment (including the four treatment groups), age subgroup and country, as well as the continuous, fixed covariate of baseline

(1b) Estimate (Standard Error) of the adjusted difference from baseline to last post baseline value between treatment group means: Placebo minus Fluoxetine using an ANCOVA including the fixed, categorical effects of treatment (including the four treatment groups), age subgroup and country, as well as the continuous, fixed covariate of baseline

(2) 95% Confidence interval of the estimate

(3) Step Down Dunnett adjusted p-value for Agomelatine dose regimen and p-value for Fluoxetine (to be compared to 0.05)

The *descriptive analysis (supplementary analysis)*, in the FAS, of the change between baseline and post-baseline visits in the mean CDRS-R raw total score showed that this change was higher in the agomelatine 25 mg group than in the placebo group and similar between the agomelatine 10 mg and placebo groups, for each post-baseline visit. Roughly, the changes were also higher in the fluoxetine group than in the placebo group.

Another supplementary analysis, in the FAS, on the rate of remission at last post-baseline value defined as a CDRS-R raw total score ≤ 28 showed a higher rate of remitters in both agomelatine dose groups (13.7% in the agomelatine 10 mg group and 16.0% in the agomelatine 25 mg group) compared to placebo (10.9%) without statistically significant difference. No statistically significant difference was also observed between fluoxetine and placebo groups.

Results in adolescent patients confirmed the superiority of agomelatine 25 mg *versus* placebo on CDRS-R total raw score in terms of change from baseline to last post-baseline value in the adolescents of the FAS (ANCOVA model, LOCF approach: E(SE) = 5.22 (2.13); 95% CI [1.03 ; 9.40]; Step-Down Dunnett adjusted p-value = 0.028). Difference between fluoxetine and placebo was not statistically significant. Superiority of agomelatine 25 mg was also confirmed by the sensitivity analyses (unplanned) (MMRM, complete cases and multiple imputation), a statistically significant difference between placebo and fluoxetine was observed only with the MMRM model. As for the total population of the FAS, the change from baseline to post baseline-visits was higher in the agomelatine 25 mg group than in the placebo group and similar between the agomelatine 10 mg and placebo groups, at each visit, in the adolescents. Roughly, the changes were also higher in the fluoxetine group than in the placebo group.

A higher proportion of adolescents with remission at last post-baseline value, based on CDRS-R total score, was observed in both agomelatine groups (16.0% in the agomelatine 10 mg group and 17.3% in the agomelatine 25 mg group) compared to the placebo group (8.6%), without statistical significance (unplanned analysis).

By contrast, *in the children of the FAS*, the change from baseline to last post-baseline value in the mean CDRS-R raw total score was lower in the agomelatine 25 mg group (-17.1 ± 13.3) than in the placebo group (-19.0 ± 18.3). This change was quite similar between the agomelatine 10 mg (-20.0 ± 13.9) and placebo groups. Due to the few numbers of patients in each group, results should be interpreted carefully.

- **Secondary efficacy endpoints**

Clinical Global Impression

The means of CGI-S score and CGI-I score gradually decreased at each visit up to W012 in each treatment group, in the FAS.

Two statistical tests (Student t-test [parametric test] and Mann-Whitney test [non-parametric test]) were performed to assess the difference in means of the last post baseline value between treatment groups.

In the FAS, the difference in ***CGI-S score*** means of the last post-baseline value between placebo (3.8 ± 1.2) and each agomelatine dose regimen (3.5 ± 1.1 for both agomelatine doses) was statistically significant in favour of agomelatine 10 mg with the Mann-Whitney test (p = 0.035). In addition, a trend in favour of agomelatine 25 mg group was observed, the result being close to the significance with the Mann-Whitney test (p = 0.051). The difference between placebo and fluoxetine was not statistically significant. In the adolescents of the FAS, no statistically significant difference between treatment groups was observed (unplanned analysis).

Regarding the mean ***CGI-I score***, no statistically significant difference of the last post-baseline value, between placebo (2.7 ± 1.1) and each agomelatine dose (2.6 ± 1.1 in the agomelatine 10 mg group and 2.5 ± 1.0 in the agomelatine 25 mg group) and between placebo and fluoxetine (2.6 ± 1.0), was observed. Similar results were observed in the adolescents of the FAS.

In children of the FAS, the mean CGI-I score for the last post-baseline value was 2.7 ± 0.9 in both agomelatine groups, 3.0 ± 1.2 in the placebo group and 2.8 ± 0.8 in the fluoxetine group.

The proportion of patients with ***response to treatment*** (defined as a CGI-I score = 1 or 2) at last post-baseline value was 48.0% in the agomelatine 10 mg group and 48.9% in the agomelatine 25 mg group *versus* 44.6% in the placebo group without statistically significant difference. Similar result was observed for the difference between placebo and fluoxetine. Results were similar in the adolescents of the FAS (unplanned analysis).

Children's Global Assessment Scale (*level of global functioning*)

In the FAS, the mean ***CGAS total score*** gradually increased at each visit between baseline and W012 to achieve a change from baseline to last post-baseline value of 13.2 ± 11.3 in the agomelatine 10 mg group, 14.4 ± 13.0 in the agomelatine 25 mg group, 12.1 ± 14.0 in the placebo group and 13.9 ± 12.5 in the fluoxetine group, indicating an improvement in global functioning of patients.

Adolescent Depression Rating Scale (only in the adolescents of the FAS)

The mean ADRS total score greatly decreased between baseline and W004 and continued to gradually decrease at each visit between W004 and W012 in each treatment group to achieve a last post-baseline value of 18.8 ± 10.1 in the agomelatine 10 mg group, 18.1 ± 10.6 in the agomelatine 25 mg group and 22.2 ± 10.7 in the placebo group.

The difference of means of the last post-baseline value between placebo and each agomelatine dose regimen was statistically significant in favour of agomelatine 10 mg with Student t-test (E (SE) = 3.40 (1.65); 95% CI [0.14 ; 6.67], p = 0.041) but not with Mann-Whitney test (p = 0.064) and in favour of agomelatine 25 mg with both statistical tests (E (SE) = 4.07 (1.72), 95% CI [0.68 ; 7.46], p = 0.019 and 0.032, respectively).

The difference of means between placebo and fluoxetine were not statistically significant.

SAFETY RESULTS

- **Emergent adverse events (EAE)**

The following table summarises the reported adverse events by treatment group in the total population (N = 399), adolescents (N = 319) and children (N = 80) of the Safety Set.

Overall summary for adverse events in the Safety Set

		Agomelatine 10 mg	Agomelatine 25 mg	Placebo	Fluoxetine
Total population	N	102	94	103	100
Adolescents	N	81	75	82	81
Children	N	21	19	21	19
Patients having reported at least one:					
EAE					
Total population	n (%)	62 (60.8)	60 (63.8)	63 (61.2)	57 (57.0)
Adolescents	n (%)	51 (63.0)	47 (62.7)	49 (59.8)	47 (58.0)
Children	n (%)	11 (52.4)	13 (68.4)	14 (66.7)	10 (52.6)
Treatment-related EAE					
Total population	n (%)	30 (29.4)	35 (37.2)	28 (27.2)	29 (29.0)
Adolescents	n (%)	27 (33.3)	28 (37.3)	24 (29.3)	24 (29.6)
Children	n (%)	3 (14.3)	7 (36.8)	4 (19.0)	5 (26.3)
Serious EAE*					
Total population	n (%)	6 (5.9)	3 (3.2)	-	7 (7.0)
Adolescents	n (%)	5 (6.2)	2 (2.7)	-	7 (8.6)
Children	n (%)	1 (4.8)	1 (5.3)	-	-
Treatment-related serious EAE					
Total population	n (%)	-	1 (1.1)	-	2 (2.0)
Adolescents	n (%)	-	1 (1.3)	-	2 (2.5)
Children	n (%)	-	-	-	-
EAE leading to treatment withdrawal					
Total population	n (%)	3 (2.9)	4 (4.3)	2 (1.9)	3 (3.0)
Adolescents	n (%)	2 (2.5)	3 (4.0)	1 (1.2)	3 (3.7)
Children	n (%)	1 (4.8)	1 (5.3)	1 (4.8)	-
Serious EAE leading to treatment withdrawal					
Total population	n (%)	3 (2.9)	2 (2.1)	-	2 (2.0)
Adolescents	n (%)	2 (2.5)	2 (2.7)	-	2 (2.5)
Children	n (%)	1 (4.8)	-	-	-
Treatment-related EAE leading to treatment withdrawal					
Total population	n (%)	-	3 (3.2)	1 (1.0)	3 (3.0)
Adolescents	n (%)	-	2 (2.7)	1 (1.2)	3 (3.7)
Children	n (%)	-	1 (5.3)	-	-
Treatment-related serious EAE leading to treatment withdrawal					
Total population	n (%)	-	1 (1.1)	-	2 (2.0)
Adolescents	n (%)	-	1 (1.3)	-	2 (2.5)
Children	n (%)	-	-	-	-

** all serious AEs were emergent during the treatment period.*

During the 12-week treatment period in the Safety Set, the percentage of patients who reported at least one EAE was similar in the agomelatine 10 mg (60.8%) and 25 mg (63.8%) groups and in the placebo group (61.2%) whereas slightly lower in the fluoxetine group (57.0%).

Among the **most frequently affected system organ classes** (SOC) on agomelatine (≥ 10.0% of patients in at least one of the 2 groups), metabolism and nutrition disorders were more frequently reported (*i.e.* a difference of at least 3 patients) in the agomelatine 10 and 25 mg groups (9.8% of patients and 11.7%, respectively) than in the placebo group (6.8%) (7.0% in the fluoxetine group).
In addition, gastrointestinal (GI) disorders and investigations were more frequently reported in the agomelatine 10 mg group than in the placebo group (31.4% *versus* 25.2%, respectively, for GI disorders and 20.6% *versus* 16.5%, respectively, for investigations) (25.5% in the agomelatine 25 mg group and 26.0% in the fluoxetine group for GI disorders and 17.0% and 11.0%, respectively, for investigations).

In the adolescents, GI disorders and general disorders and administration site conditions were more frequently reported in the agomelatine 10 mg group than in the placebo group (30.9% *versus* 25.6%, respectively, for GI disorders and 23.5% *versus* 18.3%, respectively, for general disorders and administration site conditions) (25.3% in the agomelatine 25 mg group and 28.4% in the fluoxetine group for GI disorders and 22.7% and 18.5%, respectively for general disorders and administration site conditions). In addition, nervous system disorders and metabolism and nutrition disorders were more frequently reported in the agomelatine 25 mg group than in the placebo group (25.3% *versus* 19.5%, respectively, for nervous system disorders and 12.0% *versus* 4.9%, respectively, for metabolism and nutrition disorders (22.2% in the agomelatine 10 mg group and 19.8% in the fluoxetine group for nervous system disorders and 7.4% in both groups for metabolism and nutrition disorders).
In the children of the SS, among the most common SOCs affected, investigations were more frequently reported in the agomelatine 10 and 25 mg groups (23.8% and 21.1%, respectively) than in the placebo group (9.5%) (10.5% in the fluoxetine group). In addition, GI disorders were more frequently reported in the agomelatine 10 mg group than in the placebo group (33.3% *versus* 23.8%) (26.3% in the agomelatine 25 mg group and 15.8% in the fluoxetine group).

In the total population of the SS, the **most common EAEs** (in more than 5 patients in one of the 2 agomelatine groups) more frequently reported (*i.e.* a difference of at least 3 patients) in the agomelatine 10 and 25 mg groups than in the placebo group were thirst (15.7% and 13.8% of the patients *versus* 9.7%, respectively and 15.0% in the fluoxetine group), increased appetite (6.9% and 6.4% *versus* none, respectively and 3.0%) and weight increased (5.9% and 5.3% *versus* none, respectively and 2.0%). In addition, dry mouth was more frequently reported in the agomelatine 10 mg group than in the placebo group (20.6% *versus* 10.7%, respectively) (13.8% in the agomelatine 25 mg and 13.0% in the fluoxetine group).
Among the other EAEs (reported in ≤ 5 patients in both agomelatine groups), blood prolactin increased was reported with a higher frequency in the agomelatine 10 mg group (3.9% of the patients, 4 patients) than in the placebo group (1.0%, one patient) (1.1%, one patient in the agomelatine 25 mg group and none on fluoxetine).
In addition, dizziness postural was more frequently reported in the agomelatine 25 mg group (5.3%, 5 patients) than in the placebo group (1.0%, 1 patient) (2.0%, 2 patients in the agomelatine 10 mg and in the fluoxetine groups).
No increase of frequency of adverse events with the dose was observed.
Similar trends were observed *in the adolescents*, except that thirst was only more frequently reported in the agomelatine 10 mg group as compared to placebo and that there was no relevant difference between agomelatine and placebo groups for blood prolactin increased.
In the children of the SS, dry mouth, abdominal pain and headache were the most frequent EAEs reported (in more than 2 children) in at least one of the 2 agomelatine groups with a higher frequency on agomelatine than on placebo: compared to placebo, the frequency was higher in both agomelatine groups for dry mouth, in the agomelatine 10 mg group for abdominal pain and in the agomelatine 25 mg group for headache. None of these events was reported in more than 4 children in any group.

A few patients of the total population of the SS (6 patients in each agomelatine group, 4 in the placebo group and 8 in the fluoxetine group) experienced **severe EAEs**. Severe EAEs were reported no more than once in any group, except fatigue and decreased appetite, each twice in the placebo group and 3 times in the agomelatine 25 mg group for fatigue.
Most severe EAEs in the total population occurred in the adolescents. Only 1 severe EAE in 1 patient in the agomelatine 10 mg group (decreased appetite) and 3 severe EAEs in 2 patients in the fluoxetine group (impulsive behaviour, learning disability and disturbance in attention) occurred in the children.

In the SS, the percentage of patients with at least one **EAE considered to be related to IMP** was higher in the agomelatine 25 mg group (37.2%) than in the placebo group (27.2%). No relevant difference was noted between the agomelatine 10 mg group (29.4%) and the placebo group, as well as between the fluoxetine group (29.0%) and the placebo group.
Among the most frequently treatment-related EAEs reported (in more than 2 patients in one of the agomelatine groups), dry mouth was more frequently reported (*i.e.* a difference of at least 2 patients) in the agomelatine 10 and 25 mg groups (16.7% and 12.8% of the patients, respectively) than in the placebo group (8.7%) (10.0% in the fluoxetine group). In addition, thirst was more frequently reported in the agomelatine 10 mg group (11.8%) than in the placebo group (7.8%) (9.6% in the agomelatine 25 mg group and 10.0% in the fluoxetine group) and abdominal pain was more frequently reported in the agomelatine 25 mg group (3.2%) than in the placebo group (1.0%) (2.0% in the agomelatine 10 mg group and 1.0% in the fluoxetine group).

In the adolescents, dry mouth and thirst were the most frequent treatment-related EAEs reported in at least one of the 2 agomelatine groups with a higher frequency on agomelatine 10 mg than on placebo. *In the children*, dry mouth was the most frequent treatment-related EAE reported in at least one of the 2 agomelatine groups with a higher frequency on agomelatine 25 mg than on placebo.

No death was reported during the 12-week treatment period.

A total of 16 patients (4.0%), including 14 adolescents and 2 children, experienced 23 **serious emergent adverse events** (SEAE) during the study, all on active treatment: 6 patients (5.9%) in the agomelatine 10 mg group, 3 patients (3.2%) in the agomelatine 25 mg group and 7 patients (7.0%) in the fluoxetine group. All SEAEs were reported no more than once in any group, except syncope reported twice in the fluoxetine group.
SEAEs considered as treatment-related were hypothyroidism in the agomelatine 25 mg group and alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased (both events in one patient) and suicidal ideation in the fluoxetine group.
The SEAEs which led to IMP withdrawal were anorexia nervosa, alcohol poisoning and infectious mononucleosis (this last event occurring in one child) in the agomelatine 10 mg group, intentional self-injury, suicide attempt, somnolence, intentional overdose (all events in one patient) and hypothyroidism in the agomelatine 25 mg group and suicidal ideation (one patient), ALT increased and AST increased (one patient) in the fluoxetine group.

In the SS, a total of 12 patients, including 9 adolescents and 3 children, experienced at least one **EAE leading to treatment withdrawal**, without relevant difference between groups: 3 patients (2.9%) in the agomelatine 10 mg group, 4 patients (4.3%) in the agomelatine 25 mg group, 2 patients (1.9%) on placebo and 3 patients (3.0%) on fluoxetine. All EAEs leading to IMP withdrawal were reported no more than once in any group.

In addition to SEAEs, an **immediate notification** was also done for 2 non-serious EAEs in the agomelatine 25 mg group (ALT increased and AST increased in one patient) and for 3 non-serious EAEs in the fluoxetine group (accidental overdose in 2 patients and 2 episodes of AST increased in one third patient).

- **PAERS, clinician form**

Among the most frequent PAERS symptoms reported (in more than 50.0% of patients) in at least one of the 2 agomelatine groups, sad or depressed mood, irritability, trouble paying attention/concentrating, fatigue, apathy, emotional lability and anxious mood were more frequently reported on agomelatine 10 mg than on placebo at W001, whereas no relevant difference between agomelatine 25 mg and placebo groups was observed. At W012, the rate of patients presenting these symptoms tended to decrease in both agomelatine groups with still a higher frequency on agomelatine 10 mg compared to placebo for irritability, trouble paying attention/concentrating, emotional lability and anxious mood. Globally, the percentage of patients with symptoms of severe or extreme intensity gradually decreased with each visit from W001 to W012 in each group.

Similar results were observed in the adolescents at W001. Only the higher frequency for emotional lability on agomelatine 10 mg compared placebo persisted at W012.

- **Laboratory tests**

Globally, for all ***biochemical other than liver parameters, haematological parameters and hormonology*****,** neither clear clinically relevant changes nor differences between the 2 agomelatine groups and the placebo group over time were detected in the 2 age subgroups of the SS except a slight increase of mean triglycerides from baseline to last-post-baseline value on agomelatine 10 mg (0.304 ± 0.538 mmol/L) compared to placebo (0.073 ± 0.403 mmol/L) in children.

- Regarding *biochemical parameters other than liver*, in the total population of the SS, emergent potentially clinically significant abnormal (PCSA) values were sparse except low high-density lipoprotein (HDL) cholesterol more frequently reported (*i.e.* a difference of at least 2 patients) in the agomelatine 10 mg group (4.0%) than in the placebo group (2.0%). This difference was due to the children subgroup where 3 children had low emergent PCSA value for HDL cholesterol in the agomelatine 10 mg group (14.3%) *versus* no child in the placebo group.
- Regarding *haematological parameters*, in the total population of the SS, emergent PCSA values were sparse without relevant difference between agomelatine and placebo groups. Of note, low haematocrit values were reported by 2 patients on agomelatine 10 mg *versus* none on placebo and high leucocytes values were reported by 2 patients on agomelatine 25 mg *versus* none on placebo. Similar trends were observed in the adolescents of the SS whereas no noticeable difference was observed between agomelatine groups and placebo group in the children.

- Regarding *hormonology parameters*, in the total population of the SS, emergent abnormal values on treatment (no PCSA limit defined for hormonology parameters) were more frequently reported (*i.e.* a difference of at least 3 patients) on agomelatine 10 mg than on placebo for low follicle-stimulating hormone (FSH) (25.0% *versus* 20.0%, respectively) (23.9% on agomelatine 25 mg and 20.8% on fluoxetine). Emergent abnormal values were more frequently reported on agomelatine 25 mg than on placebo for high oestradiol (16.9% *versus* 11.6%, respectively) (9.6% on agomelatine 10 mg and 14.1% on fluoxetine) and for low thyroid-stimulating hormone (4.3% *versus* 1.0%, respectively) (2.0% on agomelatine 10 mg and 2.1% on fluoxetine).
  In the adolescents, compared to placebo, emergent abnormal values were more frequently reported (*i.e.* a difference of at least 3 patients) on agomelatine 10 and 25 mg for low FSH, on agomelatine 10 mg for high luteinizing hormone and on agomelatine 25 mg for low and high cortisol. In children, only high emergent values of oestradiol were more frequently reported (*i.e.* a difference of at least 2 patients) on agomelatine 25 mg than on placebo.

Regarding ***liver acceptability****:*

- In the adolescents of the SS, neither clinically relevant changes nor differences between groups in mean values over time were detected except a slight increase of transaminases from baseline to last post-baseline value in the agomelatine 25 mg group compared to the placebo.
  For ALT, the mean change was 2.9 ± 12.5 IU/L on agomelatine 25 mg *versus* -0.9 ± 6.8 IU/L on placebo. The mean changes were 0.0 ± 6.6 IU/L on agomelatine 10 mg and 2.1 ± 15.2 IU/L on fluoxetine.
  For AST, the mean change was 4.9 ± 38.0 IU/L on agomelatine 25 mg *versus* -0.7 ± 5.5 IU/L on placebo. The mean changes were -0.5 ± 6.3 IU/L on agomelatine 10 mg and 0.9 ± 6.9 IU/L on fluoxetine
- In the children of the SS, mean values over time showed a slight increase of transaminases and gamma-glutamyl transferase (GGT) on agomelatine 10 mg compared to placebo. Mean changes from baseline to last post-baseline value were respectively 4.8 ± 27.3 IU/L and -0.7 ± 5.6 IU/L for ALT, 3.5 ± 21.0 IU/L and -0.5 ± 5.9 IU/L for AST and 5.9 ± 29.0 IU/L and 0.3 ± 3.4 IU/L for GGT. Mean changes were 1.5 ± 5.6 IU/L on agomelatine 25 mg and -1.4 ± 7.4 IU/L on fluoxetine for ALT, -0.9 ± 8.1 IU/L and -0.3 ± 8.3 IU/L for AST and -0.2 ± 1.9 IU/L and -3.1 ± 7.9 IU/L for GGT.
- In the total population of the SS, no relevant difference between agomelatine and placebo groups was observed regarding emergent PCSA values of liver parameters. However, it was observed for high direct bilirubin a higher rate of patients on agomelatine 10 mg (9.2%) than on placebo (7.0%). However, as no high emergent PCSA values were observed for total bilirubin, data on direct bilirubin are considered as not relevant. Moreover, 2 patients on agomelatine reported high emergent PCSA values for ALT and/or AST *versus* none on placebo and 2 on fluoxetine: one child on agomelatine 10 mg in the context of infectious mononucleosis, one adolescent on agomelatine 25 mg and 2 adolescents on fluoxetine.
  Two patients on agomelatine 10 mg (one child described previously and one adolescent) *versus* one on placebo presented high emergent PCSA values of GGT.

- **Columbia-Suicide Severity Rating Scale Children's version**

In the SS, very few patients (*i.e.* one patient in each group) presented emergent suicidal ideations on treatment. Only the case in the agomelatine 10 mg group concerned a child (severity = 1). No emergent suicidal ideation was rated as serious (defined as score of 4 or 5).
In addition, a total of 7 patients had a worsening of their suicidal ideation on treatment, without relevant difference between groups. No child was affected by these aggravations.
One patient in the agomelatine 25 mg group and one in the placebo group reported emergent self-injurious behaviour without suicidal intent on treatment.
According to this scale, no patient in any group presented emergent suicidal behaviour, even if a suicide attempt was reported as a serious adverse event in one patient in the agomelatine 25 mg group.

- **Continuous Performance Task**

Regarding **selective attention** in the total population of the SS, the mean number of *missed reactions* decreased from baseline to W012 in the agomelatine 10 mg group (-1.9 ± 6.0), whereas it remained stable in other groups with however median at 0 in all groups.
The mean number of *false alarms* decreased in both agomelatine 10 and 25 mg groups (-1.8 ± 8.5 and -1.9 ± 13.5) but this decrease was slightly lower than in the placebo group (-3.0 ± 21.3) with however no relevant difference regarding medians.
The *mean reaction time* slightly increased in both agomelatine and placebo groups with a higher increase in the agomelatine 25 mg (5.2 ± 152.6 ms) than in the placebo (3.3 ± 153.5 ms) group. This increase was similar between the agomelatine 10 mg group (2.8 ± 93.7 ms) and the placebo group. Results for the mean reaction time should be interpreted with caution as medians are not in line with means with very high dispersion of values.
No relevant change in *measure of dispersion of reaction time* was observed in any group.

Similar patterns were observed in the adolescents, except that the *mean reaction time* remained stable in the agomelatine 25 mg group (0.1 ± 151.8 ms) and slightly decreased in the placebo group (-5.3 ± 135.2 ms).
Trends similar to the total population were observed in the children, except that the mean number of *missed reactions* also decreased from baseline to W012 on agomelatine 25 mg (-1.5 ± 6.8) and increased on placebo (1.6 ± 7.2) and that the *mean reaction time* decreased on agomelatine 10 mg (-7.0 ± 118.4 ms) whereas it increased in other treatment groups (26.7 ± 159.3 ms on agomelatine 25 mg and 41.1 ± 219.0 ms on placebo).
Results for the mean reaction time should be interpreted with caution as medians are not in line with means with very high dispersion of values.

Concerning **vigilance**, no relevant change in the mean number of *missed reactions* or in the *measure of dispersion of reaction time* was observed in any group. The mean number of *false alarms* decreased in both agomelatine 10 and 25 mg groups (-2.4 ± 14.9 and -5.3 ± 49.6) whereas it increased on placebo (2.3 ± 29.6) with however no relevant difference regarding medians. The mean *reaction time* increased on agomelatine 25 mg (27.7 ± 126.4 ms) as compared to placebo (1.1 ± 67.1 ms). No relevant difference was observed between agomelatine 10 mg (2.2 ± 83.0 ms) and placebo. The value was 6.9 ± 128.6 ms on fluoxetine. Results for the mean reaction time should be interpreted with caution as medians are not in line with means with very high dispersion of values.

Similar trends were observed in the adolescents.
Trends similar to the total population were observed in the children, except that the mean number of *false alarms* remained stable in both agomelatine groups and that the *mean reaction time* also increased on placebo (11.0 ± 86.3 ms) and on fluoxetine (31.4 ± 216.8 ms) and decreased on agomelatine 10 mg (-5.1 ± 66.8 ms).

- **Tanner stage**

Assessment of pubertal status by Tanner stage for pubic hair development in boys and in girls, genitalia development in boys and breast development in girls showed that the mean age in each stage at baseline and at W012 was consistent with stage according to normal development without relevant change between baseline and W012. Most of the patients remained in the same stage between baseline and W012, in each treatment group.

- **Vital signs and clinical examination**

In the total population, adolescents and children of the SS, there were no clinically relevant mean changes in sitting SBP, sitting DBP, sitting heart rate and BMI between baseline and the last post-baseline value on treatment in any group, nor relevant difference between the treatment groups.

The patients of these 3 populations gained about 1 kg between baseline and the last post-baseline value, without relevant difference between groups.

- **ECG**

At the last post-baseline value, 4 patients presented at least one clinically significant ECG abnormality in the total population: 2 (2.4%, including one child) in the agomelatine 25 mg group and 2 (2.3%) on fluoxetine.

- **Tablet acceptability**

Overall, 97.8% of patients rated as very easy or easy to swallow the tablet.
Results were similar in adolescents and children of the SS.

CONCLUSION

This international, multicentre, double-blind, two-dose level, active and placebo-controlled, randomized phase III study conducted 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 demonstrated the antidepressant short-term efficacy of agomelatine 25 mg compared to placebo after a 12-week treatment period, using the CDRS-R raw score expressed in terms of change from baseline to W012 (primary endpoint). Assay sensitivity was positive showing the superiority of fluoxetine compared to placebo. The difference between agomelatine 25 mg and placebo groups was not statistically significant on the secondary endpoints in the total population even if a trend in favour of agomelatine 25 mg was observed in the mean of CGI-S score.

The superiority of agomelatine 25 mg *versus* placebo was confirmed in the adolescent subgroup on the primary endpoint and on the ADRS. No statistically significant difference was observed between fluoxetine and placebo on these both endpoints.

In this study, due to a very limited number of patients in the children subgroup, no conclusion could be drawn.

In the paediatric population of this study, the safety profile of agomelatine 10 and 25 mg over the 12-week treatment period showed slight differences compared to that in adults: indeed, dry mouth, thirst and increased appetite were more commonly reported on agomelatine than on placebo in this study. The rate of patients reporting emergent adverse events was similar in the both agomelatine and placebo groups. No increase of frequency of adverse events with the dose was observed. Regarding liver acceptability, one case of emergent ALT and/or AST values (> 3ULN) was reported on each agomelatine dose and 2 cases were reported on fluoxetine. Analysis using the C-SSRS-C showed that very few patients (4 patients, *i.e* one per group) presented emergent suicidal ideations on treatment. One suicide attempt was reported in one patient in the agomelatine 25 mg group. No unexpected safety concern was highlighted for agomelatine 10 or 25 mg in this 12-week study period neither for the adolescents nor for the children subgroup. Treatment compliance was high and tablet acceptability was good, in this paediatric population.

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