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:** Not applicable **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.

This report concerns the results of the selection-Week104 (ASSE-W104) period including the optional open-label 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 2 substantial amendments to the protocol.

Main Investigator
Not applicable. Nine national coordinators supervised this study.

Study countries:
For the double-blind period, 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) and 6 patients in Finland (2 centres).

Concerning the extension period, 45 centres in 9 countries included 339 patients in the extension period: 105 patients in Russia (8 centres), 65 patients in Ukraine (10 centres), 63 patients in Hungary (5 centres), 52 patients in Romania (6 centres), 24 patients in Poland (4 centres), 13 patients in South Africa (3 centres), 9 patients in Serbia (4 centres), 5 patients in Bulgaria (3 centres) and 3 patients in Finland (2 centres).

Publication (reference):
(Arango C and al, 2021): Safety and efficacy of agomelatine in children and adolescents with major depressive disorder receiving psychosocial counselling: a double-blind, randomised, controlled, phase 3 trial in nine countries. Lancet Psychiatry, 2021; 9 (2):113-124.

Studied period:	**Phase of development of the study:**
Initiation date: 23 February 2016 (first visit first patient) Completion date: 27 October 2021 (last visit last patient)	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 adolescent 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.

The first clinical study report (namely primary CSR) of 24 June 2020 concerning the results of the ASSE-W012 period was written at the end of the 12-week double-blind period (NP40580)**.**
This second report concerns the results of the ASSE-W104 period including the optional open-label extension period.

Methodology:
This study was an international, multicentre phase III study divided into a 12-week, randomized, double-blind, two-dose level, active and placebo-controlled, parallel groups period and an optional open-label 21-month extension period, 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.

Possible impact of Covid-19 pandemic starting during the W012-W104 extension period was considered in this report.

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:

- Double-blind period: 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)], randomised as follows: 102 patients in the agomelatine 10 mg group, 95 in the agomelatine 25 mg group, 103 in the placebo group and 100 in the fluoxetine group.
- Optional open-label extension period: 339 patients (including 271 adolescents) distributed as follows: 170 patients in the agomelatine 10 or 25 mg / 10-25 mg group (hereafter referred to as the ago/ago group), 85 in the placebo / agomelatine 10-25 mg group (hereafter referred to as the placebo/ago group) and 84 in the fluoxetine 10-20 mg / agomelatine 10-25 mg group (hereafter referred to as the fluox/ago 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.

At W012 visit, all patients who could benefit from a continuation of a treatment with agomelatine were offered to enter in the open-labelled safety extension period.

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), only during the double-blind period:
Fluoxetine: 10 mg (2.5 mL) with a possible increase to 20 mg (5 mL) at W002, 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, without any investigational medicinal product (IMP) treatment.
Double-blind treatment period: 12 weeks, with agomelatine 10 mg or agomelatine 25 mg or placebo or fluoxetine.
Optional open-label extension period: 21 months, with agomelatine 10 mg from W012 to W014, then dose adjustment possible at each visit (flexible dose, either to increase to 25 mg or decrease again to 10 mg).
Follow-up period: 5 to 7 days after the last intake IMP, without any IMP treatment.

Criteria for evaluation:

Efficacy measurements:
Primary efficacy endpoint:
CDRS-R Raw total score, expressed in terms of:

- values at baseline, at each post-baseline visit and at last post-baseline visit as well as change from baseline to each post-baseline visit and to last post-baseline visit.
- remission defined as CDRS-R raw total score ≤ 28.

Secondary efficacy endpoints:

- Clinical Global Impression – Severity (CGI-S) and Improvement (CGI-I) scores.
- Response to treatment based on CGI-I score 1 or 2.
- Relapse defined as a CDRS score ≥ 40 or a withdrawal due to lack of efficacy and stringent relapse defined as a CDRS score ≥ 40.

Safety measurements:

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

Pharmacokinetic (PK) measurements:
No PK data for the open-label extension period.

Other measurements:
Not applicable.

Statistical methods:

Treatment groups and analysed periods:

On the W000-W012 period, the treatment groups considered were agomelatine 10 mg, agomelatine 25 mg, placebo and fluoxetine 10-20 mg. They correspond to randomised treatment except for safety analyses for which treatment taken at inclusion visit was considered.
On the W012-W104 period, the treatment groups considered were agomelatine 10 or 25 mg / 10-25 mg, placebo / agomelatine 10-25 mg and fluoxetine 10-20 mg/ agomelatine 10-25 mg.
On the W000-W104 period, focusing in patients already under agomelatine (10 or 25 mg) on the W000-W012 period, the treatment group considered was agomelatine 10 or 25 mg / 10-25 mg.

All analyses were performed by treatment group and overall.

Analysis Sets and Subgroups:

- *Sub-Modified Randomised Set (Sub-MRS):*

All patients of the MRS (*i.e.* all included patients to whom a therapeutic unit was randomly assigned using Interactive Web Response System) carrying on in the optional prolongation period W012-W104.

- *Sub-Safety Set (Sub-SS):*

All patients of the SS (*i.e.* all patients having taken at least one dose of IMP during the double-blind period) carrying on in the optional prolongation period W012-W104 and having taken at least one dose of IMP on the W012-W104 period.

The adolescent subgroup was planned for this extension period. As only 20% of patients were children, the children subgroup was not analysed.

Efficacy analysis:

All efficacy analyses were carried out in the Sub-MRS and in the adolescents from the Sub-MRS (except CGI-S score).

Primary endpoint: CDRS-R Raw total score

Descriptive statistics by visit and in terms of last post-baseline value were provided for all analytical approaches of CDRS-R raw total score (value at the visit, change from baseline and remission) on the W000-W104 and W012-W104 periods.

An evolution graph of the value at the visit and of the change was provided for each period.

Secondary endpoints:

Descriptive statistics by visit were provided for CGI-S and CGI-I scores and response to treatment, on both periods.

Time to relapse was analysed until W040 (included) (for both relapse definitions) in patients considered as responders* on the double-blind period (based on CGI and/or CDRS criteria) in patients randomised under agomelatine 25 mg in the double-blind period and in patients randomised under agomelatine 10 mg or 25 mg in the double-blind period. Survival curves using Kaplan-Meier's method and associated tables were provided.

* Patients were considered as responders on the double-blind period, if at W012, they had remitted (defined as: either a CDRS-R score ≤ 28 or a CGI-S of 1 or 2 and a CDRS-R score < 40) or they had presented a significant clinical response (defined as : either a CDRS-R score < 40 and a CGI-I score of 1 or 2 or a decrease of 50% or more on the CDRS-R score).

Study patients:

Disposition, baseline characteristics and concomitant treatments:
Descriptive statistics were provided in the Sub-MRS and in the adolescent subgroup of the Sub-MRS.

Extent of exposure:
Descriptive statistics were provided in the Sub-SS and in the adolescent subgroup of the Sub-SS.

Safety analysis:

All safety analyses were performed on the taken treatment, in the Sub-SS and in the adolescent subgroup of the Sub-SS.
Descriptive statistics were provided on both periods.

SUMMARY – CONCLUSIONS

Conclusions relating to the double-blind period are presented in the primary CSR (NP40580). Data presented hereafter are those of patients continuing in the extension period.

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 400 patients were included in the study and randomly assigned to one of the 4 groups (MRS). Of them, 339 patients entered the optional open-label extension period (Sub-MRS) during which all received agomelatine 10-25 mg. The Sub-MRS consisted of 79.9% of adolescents (271 patients). The following table gives the disposition of included patients by group.

Disposition of included patients by group – Overall patients

STATUS		**Agomelatine 10 or 25 mg / 10-25 mg (N = 170)**		**Placebo / Agomelatine 10-25 mg (N = 85)**		**Fluoxetine 10-20 mg / Agomelatine 10-25 mg (N = 84)**		**ALL (N = 339)**	
Included in W000-W104 period	**n[1]**	**170**		**85**		**84**		**339**	
Withdrawn on W012-W104 period due to	**n (%[1])**	**77**	**(45.3)**	**37**	**(43.5)**	**38**	**(45.2)**	**152**	**(44.8)**
Lost to follow-up	n (%[1])	1	(0.6)	1	(1.2)	-	-	2	(0.6)
Adverse event	n (%[1])	6	(3.5)	5	(5.9)	3	(3.6)	14	(4.1)
Lack of efficacy	n (%[1])	4	(2.4)	2	(2.4)	2	(2.4)	8	(2.4)
Recovery	n (%[1])	40	(23.5)	14	(16.5)	15	(17.9)	69	(20.4)
Non-medical reason	n (%[1])	25	(14.7)	12	(14.1)	17	(20.2)	54	(15.9)
Protocol violation	n (%[1])	1	(0.6)	3	(3.5)	1	(1.2)	5	(1.5)
Completed the W012-W104 period	**n (%[1])**	**93**	**(54.7)**	**48**	**(56.5)**	**46**	**(54.8)**	**187**	**(55.2)**
Performed the follow-up visit	**n (%[1])**	**136**	**(80.0)**	**69**	**(81.2)**	**67**	**(79.8)**	**272**	**(80.2)**
Sub-Modified Randomised Set	n (%)	170	(50.1)[2]	85	(25.1)[2]	84	(24.8)[2]	339	
Sub-Safety Set	n (%)	170	(50.1)[2]	85	(25.1)[2]	84	(24.8)[2]	339	(100)[3]

N number of patients by group.
n number of patients.
[1] Percentages are based on n[1].
[2] Percentages are based on All of the corresponding analysis set.
[3] % calculated as % of the Sub-Modified Randomised Set

In the Sub-MRS, 152 patients (44.8%) were withdrawn from the study on W012-W104 period with similar frequency in each group. The most frequent reasons for premature study withdrawals were recovery (20.4% of patients) with a higher frequency in the ago/ago group (23.5% of patients) than in the other 2 groups (16.5% in the placebo/ago group and 17.9% in the fluox/ago group) followed by non-medical reasons (15.9%) with a lower frequency in the ago/ago (14.7%) and placebo/ago (14.1%) groups than in the fluox/ago group (20.2%).

Overall, 187 patients (55.2%) completed the W012-W104 period with similar frequency in each group, 109/187 patients (58.3%) after the start of Covid-19 effects on study sites, if any. In the adolescents, 145 (53.5%) completed the W012-W104 period.

BASELINE CHARACTERISTICS in the Sub-MRS

At baseline of the study, the patients of the Sub-MRS were 7 to 17 years old with a mean ± standard deviation age of 13.6 ± 2.7 years. Almost 2 thirds of patients were female (61.9%). The mean age of the adolescents was 14.7 ± 1.6 years.
At the selection in the study, the patients carrying on thereafter in the extension period had their current Major Depressive Episode (MDE) for 133.6 ± 134.1 days on average (ranging from 29 to 961 days, median = 90.0 days). According to DSM-IV-TR criteria, the MDE was diagnosed as moderate in almost 2 thirds of patients (62.5%) and as severe without psychotic features in 37.5%. MDE presented melancholic features in 19.2% of patients. Overall, 27.7% of patients had a history of previous MDE (1 to 4 previous episodes).
Criteria on the characteristics and history of MDD in the adolescents were close to those presented in the total population.

Most of the patients (59.9%) reported at least one medical history besides MDD.

At W012, the patients weighted from 22.8 to 108.0 kg and according to the BMI, 3.2% were underweight, 18.3% overweight and 6.2% obese. The adolescents weighted from 31.1 to 108.0 kg.
At baseline of the study, the patients initially randomised in agomelatine groups weighted from 21.0 to 103.0 kg and according to the BMI, 4.1% were underweight, 15.9% overweight and 9.4% obese. The adolescents weighted from 38.0 to 103.0 kg.

At W012, 2.1% of patients received psychotropic concomitant treatment, 10.9% at least one non-psychotropic concomitant treatment and 0.9% at least one concomitant psychotherapy. The rates were 4.7%, 37.5% and 0.9%, respectively, during the W012-W104 period.
At inclusion, in patients initially randomised with agomelatine, 1.8% of patients received psychotropic concomitant treatment, 11.2% at least one non-psychotropic concomitant treatment and 0.6% at least one concomitant psychotherapy. The rates were 4.1%, 48.2% and 0.6%, respectively, during the W000-W104 period.
Results in the adolescents concerning the concomitant treatments were similar to those in the total population, for both periods.

EXTENT OF EXPOSURE in the Sub-SS

The treatment duration over the W012-W104 period ranged between 0.1 and 22.1 months with a mean of 15.5 ± 7.5 months. The tablet compliance was on average 97.4 ± 9.8%.
The treatment duration over the W000-W104 period in patients treated all along with agomelatine ranged between 2.8 and 24.5 months with a mean of 18.3 ± 7.5 months. The tablet compliance was on average 97.8 ± 6.6%.
Results in the adolescents concerning the treatment duration and the tablet compliance were similar to those in the total population, for both periods.

EFFICACY RESULTS in the Sub-MRS

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

The mean CDRS-R raw total score gradually decreased during the W012-W104 period, indicating a continuous improvement of patients receiving agomelatine all along the extension period, whatever the treatment previously received during the double-blind period.
The mean change from baseline of the W012-W104 period (*i.e.* W012) was -22.0 ± 11.8 at W104 (-21.0 ± 10.3 in the ago/ago group, -23.6 ± 14.0 in the placebo/ago group and -22.2 ± 12.4 in the fluox/ago group) and -16.9 ± 14.1 at the last post-baseline value (-16.3 ± 12.2, -18.9 ± 16.1 and -16.1 ± 15.5 in the 3 groups, respectively).
The greater decrease in the placebo/ago group could be explained by the higher mean value at W012 (baseline of the extension period) in the placebo/ago group who had not yet received active treatment.

On the same way, the percentage of patients considered in remission (CDRS-R raw total score ≤ 28) increased all along the extension period, from 13.6% at W012 to 83.5% at W104. Considering the last post-baseline value, 74.6% of patients were considered in remission.Considering the patients of the Sub-MRS receiving agomelatine all along the study, the mean CDRS-R raw total score decreased all along the W000-W104 period with a more marked decrease during the first 24 weeks of treatment.
The mean change from baseline was -29.5 ± 14.0 at W024, -41.6 ± 12.6 at W104 and -38.8 ± 13.2 considering the last post-baseline value.
In addition, the percentages of remitters increased all along the W000-W104 period, reaching 30.0% of patients in remission at W024 and 87.1% at W104. Considering the last post-baseline value, 75.9% of patients were considered in remission.

Focusing on adolescents, efficacy results on this primary endpoint were similar to those observed in the total population during the W012-W104 period as well as during the W000-W104 period.

- **Secondary efficacy endpoints:**

Clinical Global Impression

The mean CGI-S and CGI-I scores also decreased during the W012-W104 period whatever the treatment previously received during the double-blind period.
The mean CGI-S score improved from 3.5 ± 1.1 at baseline (W012) to 1.7 ± 1.0 at W104 and the mean CGI-I score from 2.5 ± 1.0 to 1.5 ± 0.8. The mean scores considering the last post-baseline value were 1.9 ± 1.1 for the CGI-S score and 1.6 ± 0.9 for the CGI-I score.
On the same way, the percentage of responders (defined as CGI-I score ≤ 2) increased all along the extension period, from 49.6% of responders at W012 to 87.8% at W104. Considering the last post-baseline value, 84.9% of patients were considered as responders.

Considering the patients of the Sub-MRS receiving agomelatine all along the study, as for the CDRS-R raw total score, the mean CGI-S and CGI-I scores improved all along the W000-W104 period with a more marked decrease during the first 24 weeks of treatment.
The mean CGI-S score decreased from 4.8 ± 0.6 at baseline to 2.8 ± 1.1 at W024, to 1.7 ± 1.0 at W104 and to 1.8 ± 1.1 considering the last post-baseline value.
The mean CGI-I score decreased from 3.7 ± 0.6 at W001 to 2.1 ± 0.9 at W024, to 1.5 ± 0.8 at W104 and to 1.6 ± 0.9 considering the last post-baseline value.
In addition, the percentages of responders increased all along the W000-W104 period, reaching 67.5% of responders at W024 and 86.0% at W104. Considering the last post-baseline value, 82.9% of patients were considered as responders.

Results in the adolescents on CGI-S and CGI-I scores and rate of responders were similar to those observed in the total population during the W012-W104 period as well as during the W000-W104 period.

Relapse

Identical results were observed when considering the "relapse" and "stringent relapse" criteria, both analysed on the W012-W040 period in patients initially randomised under agomelatine 10 mg or 25 mg (agomelatine 25 mg respectively) and presenting at least a significant clinical response (according to CGI and/or CDRS-R criteria) at W012.
Among the patients of the Sub-MRS initially randomised under agomelatine 10 or 25 mg and presenting at least a significant clinical response at W012, the estimates of the percentage of patients (Standard Error; [95% Confidence Interval]) with a relapse during the extension period were 8.8% (3.4%; [4.06 ; 18.59]) at the 6th week and 12.5% (4.2%; [6.40 ; 23.65]) at the 28th week. These estimates of percentage were 13.3% (6.2%; [5.22 ; 31.72]) and 17.7% (7.3%; [7.69 ; 37.66]), respectively, in the patients initially randomised under agomelatine 25 mg. Of note, the sample sizes of the 2 analysis groups were only 69 and 31 patients, respectively.

Regarding relapses, results observed in adolescents were very close to those in the total population.

SAFETY RESULTS in the Sub-SS

- **Emergent adverse events (EAE)**

The following table summarises the reported adverse events, in the total population and adolescents of the Sub-SS, over the W012-W104 period.

Overall summary for adverse events in the Sub-Safety Set - W012-W104 period

		Agomelatine 10 or 25 mg / 10-25 mg	Placebo / Agomelatine 10-25 mg	Fluoxetine 10-20 mg / Agomelatine 10-25 mg	ALL
Total population	N	170	85	84	339
Adolescents	N	134	69	68	271
Patients having reported at least one:					
TEAE[a]					
Total population	n (%)	105 (61.8)	55 (64.7)	52 (61.9)	212 (62.5)
Adolescents	n (%)	80 (59.7)	47 (68.1)	42 (61.8)	169 (62.4)
Treatment-related TEAE					
Total population	n (%)	26 (15.3)	14 (16.5)	9 (10.7)	49 (14.5)
Adolescents	n (%)	23 (17.2)	14 (20.3)	9 (13.2)	46 (17.0)
Serious EAE[b]					
Total population	n (%)	9 (5.3)	12 (14.1)	9 (10.7)	30 (8.8)
Adolescents	n (%)	7 (5.2)	11 (15.9)	8 (11.8)	26 (9.6)
Serious TEAE					
Total population	n (%)	8 (4.7)	12 (14.1)	9 (10.7)	29 (8.6)
Adolescents	n (%)	7 (5.2)	11 (15.9)	8 (11.8)	26 (9.6)
Treatment-related serious TEAE					
Total population	n (%)	-	-	-	-
TEAE leading to treatment withdrawal					
Total population	n (%)	5 (2.9)	5 (5.9)	3 (3.6)	13 (3.8)
Adolescents	n (%)	3 (2.2)	5 (7.2)	3 (4.4)	11 (4.1)
Serious TEAE leading to treatment withdrawal					
Total population	n (%)	-	3 (3.5)	3 (3.6)	6 (1.8)
Adolescents	n (%)	-	3 (4.3)	3 (4.4)	6 (2.2)
Treatment-related TEAE leading to treatment withdrawal					
Total population	n (%)	1 (0.6)	2 (2.4)	-	3 (0.9)
Adolescents	n (%)	1 (0.7)	2 (2.9)	-	3 (1.1)
Treatment-related serious TEAE leading to treatment withdrawal					
Total population	n (%)	-	-	-	-
Death					
Total population	n (%)	-	-	-	-

n number of patients
Percentages are based on N
[a] *EAE occurring on treatment during the W012-W104 period, i.e. TEAEs which occurred between the first IMP intake date (included) and the last IMP intake date + 1 day (included) on the W012-W104 period, or which occurred before the first IMP intake date and which worsened (in terms of intensity) or became serious according to the investigator opinion between the first IMP intake date (included) and the last IMP intake date + 1 day (included) on the W012-W104 period.*
[b] *EAE which occurred between the W012 visit date (excluded) and the end of extension period (including W104 and follow-up) or which occurred before the W012 visit date (excluded) and which worsened (in terms of intensity) or became serious according to the investigator opinion between the W012 visit date (excluded) and the end of extension period (including W104 and follow-up).*

In the Sub-SS, 62.5% of patients reported at least one TEAE under agomelatine, during the W012-W104 period (long-term follow-up of 21 months).

The **most frequently affected System Organ Classes (SOCs)** (*i.e.* in at least 10.0% of patients) during the W012-W104 period were Infections and infestations (27.1% of patients), Investigations (17.7%), Nervous system disorders (17.4%), Gastrointestinal disorders (14.2%) and Psychiatric disorders (10.0%).

The **most frequently reported TEAEs** (*i.e.* in at least 3.0% of patients) during the W012-W104 period were headache (11.8% of patients), nasopharyngitis (7.1%), nausea (5.3%), weight increased and decreased appetite (3.8% each), abdominal pain, blood prolactin increased, thirst and fatigue (3.5% each) and dizziness (3.2%).

Similar results were observed in the adolescents (62.4% presenting TEAEs) with roughly the same most common TEAEs as in the total population.

Overall, 5.6% of patients presented at least one **severe TEAE** during the W012-W104 period: 2.9% in the ago/ago group, 15.3% in the placebo/ago group and 1.2% in the fluox/ago group. In the adolescents, 6.3% presented severe TEAEs.

In the Sub-SS, 14.5% of patients presented at least one **TEAE considered as related to IMP** during the W012-W104 period (15.3% of patients in the ago/ago group, 16.5% in the placebo/ago group and 10.7% in the fluox/ago group). The most frequent IMP-related TEAEs (*i.e.* in more than 2 patients overall) were headache (2.4% of patients), dizziness (2.1%), dry mouth and thirst (1.8% each), somnolence and ALT increased (1.2% each) and aspartate amino transferase (AST) increased and nausea (0.9% each). In the adolescents, 17.0% presented TEAEs considered as related to IMP.

Overall, 8.6% of patients had at least one **serious TEAE** during the W012-W104 period: 4.7% in the ago/ago group, 14.1% in the placebo/ago group and 10.7% in the fluox/ago group. The most common serious TEAE was depression reported in 4 patients. Platelet count decreased, pneumonia, syncope, ALT increased, AST increased and suicidal ideation were reported by 2 patients each. All other serious TEAEs were reported once. No serious TEAE was considered as related to IMP. Ten serious TEAEs led to IMP withdrawal in 6 patients (1.8%), mainly Psychiatric disorders. In the adolescents, 9.6% had serious TEAEs during the W012-W104 period.

In addition to TEAEs considered as serious by the investigator, an **immediate notification** was also done for 5 TEAEs: ALT increased, AST increased, intentional overdose, accidental overdose and pregnancy.

In the Sub-SS, 3.8% of patients experienced 18 **TEAEs leading to IMP withdrawal** during the W012-W104 period, mainly depression reported in 5 patients. In the adolescents, 4.1% experienced 16 TEAEs leading to IMP withdrawal.

- **Laboratory tests**

Regarding the **biological (other than liver) parameters** during the W000-W104 period in patients treated all along with agomelatine, no clinically relevant mean change over time (in the adolescents) was detected. In the total population, emergent PCSA biochemical values on treatment were reported once except low HDL cholesterol (6.5%, 11 patients including 4 adolescents). Emergent PCSA haematological values on treatment were rather few [the most frequent, reported in 3.6% (6 patients), were low haematocrit (including 5 adolescents) and low leucocytes (including 4 adolescents)]. No limits for PCSA values were considered for thyrotropin and cortisol.

Regarding the **liver acceptability** on the W000-W104 period in patients treated all along with agomelatine, no clinically relevant mean/median change over time was detected in the adolescents. In the total population, the most common emergent liver PCSA values on treatment were high direct bilirubin (11.2%, 19 patients including 16 adolescents) and high indirect bilirubin (4.1%, 7 patients including 6 adolescents). No emergent PCSA value was reported for high total bilirubin. A total of 2 patients (one adolescent and one child) reported high emergent PCSA values (> 3 ULN) of **ALT or AST** on treatment and 3 patients (including 2 adolescents) high emergent PCSA values (> 3 ULN) of **GGT** on treatment.

- **Other safety criteria (CSSRS-C, Tanner stage, vital signs and ECG)**

In the Sub-SS, the analysis of suicide risk using the **C-SSRS-C** showed that 12 patients (3.6%) [including 11 adolescents] presented **emergent suicidal ideations** on treatment during the W012-W104 period. In addition, one patient (adolescent) had a **worsening of his/her suicidal ideation** on treatment.
A total of 6 patients (1.8%, all adolescents) reported **emergent self-injurious behaviour without suicidal intent** on treatment.
Based on this scale, two patients (both adolescents) presented 3 **emergent suicidal behaviours:** both made **emergent actual suicide attempt** on treatment; in addition, one of them also undertook **emergent preparatory actions toward imminent suicidal behaviour**.

Assessment of pubertal status by **Tanner stage** showed that the mean age at each stage was consistent with normal development and globally stable all over the extension period.

Regarding **vital signs**, in the total population and adolescents, no clinically relevant mean change was observed in sitting systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate, over the W012-W104 period.
As expected in a paediatric population, patients gained on average 4.23 ± 5.27 kg over the W012-W104 period. The mean BMI increased slightly and gradually over the W012-W104 period (0.66 ± 1.55 kg/m^2). However, 5.6% of the patients switched from a BMI class to a lower one *versus* 4.4% to an upper one.
In the adolescents, weight gain was on average 3.47 ± 5.47 kg over the W012-W104 period, with a slight gradual increase of mean BMI (0.50 ± 1.60 kg/m^2).

No patient had **clinically significant ECG abnormality** under treatment at W104 or considering the last post-baseline value.

W000-W104 period

- **Emergent adverse events**

The following table summarises the reported adverse events, in the total population and adolescents of the Sub-SS treated all along with agomelatine, over the W000-W104 period.

Overall summary for adverse events in the Sub-Safety Set in patients treated all along with agomelatine - W000-W104 period

			Agomelatine 10 or 25 mg / 10-25 mg
	Total population	N	170
	Adolescents	N	134
Patients having reported at least one:			
TEAE[a]			
	Total population	n (%)	138 (81.2)
	Adolescents	n (%)	108 (80.6)
Treatment-related TEAE			
	Total population	n (%)	63 (37.1)
	Adolescents	n (%)	53 (39.6)
Serious EAE[b]			
	Total population	n (%)	12 (7.1)
	Adolescents	n (%)	8 (6.0)
Serious TEAE			
	Total population	n (%)	11 (6.5)
	Adolescents	n (%)	8 (6.0)
Treatment-related serious TEAE			
	Total population	n (%)	-
TEAE leading to treatment withdrawal			
	Total population	n (%)	6 (3.5)
	Adolescents	n (%)	3 (2.2)
Serious TEAE leading to treatment withdrawal			
	Total population	n (%)	1 (0.6)
	Adolescents	n (%)	-
Treatment-related TEAE leading to treatment withdrawal			
	Total population	n (%)	1 (0.6)
	Adolescents	n (%)	1 (0.7)
Treatment-related serious TEAE leading to treatment withdrawal			
	Total population	n (%)	-
Death			
	Total population	n (%)	-

n number of patients
Percentages are based on N
[a] EAE occurring on treatment during the W000-W104 period, i.e. TEAEs which occurred between the first IMP intake date (included) and the last IMP intake date + 1 day (included) on the W000-W104 period, or which occurred before the first IMP intake date and which worsened (in terms of intensity) or became serious according to the investigator opinion between the first IMP intake date (included) and the last IMP intake date + 1 day (included) on the W000-W104 period.
[b] EAE which occurred between the W000 visit date (included) and the end of extension period (including W104 and follow-up) or which occurred before the W000 visit date (included) and which worsened (in terms of intensity) or became serious according to the investigator opinion between the W000 visit date (included) and the end of extension period (including W104 and follow-up).

In the Sub-SS, 81.2% of patients treated all along with agomelatine presented at least one TEAE, during the W000-W104 period (long-term follow-up of 2 years).

The **most frequently affected SOCs** (*i.e.* in at least 20.0% of patients) were Infections and infestations (37.6%), Gastrointestinal disorders (35.3%), Nervous system disorders (32.9%), Investigations (32.4%) and General disorders and administration site conditions (24.7%).

The **most frequently reported TEAEs** (*i.e.* in at least 5.0% of patients) were headache (23.5%), dry mouth (18.2%), thirst (15.3%), nausea (14.1%), nasopharyngitis (11.2%), abdominal pain (10.0%), decreased appetite and weight increased (8.8% each), fatigue (8.2%), increased appetite (7.6%), blood prolactin increased and diarrhoea (6.5% each), dizziness (5.9%), acne and dizziness postural (5.3% each).

In the adolescents, 80.6% reported at least one TEAE. The most common TEAEs were roughly the same as in the total population.

Overall, 7.6% of patients and 9.0% of adolescents treated all along with agomelatine presented at least one **severe TEAE** during the W000-W104 period.

In the Sub-SS, 37.1% of patients and 39.6% of adolescents treated all along with agomelatine presented at least one **TEAE considered as related to IMP**. The most frequent IMP-related TEAEs (*i.e.* in at least 5 patients) in overall patients were dry mouth (15.9%), thirst (11.8%), nausea (8.8%), headache (4.7%), dizziness (4.1%) and abdominal pain (2.9%).

Overall, 6.5% of patients and 6.0% of adolescents treated all along with agomelatine had at least one **serious TEAE** during the W000-W104 period. All serious TEAEs were reported only once, except syncope reported in 2 patients. No serious TEAE was considered as related to IMP and only one serious TEAE (in a child), infectious mononucleosis, led to IMP withdrawal.

In addition to TEAEs considered as serious by the investigator, an **immediate notification** was also done for 2 TEAEs: ALT increased, and AST increased.

In the Sub-SS, 3.5% of patients treated all along with agomelatine experienced 7 **TEAEs leading to IMP withdrawal** during the W000-W104 period, mainly depression reported in 2 patients. Overall, 2.2% of adolescents reported 4 TEAEs leading to IMP withdrawal.

- **Laboratory tests**

Regarding the **biological (other than liver) parameters** during the W000-W104 period in patients treated all along with agomelatine, no clinically relevant mean change over time (in the adolescents) was detected. In the total population, emergent PCSA biochemical values on treatment were reported once except low HDL cholesterol (6.5%, 11 patients including 4 adolescents). Emergent PCSA haematological values on treatment were rather few [the most frequent, reported in 3.6% (6 patients), were low haematocrit (including 5 adolescents) and low leucocytes (including 4 adolescents)]. No limits for PCSA values were considered for thyrotropin and cortisol.

Regarding the **liver acceptability** on the W000-W104 period in patients treated all along with agomelatine, no clinically relevant mean/median change over time was detected in the adolescents. In the total population, the most common emergent liver PCSA values on treatment were high direct bilirubin (11.2%, 19 patients including 16 adolescents) and high indirect bilirubin (4.1%, 7 patients including 6 adolescents). No emergent PCSA value was reported for high total bilirubin. A total of 2 patients (one adolescent and one child) reported high emergent PCSA values (> 3 ULN) of **ALT or AST** on treatment and 3 patients (including 2 adolescents) high emergent PCSA values (> 3 ULN) of **GGT** on treatment.

- **Other safety criteria (CSSRS-C, Tanner stage, vital signs and ECG)**

In the Sub-SS in patients treated all along with agomelatine, the analysis of suicide risk using the **C-SSRS-C** showed that 3 patients (1.8%) [including 2 adolescents] presented **emergent suicidal ideations** on treatment during the W000-W104 period. In addition, 3 patients (all adolescents) had a **worsening of their suicidal ideation** on treatment.
A total of 4 patients (2.4%, all adolescents) reported **emergent self-injurious behaviour without suicidal intent** on treatment.
Based on this scale, no patient treated all along with agomelatine presented **emergent suicidal behaviour**.

Assessment of pubertal status by **Tanner stage** showed that the mean age at each stage was consistent with normal development and globally stable all over the study.

Regarding **vital signs**, in the total population and adolescents treated all along with agomelatine, no clinically relevant mean change was observed in sitting SBP, DBP and heart rate, over the W000-W104 period.
As expected in a paediatric population, patients gained on average 4.37 ± 5.07 kg over the W000-W104 period. The mean BMI increased slightly and gradually over the W000-W104 period (0.60 ± 1.71 kg/m^2). However, 7.6% of the patients switched from a BMI class to a lower one *versus* 5.9% to an upper one.
In the adolescents, weight gain was on average 3.29 ± 5.12 kg over the W000-W104 period, with a rather stable mean BMI.

Three patients (1.8%, all adolescents) treated all along with agomelatine presented at least one **clinically significant ECG abnormality** at baseline. Overall, 2 patients (including one adolescent) at W012 and none at W104 had clinically significant ECG abnormality under treatment.

CONCLUSION

This international, multicentre, phase III study divided into a 12-week, double-blind, two-dose level, active and placebo-controlled period and an optional open-label 21-month extension period, was 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.

The antidepressant short-term efficacy of agomelatine 25 mg compared to placebo after a 12-week treatment period has been demonstrated during the double-blind part of the study, using the CDRS-R raw total score (primary endpoint). Long-term efficacy was also observed in patients carrying on in the extension period with a continuous decrease of the CDRS-R score over the 21-month extension period under agomelatine 10 or 25 mg, whatever treatment they had previously received during the double-blind period. The rate of responders (defined as CGI-I score ≤ 2) at the last post-baseline visit of the extension period was 84.9%.

Short-term and long-term efficacy of agomelatine was also observed in the adolescent subgroup.

In the paediatric population of this study, the safety profile of agomelatine 10 and 25 mg showed only slight and non-relevant differences compared to that in adults.

Regarding liver acceptability, 2 patients during the double-blind period and 3 during the extension period reported emergent ALT and/or AST values (> 3ULN) under agomelatine. Concerning the suicidality, no safety concern was observed under agomelatine. Based on C-SSRS-C, 2 patients during the double-blind period and 12 during the extension period presented emergent suicidal ideations on agomelatine. One patient during the double-period period and 2 during the extension period committed suicide attempt on agomelatine. No completed suicide occurred during the study. Long-term treatment compliance was high in this paediatric population.

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