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RESEARCH

Agomelatine in pediatric patients with moderate to severe major depressive disorder: an open-label extension study

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Abstract

Major depressive disorder (MDD) in young people is a common psychiatric disorder, but treatment options are limited. Agomelatine has demonstrated short-term efficacy and safety in pediatric patients. We report here the results of a 92-week open-label extension (OLE). The international, multicenter, double-blind, study randomized 400 patients (80 children, 320 adolescents) with moderate-to-severe MDD to one of four treatment groups: agomelatine 10 mg (n = 102), agomelatine 25 mg (n = 95), placebo (n = 103), and fluoxetine 10–20 mg (n = 100). After 12 weeks, patients who could benefit from treatment continuation were offered entry into an optional OLE during which they received agomelatine 10 or 25 mg for a further 92 weeks. A total of 339 patients (271 adolescents) entered the OLE. Treatment groups considered for the OLE analysis reflected those received in the double-blind and OLE periods: agomelatine (10 or 25 mg) in both (ago/ago, n = 170); placebo then agomelatine 10–25 mg (pcb/ago, n = 85); or fluoxetine then agomelatine 10–25 mg (fluox/ago, n = 84). Mean age (± SD) at entry into the double-blind phase (Week 0) was 13.6 ± 2.7 years and 61.9% were female. Mean changes in Children's Depression Rating Scale revised (CDRS-R) raw total score from Week 12 to last post-Week 12 value in the three groups were − 16.3 ± 12.2 (ago/ago), − 18.9 ± 16.1 (pcb/ago), and − 16.1 ± 15.5 (fluox/ago), reflecting the difference in efficacy between treatments during the double-blind period, and heterogeneity at W12 between the treatment groups. Adverse events considered related to treatment occurred in 14.5% of patients: 15.3% ago/ago, 16.5% pcb/ago, and 10.7% fluox/ago. Three patients (all adolescents) experienced treatment-related severe adverse events: two treated with ago/ago and one treated with pcb/ago. Among the adolescents, one treatment-related severe adverse event in a patient in the pcb/ago group led to study withdrawal. Agomelatine was associated with continuous improvement in depressive symptoms without unexpected safety signals. These findings support the safe use of agomelatine in a pediatric population with moderate-to-severe MDD for up to 104 weeks.

Trial registration No: EUDRACT No. 2015-002181-23.

Keywords Adolescent · Agomelatine · Children · Major depressive disorder · Open-label extension · Pediatric

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Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders in children and adolescents [1, 2]. In the USA, data from national surveillance systems including the National Survey of Children's Health (2016–2019) and National Health and Nutrition Examination Survey (NHANES) (2013–2018) indicate that the likelihood of ever having had a diagnosis of depression increases with age, with a prevalence of 0.1% for children aged 3–5 years, 2.3% in those aged 6–11 years, and 8.6% for adolescents aged 12–17 years [3]. Similar percentages were reported in a 2017 UK National Health Service survey of the mental health of children and young people [4]. Data from NHANES 2013–2018 indicate that 5.8% of adolescents aged 12–17 years reported having major depression during the past 2 weeks [3]. In the WHO European Region, depression and anxiety disorders were listed among the top five causes of overall disease burden among children and adolescents in 2018 (as measured by disability-adjusted life years) [5, 6]. Suicide was the leading cause of death among European adolescents aged 10–19 years old in low- and middle-income countries, and the second leading cause in high-income countries [5, 6]. Levels of anxiety and depression in young people have increased during the recent coronavirus disease 19 (COVID 19) pandemic, probably as a result of social isolation due to school closures and physical distancing, disruptions in daily routines, and/or concerns for the health of family and friends [7, 8].

Early-onset depression often recurs and continues into adulthood, particularly if untreated, and may also predict more severe illness later in life [9]. Untreated depression in children and adolescents may also increase the risk of substance abuse; poor work, academic, and social functioning; and risk of suicidal behaviors [10–12]. Early intervention is important to prevent long-lasting and severe outcomes [13], but few medications are licensed for use in pediatric depression. Recommendations for antidepressant therapy in pediatric populations are mostly based on data from randomized clinical trials with three selective serotonin reuptake inhibitors (SSRI): fluoxetine [14], sertraline [15, 16], and escitalopram [17]. Fluoxetine, has the largest evidence base in this age group [14, 18] and is authorised for children and adolescents aged 8 and above with moderate to severe MDD unresponsive to psychological therapy after 4–6 sessions by the European Medicines Agency and US Food and Drug Administration; the latter has also authorised escitalopram for use in adolescents [19]. Clinical guidelines for the treatment of moderate to severe depression in children and young people recommend first-line interpersonal psychotherapy or cognitive behavioral therapy (CBT), which may be combined with antidepressant therapy, generally in the form of fluoxetine, depending on symptom severity or persistence [20–22]. This is supported by a systematic review and network meta-analysis of 71 trials of psychotherapy, pharmacotherapy, or psychotherapy plus pharmacotherapy in young people with MDD, which found that only fluoxetine (alone or in combination with CBT) was more efficacious than placebo, psychological control and some active treatments [23].

Although there are a number of antidepressant alternatives to SSRIs licenced for use in adult populations with MDD, their benefits for the treatment of young people with MDD are less clear cut [18, 23–25]. It has previously been suggested that age differences may influence which antidepressants are effective for adolescents compared with adults, possibly related to the effects of neuromaturation, or sensitivity to medication increasing with each major depressive episode (MDE) [26, 27]. Further research is required, but until then it would seem judicious to use agents for which efficacy has been demonstrated in a pediatric population.

Agomelatine is a first-in-class antidepressant for major depression, approved for use in adults, that acts as an agonist to the melatonin receptors MT1 and MT2 and an antagonist of the serotonin 5HT2C receptors [28]. Agomelatine is as effective as other anti-depressants for the treatment of MDD in adults and has one of the highest acceptability rates [24, 29]. There is some evidence to suggest that agomelatine may be particularly beneficial in adolescents and young adults with MDD. Young people with depression have been shown to have high rates of delayed circadian rhythms [30, 31]. This led researchers to initiate a proof-of-concept study in young adults (aged 17–28) with moderate depression, in which they combined psychoeducation about sleep and circadian rhythms with 8 weeks of agomelatine 25 mg [32]. Depressive symptoms were significantly reduced, with earlier secretion of higher levels of melatonin in the evening. Further benefits included an advanced sleep onset time, and extended duration of sleep.

In children and adolescents with MDD, a large placebo-controlled trial using fluoxetine as an active control confirmed the short-term antidepressant efficacy and safety of agomelatine in this population [33]. In an optional open-label extension of this trial, patients could be treated for an additional 92 weeks. This allowed additional information on the long-term tolerability, safety and effectiveness of the drug to be collected. The effects of agomelatine 10 or 25 mg on tolerability and safety signals and in achieving and maintaining clinical response and/or remission among children and adolescents with MDD who completed the double-blind period and entered the extension period are reported herein.

Methods

This study was an international, multicenter, randomized, double-blind, placebo and active comparator-controlled phase 3 trial, which investigated the efficacy and safety of two agomelatine doses in children (7–11 years) and adolescents (12–17 years) with MDD [33].

Details of the study design and the double-blind results have been reported previously [33]. Briefly, eligible participants were aged 7–17 years and unresponsive to psychosocial therapy during a 3-week run-in period (Children's Depression Rating Scale revised [CDRS-R] score of ≥ 45). Major exclusion criteria included: presence of treatment-resistant depression, psychotic depression, current suicidal risk, pregnant or not using effective contraception, major comorbid psychiatric conditions, and severe hepatic or renal impairment. Patients were randomized 1:1:1:1 to agomelatine 10 mg, agomelatine 25 mg, placebo, or fluoxetine for 12 weeks via an interactive response system. All those involved in the conduct of the clinical trial and the patients were masked to treatment allocation. Patients who completed the 12-week double-blind study who could benefit from treatment continuation were eligible to enrol in an optional open-label extension during which they received agomelatine 10 mg from Week 12–14 (W12–14) with dose adjustment possible at each visit, either as an increase dose to 25 mg or decrease back to 10 mg (Fig. 1). The double-blind phase of the study was conducted over the period February 2016–January 2020, and the open-label extension period ended in October 2021 (last patient, last visit). All tablets were taken once a day, orally, in the evening at bedtime. Patients were followed for 5–7 days after their last intake of study medication. Standardised manualised psychosocial counselling, developed for this trial, was provided to all patients, beginning at the selection visit and continuing throughout the study, including the open-label extension. Further details are provided in the supplementary information (Suppl 1).

This study was performed in strict accordance with Good Clinical Practice. The patients (when intellectual maturity and capacity were appropriate) and their parents or their legally authorised representatives provided written informed consent prior to participation, in line with local regulatory requirements. The study was registered under EUDRACT No. 2015-002181-23.

The primary efficacy endpoint was the CDRS-R raw total score. CDRS-R is a 17-item scale, with items ranging from 1 to 5 or 1 to 7 (possible total score from 17 to 113), rated by a clinician via interviews with the child and parent [34]. Secondary efficacy endpoints assessed over the short and long term, included Clinical Global Impression (CGI) scale ratings for severity of illness (CGI-S) and global improvement (CGI-I), and response to treatment. CGI was used to rate the global improvement in comparison with the patient's condition at inclusion for any visit from W001 to W104. Response to treatment was defined as a CGI-I score equal to 1 or 2 (much or very improved). Remission was defined as a CDRS-R raw total score of ≤ 28. Relapse, which was defined as a CDRS-R score ≥ 40 or a withdrawal due to lack of efficacy, was also assessed during the W12-W40 period among responders in the double-blind period (based on CGI and CDRS-R). During the extension period, the agomelatine dose was 10 mg until W14, after which it could be adjusted at each visit according to the investigator's judgement. For the purpose of the extension period analysis, results for the two dose groups (10 mg and 25 mg) corresponding to the agomelatine randomized groups at the beginning of the double-blind period were combined. For each of the primary and secondary endpoints, descriptive statistics at W12 (when applicable), and at each post-W12 visit were described

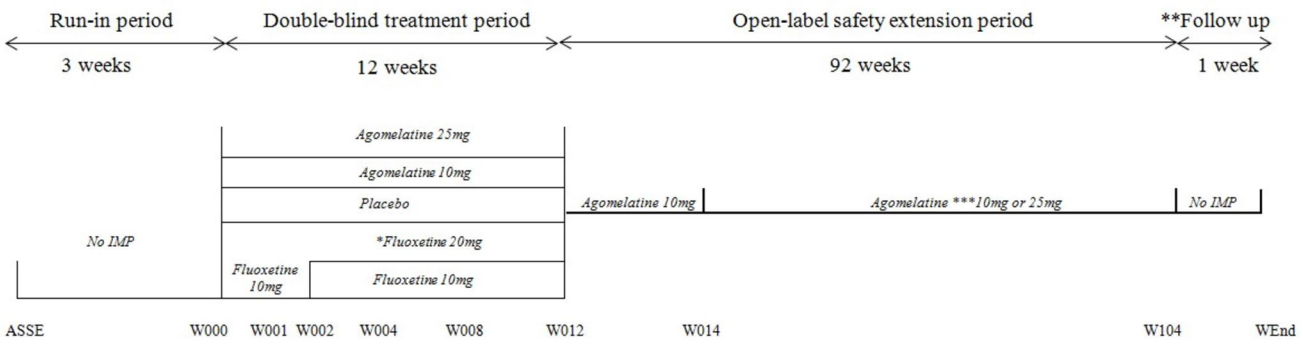

Fig. 1 Study plan. The following visits were performed between W12 and W104: W14, W18, W24, W32, W40, W48, W52, W60, W68, W77, W86, W95. *If no improvement at W2, the fluoxetine dose could be increased to 20 mg at the investigator's judgment. **The follow up period was dedicated to: all patients who withdrew prematurely from the study at any moment. All patients who did not continue into the extension period. All patients who completed the extension period. ***From W14, the agomelatine dose could be adjusted at each visit (flexible dose, either to increase to 25 mg or decrease back to 10 mg) by the investigator based on the clinical picture of patient

according to the randomized treatment groups at baseline, but pooling the two agomelatine arms, and overall.

Statistical analyses

Results are presented for the total population and the adolescent subgroup, but not for the subgroup of children alone, due to the small sample size. For qualitative data, number of observed values, and number and percentage of patients per class are presented. For quantitative data, number of observed values, mean, standard deviation, median, first and third quartiles, and minimum and maximum are presented. Missing data were handled using a last observation carried forward approach.

Safety was assessed in patients who received at least one dose of study drug during the open-label phase. Additional tools used to assess safety were the Pediatric Adverse Event Rating Scale and the Columbia Suicide Severity Rating Scale for Children (C-SSRS-C). Data regarding Tanner stage and hormonal profile were also collected. Statistical analyses were performed using SAS® Software version 9.4.

Results

Demographic and clinical characteristics at the start of the extension period (Week 12)

A total of 466 patients were screened and 447 patients were enrolled in the double-blind phase of the study. After a 3-week run-in period, 400 patients (80 children and 320 adolescents) were included and randomly assigned to one of the four treatments [33]. A total of 352 (88%) patients completed the 12-week double-blind phase of whom 339 (96%) including 68 children and 271 adolescents, entered the open-label extension. Patients in the open-label extension had previously received: agomelatine, either at 10 or 25 mg (ago/ago, n = 170), placebo then agomelatine 10–25 mg (pcb/ago, n = 85), or fluoxetine then agomelatine 10–25 mg (fluox/ago, n = 84). Among the ago/ago patients, 39% remained on ago 10 mg during the extension phase, 45% started on ago 10 mg and increased to ago 25 mg, and 14.5% started on ago 10 mg, increased to ago 25 mg, and then decreased once more to ago 10 mg for the duration of the extension. Of the 339 patients included in the extension period, 187 (55.2%) completed the open-label extension: 93 (54.7%, ago/ago); 48 (56.5%, pcb/ago); and 46 (54.8%, fluox/ago).

The most frequent reason for premature study withdrawal during the extension period was recovery (20.4%), with a numerically higher frequency in patients who received agomelatine 10–25 mg in both the double-blind and extension periods (23.5%) than in the other two groups (16.5% in the pcb/ago group and 17.9% in the fluo/ago group). Withdrawals for non-medical reasons were reported in 14.7% who received agomelatine in both periods, 14.1% of pcb/ago patients, and 20.2% of fluo/ago patients. Other reasons for withdrawal were: adverse events (14, 4.1% patients overall), lack of efficacy (8, 2.4%), protocol violation (5, 1.5%), and loss to follow up (2, 0.6%). Of the 271 adolescents, 145 (53.5%) completed the open-label extension. The disposition of adolescents and their reasons for withdrawal were similar to the overall population.

Patient demographics and characteristics at the start of the extension period (W12) are shown in Table 1 for the overall population. Mean age (± SD) was 13.6 ± 2.7 years and 61.9% were female. BMI ranged from 13.5 to 35.2 kg/m^2; 11 patients (3.2%) were considered underweight, 18.3% overweight and 6.2% obese. Current MDE was diagnosed as moderate in 62.5%, and severe without psychotic features in 37.5% of patients; MDE presented with melancholic features in 19.2%. At inclusion (W0), the mean duration of the current MDE for patients entering the extension period was 133.6 ± 134.1 days with a median of 90.0 days (range from 29 to 961 days). A total of 94 patients (27.7%) had a history of previous MDE, and 57 patients (16.8%) had a family history of mood disorders. Nearly two-thirds of patients (59.9%) reported at least one medical history besides MDD. At each visit during the extension period (except W14), most patients (≥ 94%) participated in the Manualized Psychosocial Counselling session.

Mean treatment duration in the extension period was 15.5 ± 7.5 months (median of 21.0 months) and mean tablet adherence was 97.4 ± 9.8%.

Primary efficacy endpoint: CDRS-R raw total score

In the children and adolescent population combined, the mean CDRS-R raw total score gradually decreased over the W12-W104 period in all groups, indicating a continuous improvement of patients receiving agomelatine all along the extension period, whatever the treatment previously received during the double-blind period (Fig. 2). Mean W12 values for the three groups and overall were 42.1 ± 12.4 (ago/ago), 46.2 ± 15.1 (pcb/ago), 42.7 ± 11.7 (fluox/ago), and 43.3 ± 13.0 (overall), respectively, reflecting the difference of efficacy between treatments during the double-blind period. Mean changes from W12 to last post-W12 value in the three groups were − 16.3 ± 12.2, − 18.9 ± 16.1, and − 16.1 ± 15.5, respectively, leading to last post-W12 values of 25.8 ± 10.5 (ago/ago), 27.3 ± 12.1(pcb/ago), 26.6 ± 12.2 (fluox/ago), and 26.4 ± 11.3 overall. These differences were due to the heterogeneity at W12 between treatment groups. In all groups, agomelatine treatment was associated with a continuous decrease in depressive symptoms, but the most marked improvement in mean CDRS-R score was observed during the first 24 weeks of open-label treatment (Fig. 3).

Table 1 Main demographic and patient characteristics, according to the treatment received during the double-blind period, and overall

Characteristics	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)
Age, years (mean ± SD)	13.4 ± 2.8	13.8 ± 2.6	13.8 ± 2.8	13.6 ± 2.7
Children, n (%)	36 (21.2)	16 (18.8)	16 (19.0)	68 (20.1)
Adolescents, n (%)	134 (78.8)	69 (81.2)	68 (81.0)	271 (79.9)
Female, n (%)	111 (65.3)	54 (63.5)	45 (53.6)	210 (61.9)
BMI class[a], n (%)				
Underweight	7 (4.1)	2 (2.4)	2 (2.4)	11 (3.2)
Normal weight	119 (70.0)	64 (75.3)	62 (73.8)	245 (72.3)
Overweight	30 (17.6)	16 (18.8)	16 (19.0)	62 (18.3)
Obese	14 (8.2)	3 (3.5)	4 (4.8)	21 (6.2)
Years of school education (mean ± SD)	7.0 ± 2.8	7.4 ± 2.6	7.3 ± 2.8	7.2 ± 2.7
Current MDE duration, days (mean ± SD)	146.3 ± 151.8	127.3 ± 123.6	114.4 ± 100.7	133.6 ± 134.1
Patients with history of previous MDE, n (%)	38 (22.4)	30 (35.3)	26 (31.0)	94 (27.7)
Number of previous MDE (mean ± SD)	1.4 ± 0.5	1.3 ± 0.5	1.4 ± 0.8	1.4 ± 0.6
Patients with family history of mood disorders, n (%)	30 (17.6)	15 (17.6)	12 (14.3)	57 (16.8)
Diagnosis according to DSM IV criteria, n (%)				
Single episode	132 (77.6)	55 (64.7)	58 (69.0)	245 (72.3)
Recurrent episode	38 (22.4)	30 (35.3)	26 (31.0)	94 (27.7)
Moderate severity	115 (67.6)	46 (54.1)	51 (60.7)	212 (62.5)
Severe without psychotic features	55 (32.4)	39 (45.9)	33 (39.3)	127 (37.5)
Treatment duration, months (mean ± SD)	15.51 ± 7.50	15.85 ± 7.32	15.21 ± 7.62	15.52 ± 7.47

[a]BMI classes were defined according to WHO Growth Reference as follows: underweight is BMI-for-age of more than 2 standard deviations (SD) from the WHO Growth Reference. Normal range is between 2 SD below and 1 SD above. Overweight is between 1 and 2 SD above. Obesity is greater than 2 SD above

Similar results were observed in the adolescent population with changes from W12 to last post-W12 value of − 15.2 ± 12.1 (ago/ago, n = 134), − 18.4 ± 16.1 (pcb/ago, n = 69), and − 15.8 ± 14.9 (fluo/ago, n = 68).

Among patients receiving agomelatine in both periods, mean decreases from W0 in CDRS-R raw total score were: − 29.5 ± 14.0 at W24 (N = 160), − 41.6 ± 12.6 at W104 (N = 93), and − 38.8 ± 13.2 at last post-W0 value (N = 170).

In the total population, the rate of patients considered in remission gradually increased during the extension period from 13.6% at W12 (N = 339) to 83.5% at W104 (N = 187), whatever the treatment previously received during the double-blind period (Fig. 4). Values for adolescents were 14.0% (N = 271) and 80.1% (N = 146), respectively. When considering the last post-W12 value, 74.6% of patients in the total population (N = 338) and 72.2% of adolescents (N = 270) were considered in remission. For patients treated exclusively with agomelatine, 129 (75.9%) were in remission at last post-W12 visit, and 81 (87.1%) were in remission at W104.

Secondary efficacy endpoints

All treatment groups

In the overall population, there was a continuous decrease in mean CGI-S and CGI-I scores during the extension period indicating an improvement under agomelatine, whatever the treatment previously received during the double-blind period. Mean scores improved from 3.5 ± 1.1 at W12 to 1.7 ± 1.0 at W104 for the CGI-S score, and from 2.5 ± 1.0 at W12 to 1.5 ± 0.8 at W104 for the CGI-I score. Mean scores at the last post-baseline visit were 1.9 ± 1.1 for the CGI-S score and 1.6 ± 0.9 for the CGI-I score. The proportion of responders (defined as CGI-I score ≤ 2) increased from 49.6% at W12 to 87.8% at W104. The rate of responders at the last post-baseline visit was 84.9%.

Similar improvements in CGI scores during the extension period were observed in the adolescent population, with mean CGI-S score decreasing from 3.5 ± 1.1 at W12 to 1.7 ± 1.0 at W104 and mean CGI-I score decreasing from 2.5 ± 1.0 at W12 to 1.5 ± 0.9 at W104. The proportion of

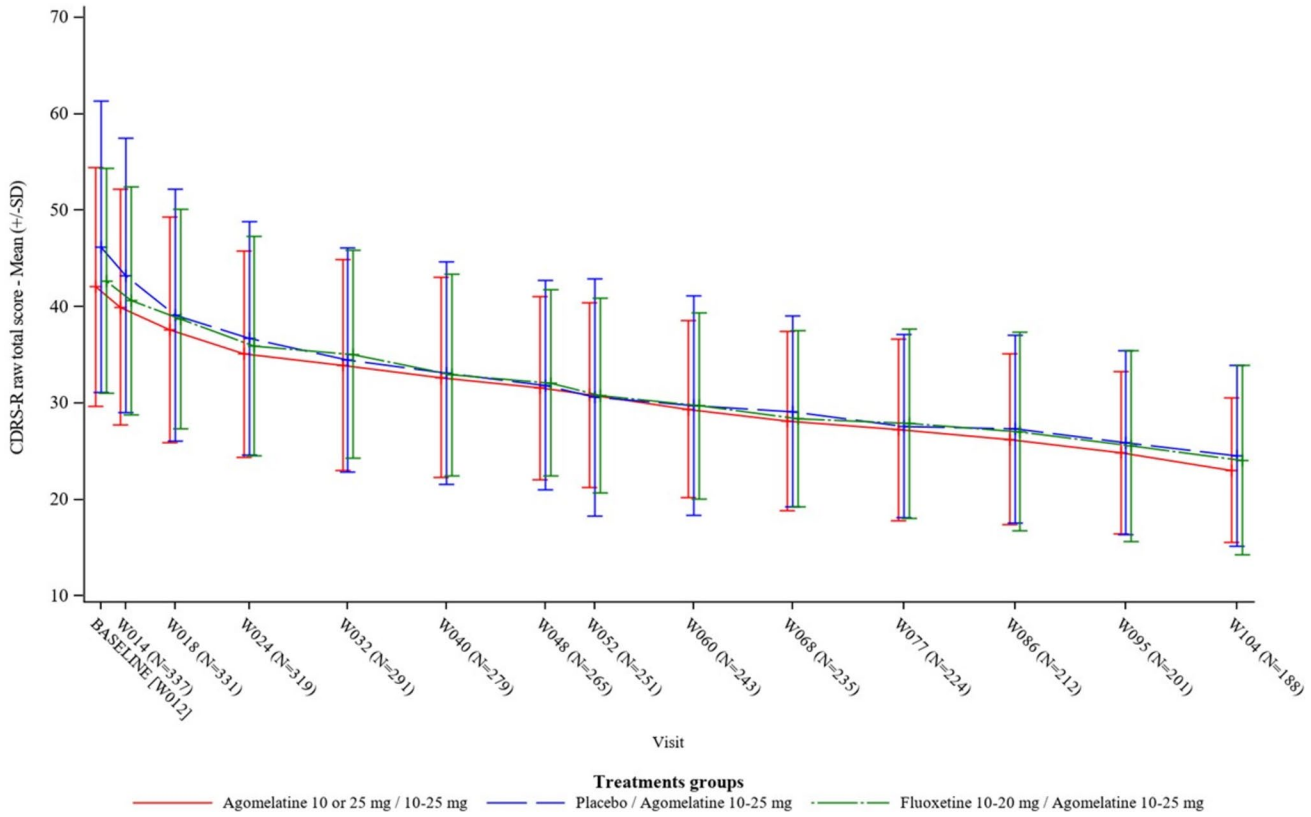

Fig. 2 CDRS-R raw total score: mean value (±SD) at each visit during the W12–W104 open-label extension period, according to the treatment previously received during the double-blind period

adolescent responders increased from 51.7% at W12 to 85.6% at W104.

Relapse

Although this study was not designed as a relapse prevention study, it was nevertheless of interest to measure occurring relapses.

Among the 69 patients initially randomized to either agomelatine 10 or 25 mg and presenting at least a significant clinical response at W12 (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), eight patients (11.6%) relapsed during the W12-W40 period: six during the first 6 weeks of treatment and two beyond 6 weeks.

Safety

A total of 212 patients (62.5%) presented 620 treatment-emergent adverse events (TEAE) under agomelatine during the W12-W104 period: 61.8% of patients in the agomelatine both periods group, 64.7% in the pcb/ago group, and 61.9% in the fluox/ago group. Of these, 85 TEAE in 49 patients (14.5%) were considered related to treatment during the open-label extension: 15.3% agomelatine both periods, 16.5% pcb/ago, and 10.7% fluox/ago group. The most frequent treatment-related TEAEs (in more than three patients overall) were headache (2.4% of patients), dizziness (2.1%), dry mouth and thirst (1.8% each), somnolence and increased alanine aminotransferase (ALT) (1.2% each), and increased aspartate aminotransferase (AST) and nausea (0.9% each) (Table 2). The most frequent treatment-related TEAEs were the same in adolescents as in the total population.

A total of 19 patients (5.6%) presented with 32 severe TEAEs during the W12–W104 period.

Only four severe TEAEs in three adolescents (1.1%), two treated with ago/ago and one treated with pcb/ago, were considered related to treatment: headache, thirst, and dry mouth and increased appetite, which occurred in only one patient each (0.4%).

Thirteen patients (3.8%) experienced 18 TEAEs leading to agomelatine withdrawal during the extension period, of whom 11 were adolescents who experienced 16 TEAEs. Among the TEAEs leading to agomelatine withdrawal, 4 TEAEs in three patients (0.9%) were considered related to treatment: an increase of ALT and AST reported in the same patient (ago/ago group), one case of headache (pcb/ago), and one case of hypotension (pcb/ago group).

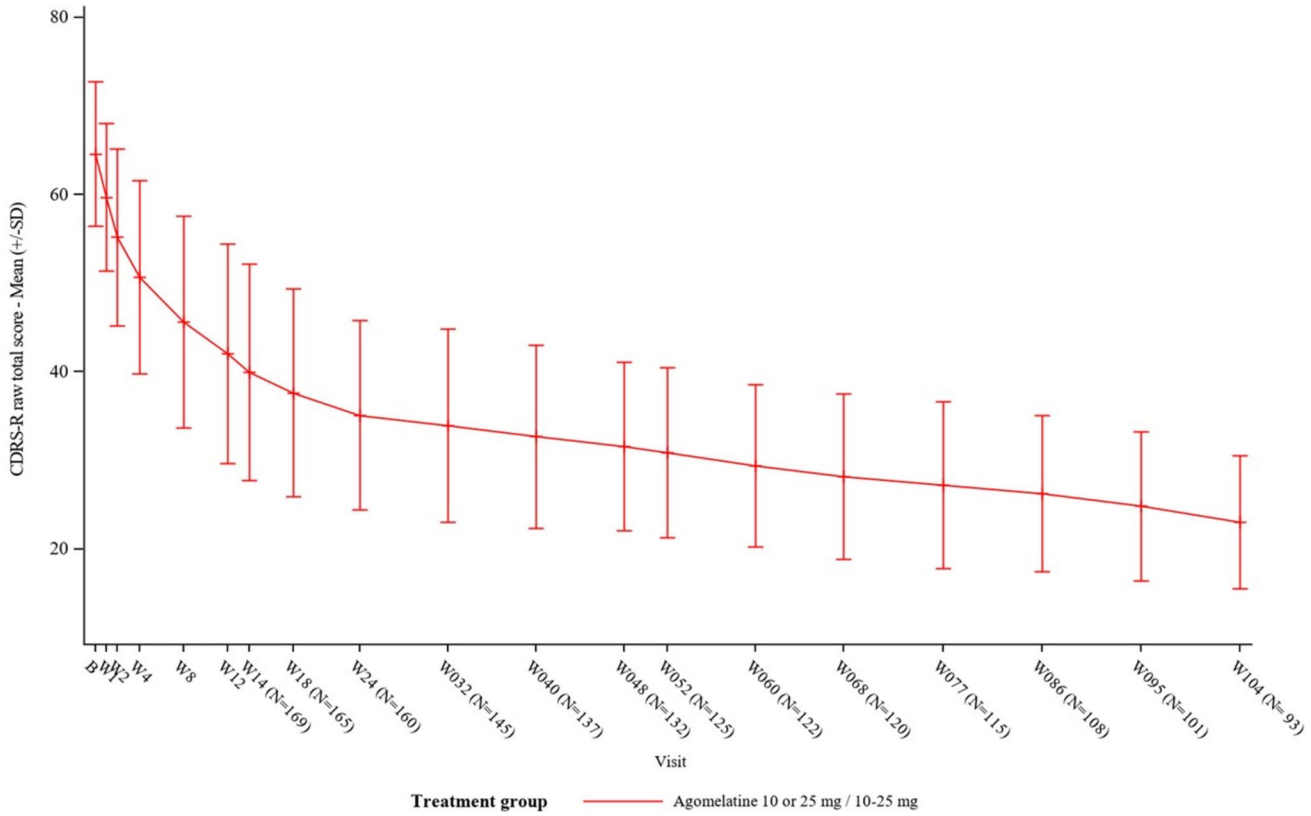

Fig. 3 CDRS-R raw total score: mean value (±SD) at each visit during W000–W104 in patients receiving agomelatine for the duration of the study and continuing in the extension period

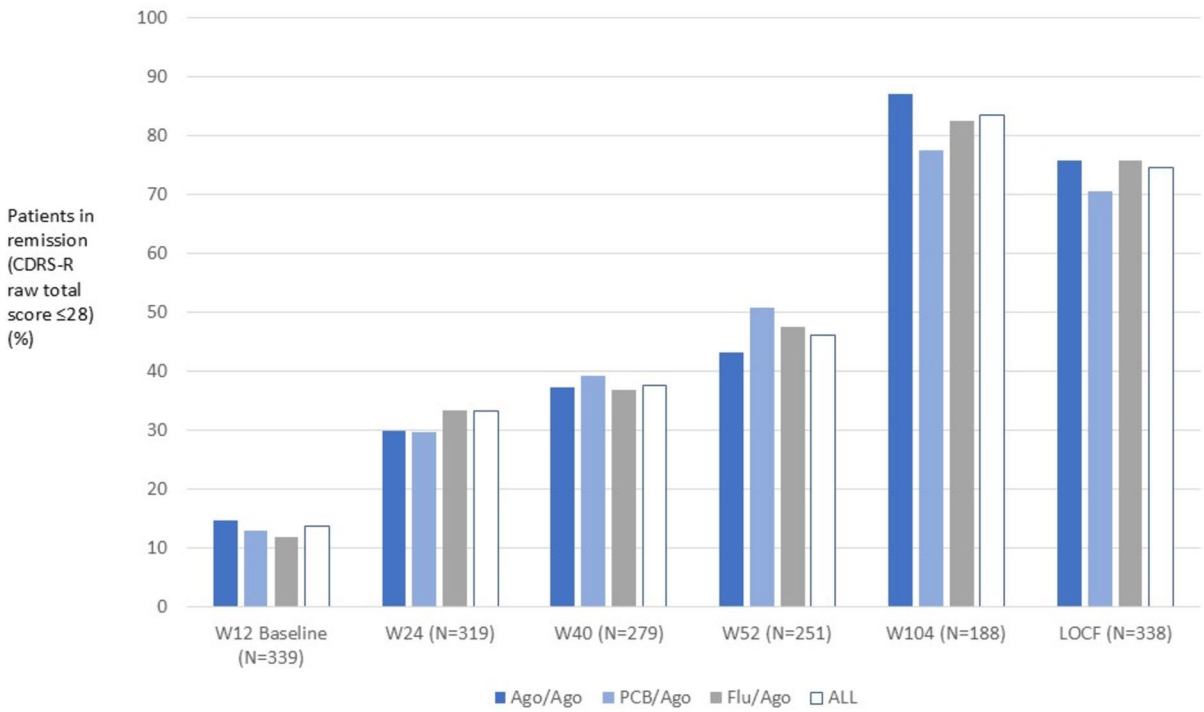

Fig. 4 Proportion of total population (children and adolescents) in remission (CDRS-R raw total score ≤28) during the extension period

Table 2 Treatment-emergent adverse events by system organ class and preferred term occurring in more than three patients in the safety population during the Week 12 to Week 104 open-label extension

System organ class and preferred term	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)	
	NEAE	n (%)	NEAE	n (%)	NEAE	n (%)	NEAE	n (%)
Nervous system disorders								
Headache	4	4 (2.4)	2	2 (2.4)	2	2 (2.4)	8	8 (2.4)
Dizziness	4	3 (1.8)	2	2 (2.4)	2	2 (2.4)	8	7 (2.1)
Somnolence	2	2 (1.2)	1	1 (1.2)	1	1 (1.2)	4	4 (1.2)
Investigations								
ALT increased	3	3 (1.8)	1	1 (1.2)	–	–	4	4 (1.2)
AST increased	2	2 (1.2)	1	1 (1.2)	–	–	3	3 (0.9)
Gastrointestinal disorders								
Dry mouth	5	5 (2.9)	–	–	1	1 (1.2)	6	6 (1.8)
Nausea	2	2 (1.2)	–	–	1	1 (1.2)	3	3 (0.9)
General disorders and administration site conditions								
Thirst	5	4 (2.4)	1	1 (1.2)	1	1 (1.2)	7	6 (1.8)

NEAE number of emergent adverse events

n (%): number and % of patients with at least one event

During the extension period, 12 patients (11 adolescents) presented emergent suicidal ideations on treatment according to the C-SSRS-C: three patients in the ago/ago group, four patients in the pcb/ago group and five patients in the fluox/ago group. Emergent suicidal ideation was rated as serious in one adolescent in the fluox/ago group. Two patients (one in each of the pcb/ago and fluox/ago groups, both adolescents) presented three emergent suicidal behaviors: both made emergent actual suicide attempt on treatment; in addition, the patient in the pcb/ago group also undertook emergent preparatory actions toward imminent suicidal behavior.

In the total population, the most common emergent liver potentially clinically significant abnormal (PCSA) values on treatment were high direct bilirubin (11.2%, 19 patients including 16 adolescents) and high indirect bilirubin (4.1%, seven patients including six adolescents).

A total of three patients (two adolescents and one child) had high emergent PCSA values (> 3 ULN) of ALT or AST on treatment. None of these events led to study withdrawal.

As expected in a pediatric population, patients gained an average of 4.2 ± 5.3 kg between W12 and W104. Among the adolescents there was a mean weight gain of 3.5 ± 5.5 kg between W12 and W104. Mean BMI slightly increased from W12 up to last post-baseline value under treatment by 0.48 ± 1.46 kg/m^2. Analysis by class showed that most patients treated with agomelatine for both study periods remained in the same BMI class. Fourteen patients moved to a higher BMI class, including three patients moving from underweight to normal class. Eighteen patients moved to a lower BMI class, including 13 patients moving from overweight to normal class and five from obese to overweight.

In this study, Tanner Staging was used to document the development and sequence of secondary sex characteristics during puberty. At enrollment and W12, W52 and W104, Tanner stage of sexual development, based on pubic hair and genitalia appearance, was evaluated by physical examination conducted by a trained clinician. Among patients taking agomelatine for the duration of the study there was no evidence of any alterations to normal puberty development. At each visit, patient age and pubertal status were consistent with normal development and stable for the duration of the study.

Discussion

In children and adolescents with MDD, up to 92 weeks of open-label treatment with agomelatine (10–25 mg/day) resulted in gradual improvement in depressive symptoms in addition to those observed in the prior 12-week double-blind, placebo-controlled trial [33]. Mean CDRS-R total scores when entering the extension phase were greater than 40, a score suggestive of moderate symptoms of depression after 3 months of treatment. Open-label treatment with agomelatine 10 or 25 mg resulted in a gradual decrease in CDRS-R, whatever the treatment previously received during the double-blind period, with a mean last post-W12 score of 26 (an individual score of ≤ 28 being indicative

of remission). At the end of the study, the proportion of patients in remission had increased from 13.6% at W12 to 83.5%, although as noted in the study limitations, a degree of spontaneous improvement may have contributed to the high rate of remission. Improvements were continuous from W12 until the last visit, but most marked during the first 24 weeks of the extension phase. A particularly noteworthy observation was that a fifth (20.3%) of the open-label extension population withdrew prematurely from the study because of recovery, with a numerically higher frequency in the ago/ago group (23.5% of patients) than in the other two groups (16.5% pcb/ago and 17.9% fluo/ago).

Overall, clinical severity and impairment due to depression symptoms, and improvement in clinical severity were measured by CGI-S and CGI-I scores, which have previously been shown to correlate with a range of depression outcome scales including the Hamilton Depression Rating Scale, on which the CDRS-R was based [35]. Both scores improved during the extension period, whichever treatment had been received in the double-blind phase. Response to treatment was prospectively defined as a CGI-I score of 1 or 2 (much or very improved). By this definition, the responder rate at the last post-W12 visit was 85% in the overall population and 83% in adolescents. For both primary and secondary endpoints, results for adolescents were very similar to those observed for the total population. It should be noted here that although this study was conducted in both children and adolescents with MDD, the number of children was small (n = 80). The improvements in the open-label extension were greater than those observed with placebo in the short-term double-blind phase of the trial [33], further supporting the effectiveness of agomelatine.

Long-term data on the treatment of children and adolescents with MDD are limited. A small, open-label, long-term extension to a controlled trial suggested that fluoxetine was clinically effective for the maintenance treatment of anxiety disorders in children and adolescents compared with no treatment [36]. A one-year naturalistic extension of the Treatment for Adolescents with Depression Study (TADS) also suggested long-term effectiveness of fluoxetine [37]. However, a 26-week open-label follow-up of vilazodone in children and adolescents with MDD did not support the effectiveness of this treatment for pediatric patients [38].

Evaluation of any drug for depression should also consider the tolerability and acceptability of agents through both the acute-phase and continuation/maintenance phase of MDD treatment. Network meta-analyses indicate that agomelatine has the highest acceptability among treatments for MDD [24] and anxiety disorders [39] in adults. In a recent meta-analysis of 80 psychotropic drugs used in pediatric populations, escitalopram and fluoxetine were found to have the best safety profile [40]. However, agomelatine was not included in the analysis, as it was published before results in MDD became available. Agomelatine has been evaluated in children and adolescents with attention-deficit/hyperactivity disorder, in which a treatment course of 6 weeks (15–25 mg/day) demonstrated a favorable safety and efficacy profile [41].

Safety data from the 12-week double-blind period of the current study showed that agomelatine was well tolerated in children and adolescents with MDD, with no differences in tolerability profile compared with fluoxetine in the short term. In addition, no unexpected safety concerns were identified.

The use of medications with the potential to affect growth hormone signaling may influence pubertal development, but the biological impact of antidepressant drugs on physical and hormonal measures of puberty have not been thoroughly explored. In this study, no abnormalities in Tanner staging by age group were detected in either girls or boys. The overall neutral effect of agomelatine on weight was also confirmed.

No additional risk of hepatotoxicity was observed in this population. The most frequent treatment-related adverse events reflected those reported in adults, namely headache, nausea, dizziness, dry mouth and thirst, which were also reported frequently in the fluoxetine and placebo groups [33]. The same safety pattern was observed during the extension period with no difference in frequency between the total population and adolescents.

Study limitations

Findings from the open-label extension should be interpreted with consideration of the study's major limitation: there was no control group. Ideally, the efficacy and safety of long-term agomelatine treatment for pediatric MDD should be evaluated in the context of a placebo control. This methodology was not chosen for this study, as it would have led to a proportion of patients being maintained on placebo for a long period (2 years), with important and unethical risk of relapse and complications such as suicidal behavior. This limits the conclusions that can be drawn from the study results in terms of effectiveness and safety.

Patient characteristics were similar at W0 and W12, but open-label extension studies can nevertheless be associated with patient selection biases as patients experiencing adverse events are withdrawn before the follow-on period of the study, and those experiencing milder side-effects will be less likely to opt to continue. However, such studies are important to gather long-term data on patient-years of exposure to agomelatine in a young population, to provide increased understanding and confidence in its safety profile. The results also compare well with an open-label extension of the TADS study, in which patients

aged 12–17 years continued treatment with fluoxetine and CBT for a further 24 weeks after the 12-week double-blind phase [42].

Another important limitation is that after 3 months of treatment, patients in the three groups (ago/ago, fluox/ago and placebo/ago) presented important differences at W12 regarding efficacy criteria, especially the pcb/ago group, reflecting the difference in efficacy of the treatments during the double-blind part of the study (agomelatine and fluoxetine being both clinically and statistically superior to placebo). As a result, direct between-group comparisons over the W12–W104 period cannot be made or can only be made with extreme caution. Nevertheless, the final effectiveness scores (mean CDRS-R, CGI and response rates) showed a tendency to homogenize during the study. The most important improvement in CDRS-R mean score over the first 12 weeks (up to W24) is suggestive of a pharmacological effect of agomelatine, which was more important in patients less improved during the double-blind treatment period.

Additional improvement beyond W12 is difficult to interpret, as a certain degree of spontaneous improvement after 6 months is likely and, in the absence of a control group, cannot be separated from agomelatine pharmacological effects.

Nevertheless, the continuous improvement of the patients under agomelatine treatment, especially marked during the first 6 months after the acute phase (i.e. before spontaneous improvement occurs), the progressively increasing number of responders all along the study, and the very low number of relapses or recurrences after 2 years of active treatment, are strongly suggestive of a probable long-term protective effect of agomelatine in pediatric population. Such an effect has previously been demonstrated in adult populations for both depressed and anxious patients [43, 44]. This led to a recommendation in adults to continue agomelatine treatment, when effective, for at least 6 months. This should also be considered for depressed pediatric patients.

Conclusion

In children and adolescents with moderate to severe depression, 92 weeks of open-label treatment with agomelatine in combination with psychosocial counselling resulted in sustained and important improvements in depressive symptoms regardless of treatment received during the double-blind phase. Treatment was well-tolerated and no unexpected safety signals were observed. Very few relapses were observed.

These findings support the safe use of agomelatine in a pediatric population with moderate-to-severe MDD for up to 104 weeks.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00787-024-02587-4.

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Author contributions CA and JB conceived and designed the study and contributed to the drafts of the manuscript. All authors commented on the manuscript and read and approved the final draft.

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Data availability The data presented in this study is available on request from the corresponding author. The data is not publicly available due to privacy reasons.

Declarations

Conflict of interest Dr. Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. Dr. Fegert has no potential conflicts with pharmaceutical companies to report during the past 3 years. Dr. Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda, Roche, Medice, Angelini, Janssen, Boehringer-Ingelheim, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. Françoise Picarel-Blanchot, Ute Marx, Lucie Truffaut-Chalet, and Pierre-François Penelaud are Servier employees.

Ethics approval This study was performed in strict accordance with Good Clinical Practice. The patients (when intellectual maturity and capacity were appropriate) and their parents or their legally authorised representatives provided written informed consent prior to participa-

tion, in line with local regulatory requirements. The study was registered under EUDRACT No. 2015-002181-23.

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