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

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Summary

Background Major depressive disorder is a severe illness that frequently manifests before the age of 18 years, often recurring later in life. Paediatric medical treatment options are scarce. The melatonin receptor agonist and 5-hydroxytryptamine$_{2C}$ receptor antagonist agomelatine is used to treat adults, and could offer a new therapeutic option for paediatric patients. Therefore, we aimed to investigate the short-term antidepressant efficacy and safety of agomelatine in children and adolescents with major depressive disorder.

Methods We performed a 12 week, randomised, double-blind, parallel-group, multicentre, phase 3 trial in 46 specialist psychiatric units or centres in Bulgaria, Finland, Hungary, Poland, Romania, Russia, Serbia, South Africa, and Ukraine. Participants (aged 7–17 years) were eligible if they were unresponsive to psychosocial therapy during the 3-week run-in period (Children's Depression Rating Scale–revised [CDRS-R] score of ≥45). Ethnicity was not recorded. We investigated short-term antidepressant efficacy of agomelatine (10 mg or 25 mg per day) versus placebo with an active control (fluoxetine 10–20 mg depending on symptom severity) after 12 weeks of treatment in children (aged 7–11 years) and adolescents (12–17 years) with major depressive disorder. Patients were randomly assigned (1:1:1:1) to agomelatine 10 mg, agomelatine 25 mg, placebo, or fluoxetine via an interactive response system with permuted-block randomisation. Standardised manualised psychosocial counselling, developed for this trial, was initiated from selection and continued throughout the study, including the open-label extension. All people involved in the conduct of the clinical trial and patients were masked to treatment allocation. Study outcomes were measured using standardised interviews at each study visit. The primary endpoint was change in CDRS-R raw score from baseline to week 12. This study is registered with EudraCT, 2015-002181-23.

Findings Between Feb 23, 2016, and Jan 14, 2020, 466 individuals were assessed for eligibility and of 400 included patients, 396 (247 [62%] girls, 149 [38%] boys; mean age 13·7 years [SD 2·7]) were analysed (full analysis set). The primary objective was met; 25 mg/day agomelatine (n=94, with n=102 receiving 10 mg/day) resulted in an improvement versus placebo (n=101) in CDRS-R raw score of 4·22 (95% CI 0·63–7·82; p=0·040) at 12 weeks, with a similar effect for fluoxetine (n=99), establishing assay sensitivity. The overall effect was confirmed in adolescents (n=317), but not in children (n=79). No unexpected safety signals were observed with agomelatine, with no significant weight gain or effect on suicidal behaviours.

Interpretation This first study in a paediatric population supports the efficacy of 25 mg/day agomelatine, in addition to psychosocial counselling, in treating adolescent patients with major depressive disorder, with no unexpected safety signals. This medication could provide another option in the limited psychopharmaceutical repertoire for management of major depressive disorder.

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See Online for appendix

Introduction

Major depressive disorder is a severe illness affecting approximately 16·6% of people throughout their lifetime,[1] with an estimated prevalence of 1·6% in children aged 8–11 years and 3·8% in adolescents aged 12–15 years.[2] Major depressive disorder has a large symptomatic overlap between patient age groups, with some characteristic presentations in adolescents and children. Anhedonia and hopelessness are seen more frequently in adolescents, whereas children are more likely to have somatic complaints, irritability, or mood-congruent hallucinations.[3,4] Major depressive disorder can be complicated by suicidality, which is considered the second or third highest cause of mortality in this age group,[1] particularly in adolescents. There is additional high risk of concurrent or subsequent comorbidities,

Research in context

Evidence before this study

Current guidelines for managing major depressive disorder in paediatric patients recommend cognitive behavioural therapy, interpersonal therapy, or family-based therapy, potentially in combination with antidepressant therapy; however, medical options are limited to two SSRIs in this population.
On Nov 30, 2021, we searched PubMed with no date or language restrictions for the following terms: (Depression [Mesh] OR Depressive Disorder, Major [Mesh] OR depression) AND ("Adolescent"[MeSH Terms] OR "adolescent*[Title/Abstract] OR Child [MeSH] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract] OR children[Title/Abstract] OR Child[Title/Abstract]) AND (randomized controlled trial [Publication Type] OR RCT OR (Clinical trial [Publication Type] AND (Random Allocation [MeSH Terms] OR randomi*[Title/Abstract]) AND (Drug Therapy [MeSH term] OR Drug Therapy [MeSH Terms] OR Antidepressive Agents [MeSH Terms]) NOT (Adult [MeSH Terms] OR Aged [MeSH Terms] OR Young Adult [MeSH Terms] OR open label). The strategy identified 343 articles. Following review, 22 articles were found to cover paediatric, double-blind, randomised controlled trials of psychopharmacological agents. Six studies had positive outcomes; three favouring fluoxetine, one favouring escitalopram, one favouring paroxetine, and one favouring sertraline, all of which are SSRIs. No randomised controlled trials with agomelatine in the paediatric population were identified in the search.

Added value of this study

This phase 3, international study is one of the largest placebo-controlled trials in paediatric major depressive disorder and the first to evaluate agomelatine, to our knowledge. The study was designed to use standardised psychosocial counselling throughout, which was specifically developed for this study. The results showed that agomelatine 25 mg/day could be an effective treatment of paediatric major depressive disorder, particularly in adolescent patients, without unexpected safety or toxicity signals. The effect size of agomelatine in adolescents was similar to those previously seen in adult depression studies.

Implications of all the available evidence

The findings support the use of agomelatine 25 mg/day, in addition to psychosocial counselling, as a new pharmacological treatment option for paediatric patients with major depressive disorder. Besides fluoxetine and escitalopram, agomelatine could provide an additional tool for the management of this debilitating condition, alone or potentially in combination with other available treatments, although possible combinations remain to be evaluated.

including ADHD, oppositional defiance disorder, or anxiety disorders.[5]

Established recommendations and guidelines for treatment of moderate to severe depression in children and adolescents recommend initial treatment with cognitive behavioural therapy, interpersonal therapy, or a family-based therapy.[6–8] These methods can be combined with psychopharmacotherapies, depending on symptom severity or persistence. Although psychotherapies are the preferred treatment for paediatric depression, they are not always easily available. Pharmacological treatments are thus a necessary alternative.

Limited evidence exists for antidepressant efficacy, tolerability, and safety in paediatric patients, with only one SSRI authorised by the US Food and Drug Administration (FDA) and European Medicines Agency for children and adolescents (fluoxetine) and one by the FDA for adolescents only (escitalopram).[9] Other antidepressants used in paediatric patients do not have the evidence base that fluoxetine has.[10]

Emergent suicidality can be a temporary issue for paediatric patients starting antidepressants, which led approval agencies to require a boxed warning (ie, a warning of potentially serious side-effects located on the drug's package insert). Prescription of antidepressants to paediatric patients is therefore complex for physicians.[9] Given the limited efficacy of available antidepressants in paediatric populations, there is a need to develop pharmacological treatment options for major depressive disorder, which act via other mechanisms of action than current treatments.

Agomelatine is an antidepressant registered for use in adults in the treatment of major depressive disorder with a unique mechanism of action; it is a melatonin receptor agonist and 5-hydroxytryptamine$_{2C}$ receptor antagonist.[11] These two properties of agomelatine support reduced anxiety, improved sleep, preservation of sexual function, and ultimately result in antidepressive properties.[12]

Agomelatine has been shown to be efficacious in treating adult patients with depression, with a favourable safety profile.[13] On the basis of these factors, and the unmet therapeutic need, it is of interest to evaluate agomelatine in paediatric populations. In this trial, we aimed to investigate, for the first time, the short-term antidepressant efficacy and safety of agomelatine after 12 weeks of treatment in children and adolescents with major depressive disorder versus placebo using fluoxetine as an active control with all participants receiving standardised care (psychosocial counselling) throughout.

Methods

Study design and participants

This 12-week, randomised, double-blind, two-dose level, active and placebo controlled, parallel group, international, multicentre, phase 3 trial recruited patients from 46 specialist psychiatric units or centres in Bulgaria,

Finland, Hungary, Poland, Romania, Russia, Serbia, South Africa, and Ukraine. An anonymised protocol is provided in the appendix (p 23).

Eligible patients (7–17 years) were divided into two age subgroups: 7–11 years (referred to hereafter as children) or 12–17 years (referred to hereafter as adolescents). Participants were eligible if they were unresponsive to psychosocial therapy during the 3-week run-in period (Children's Depression Rating Scale–revised [CDRS-R] score of ≥45). Major exclusion criteria were as follows: presence of treatment-resistant depression, psychotic depression, not living with parents or guardians, current inpatient treatment, current suicidal risk, were pregnant or were not using effective contraception (in the case of post-menarche female patients), major comorbid psychiatric conditions, or clinically significant medical conditions requiring medication, severe hepatic or renal impairment, non-controlled hyper or hypothyroidism. Full details of the eligibility criteria are included in the appendix (pp 1, 60).

Independent ethics committees reviewed the study protocol, with trial initiation after ethical committee approval according to regulations in the participating countries. Protocol amendments were applied only after ethics committee approval and according to local regulatory requirements. The trial was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, and ethical considerations for clinical trials on medicinal products conducted within the paediatric population (European Commission, 2008). The patients (when intellectual maturity and capacity were appropriate) and their parents or their legally authorised representatives provided informed consent, in line with local regulatory requirements.

Randomisation and masking

Patients were allocated to agomelatine 10 mg, agomelatine 25 mg, placebo, or fluoxetine at inclusion (week 0) via an interactive response system. A balanced (ratio 1:1:1:1) permuted-block randomisation was used, with stratification by country and children or adolescent age group. The randomisation list was generated by the sponsor using secure validated in-house application software (Servier), with access strictly controlled depending on roles and profiles of users involved in the study. All people involved in the conduct of the clinical trial and patients were masked to treatment allocation. Active and placebo treatments dispensed throughout the trial were identical in appearance (either oral solution or tablets).

Procedures

Agomelatine doses (10 mg/day or 25 mg/day) were chosen based on the results of a previous pharmacokinetic study in 51 children and adolescents with depressive and anxiety disorders, and accounted for the 25 mg/day recommended dose for adults,[12] and a dose-response study in adults that showed 10 mg/day was effective.[14]

Before and during the study, investigators were trained in study procedures and use of diagnostic and evaluation tools. Participants were assessed at week 0 (inclusion) and subsequently at weeks 1, 2, 4, 8, and 12. Age-adapted tools were used, including the Schedule for Affective Disorders and Schizophrenia for School-Age Children,[15] a validated semi-structured diagnostic interview, CDRS-R,[16] a 17-item clinician-rated depression scale exploring both verbal and non-verbal observations, and Adolescent Depression Rating Scale (ADRS), a ten-item clinician-rated depression scale adapted to adolescents.[17]

Included patients were treated as shown in the appendix (p 2). From week 0 to week 2, all patients received 2·5 mL oral solution in the morning and one tablet in the evening at bedtime. The morning solution contained either fluoxetine (10 mg) or placebo, and the evening tablet either 10 mg or 25 mg agomelatine or placebo. Although samples for pharmacokinetic analysis were collected throughout this trial, the data are not presented in this Article.

If the investigator judged that the patient had improved insufficiently at week 2 as judged by change in CDRS-R raw score, oral solution volume for fluoxetine and the equivalent morning placebo oral solution could be doubled and maintained up to week 12, potentially leading to an increased dose of 20 mg/day fluoxetine, per the summary of product characteristics for fluoxetine and to maintain blinding. The 12 week trial period was followed by a 21 month open-label extension period (appendix p 2), which finished on Oct 27, 2021 (last patient, last visit). Patients who withdrew from the trial and those who chose not to continue open-label treatment in the extension phase after the 12-week treatment phase attended a follow-up visit 1 week later.

Standardised manualised psychosocial counselling, developed for this trial, was initiated from selection and continued throughout the study, including the open-label extension. Further details of the counselling provided are shown in the appendix (p 3).

Two substantial and two non-substantial amendments were made to the protocol. The first substantial amendment (Sept 19, 2016) included the following major changes: additional exclusion criteria for liver function and additional safety measures, including liver function tests; report of data of the Paediatric Adverse Event Rating Scale (clinician part) in the electronic case report form and report of adverse events from the Paediatric Adverse Event Rating Scale in the adverse event form of the electronic case report form. The second substantial amendment (Dec 13, 2019) included the following changes: integration of agreed modifications on the Paediatric Investigation Plan (sample size and statistical analysis including the update of statistical patient sets and study completion date); update of the total number of centres and the list of participating countries; and updating sections concerning download of participants' data from the electronic case report form. Additional details, plus details of non-substantial amendments, are included in the appendix (p 17).

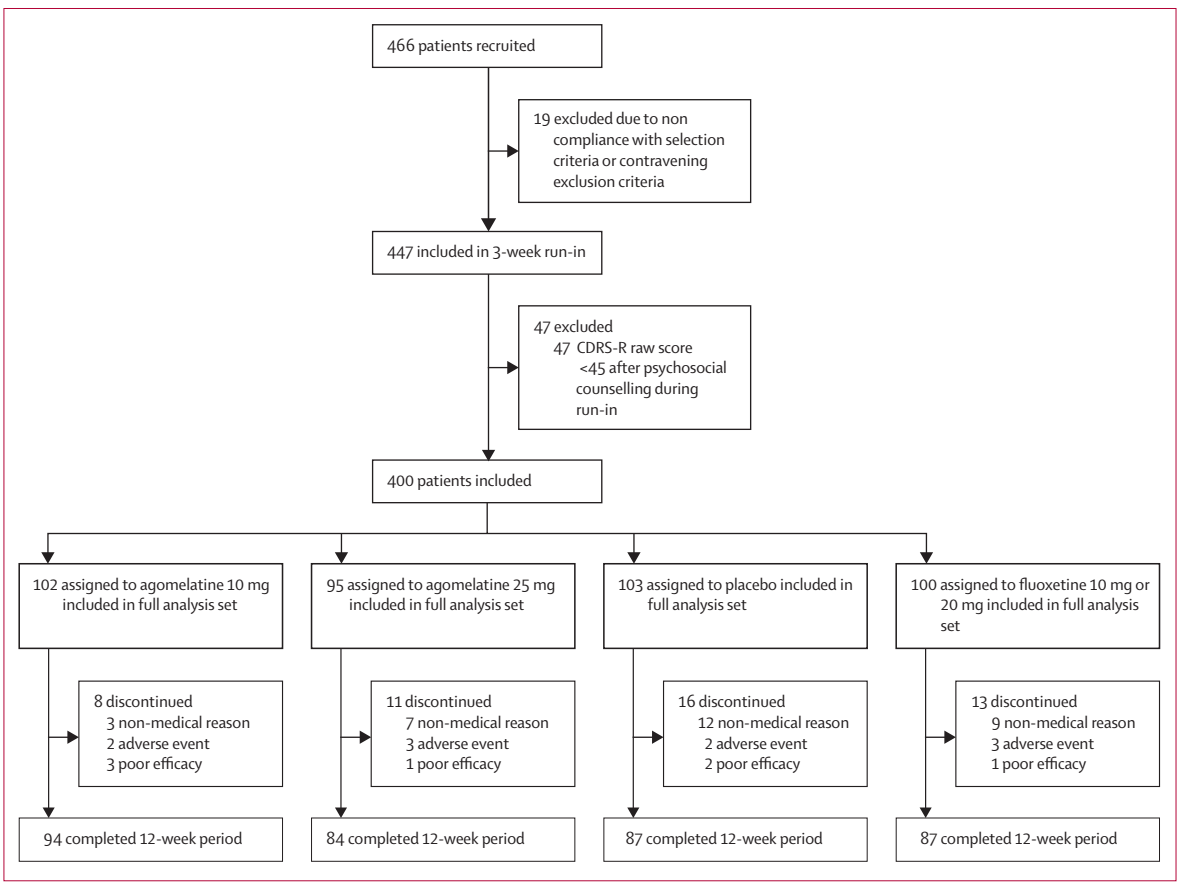

***Figure*: Trial profile**
CDRS-R=Children's Depression Rating Scale–revised.

Outcomes

The primary objective was to evaluate the superiority of at least one agomelatine dose regimen versus placebo in terms of antidepressant efficacy after the 12-week treatment period in the overall population. The primary endpoint was change in CDRS-R raw total score from baseline to 12 weeks. Further information regarding the evaluation timepoints is provided in the appendix (p 4). Assay sensitivity was studied by comparing the effect of fluoxetine versus placebo in the overall population. Exploration of efficacy in children and adolescents was a secondary objective.

Secondary efficacy endpoints were Clinical Global Impression–Severity (CGI-S) and CGI–Improvement (CGI-I) scores at week 12; response to treatment was defined as CGI-I score of 1 or 2 (much or very improved) at week 12; Children's Global Assessment Scale; and ADRS at week 12 in adolescents.

Choice of primary measure

CDRS-R is a 17-item clinician-rated instrument (range of scores 17–113) integrating multiple-source information initially designed for assessing depression severity in children aged 6–12 years,[16] and has been successfully used in adolescents.[16] Individual items are scored between 1 (no difficulties) and 5 or 7 (clinically severe difficulties). The CDRS-R was the primary efficacy endpoint in most published depression trials in adolescent patients, including the fluoxetine trials on which the European Medicines Agency and FDA approvals were based,[18–20] and also in a 2009 study on escitalopram.[21] A cutoff of 45 on the CDRS-R total score was chosen to ensure inclusion of patients with sufficiently severe major depressive disorder symptoms, and was previously used in a trial of escitalopram in adolescents.[21] Remission was defined as a CDRS-R raw total score of 28 or less, as per previous studies.[22,23] If required, the scale was translated into local languages using recognised and validated methods. CDRS-R is copyrighted on behalf of WPS (Torrance, CA, USA).

Statistical analysis

Sample size was fixed as at least 390 patients, including at least 312 adolescents (divided equally between the four treatment groups) to ensure sufficient statistical power in this subgroup. As recruitment was expected to be limited in children, no sample size nor power calculations were performed on this age subgroup. Details regarding sample

	Agomelatine 10 mg/day	Agomelatine 25 mg/day	Placebo	Fluoxetine	All
Overall population, full analysis set (n=396)					
Children (7–11 years)	21/102 (21%)	19/94 (20%)	20/101 (20%)	19/99 (19%)	79/396 (20%)
Adolescents (12–17 years)	81/102 (79%)	75 (80%)	81/101 (80%)	80/99 (81%)	317/396 (80%)
Mean age, years	13·6 (2·9)	13·4 (2·7)	13·9 (2·6)	13·8 (2·7)	13·7 (2·7)
Range	7–17	7–17	7–17	7–17	7–17
Sex					
Boys	34/102 (33%)	33/94 (35%)	39/101 (39%)	43/99 (43%)	149/396 (38%)
Girls	68/102 (67%)	61/94 (65%)	62/101 (61%)	56/99 (57%)	247/396 (62%)
Mean disease duration, days	181·2 (210·0)	129·8 (138·6)	136·4 (131·6)	121·3 (102·6)	142·6 (152·8)
Median	116·5 (59·0–217·0)	90·0 (51·0–161·0)	90·0 (55·0–169·0)	90·0 (54·0–151·0)	94·5 (55·0–175·5)
History of previous major depressive episode	22/102 (22%)	24/94 (26%)	36/101 (36%)	31 (31%)	113/396 (29%)
Mean number of previous episodes*	1·3 (0·5)	1·5 (0·7)	1·3 (0·5)	1·4 (0·7)	1·3 (0·6)
Range	1–2	1–3	1–3	1–4	1–4
History of psychiatric disorders†	30/102 (29%)	27/95 (28%)	27/103 (26%)	25/100 (25%)	109/400 (27%)
Social anxiety disorder†	6/102 (6%)	8/95 (8%)	4/103 (4%)	10/100 (10%)	28/400 (7%)
Generalised anxiety disorder†	8/102 (8%)	5/95 (5%)	4/103 (4%)	4/100 (4%)	21/400 (5%)
ADHD†	5/102 (5%)	6/95 (6%)	5/103 (5%)	3/100 (3%)	19/400 (5%)
Previous antidepressant use†	16/102 (16%)	16/95 (17%)	23/103 (22%)	18/100 (18%)	73/400 (18%)
Previous use of psychostimulants, agents used for ADHD, or nootropics†	3/102 (3%)	1/95 (1%)	2/103 (2%)	4/100 (4%)	10/400 (3%)
Previous anxiolytic use†	6/102 (6%)	12/95 (13%)	16/103 (16%)	12/100 (12%)	46/400 (12%)
Adolescents in full analysis set					
Mean age, years	14·8 (1·6)	14·5 (1·5)	14·9 (1·5)	14·9 (1·6)	14·8 (1·6)
Range	12–17	12–17	12–17	12–17	12–17
Sex					
Boys	18/81 (22%)	25/75 (33%)	26/81 (32%)	32/80 (40%)	101/317 (32%)
Girls	63/81 (78%)	50/75 (67%)	55/81 (68%)	48/80 (60%)	216/317 (68%)
Mean disease duration, days	198·5 (229·6)	135·7 (152·8)	136·6 (137·2)	125·0 (109·0)	149·3 (165·5)
Median	121·0 (62·0–242·0)	87·0 (48·0–178·0)	88·0 (54·0–169·0)	95·0 (53·5–161·0)	97·0 (54·0–181·0)
History of previous major depressive episode	20/81 (25%)	21/75 (28%)	36/81 (44%)	27/80 (34%)	104/317 (33%)
Mean number of previous episodes*	1·3 (0·5)	1·5 (0·7)	1·3 (0·5)	1·4 (0·7)	1·3 (0·6)
Range	1–2	1–3	1–3	1–4	1–4
Children in full analysis set (n=79)					
Mean age, years	8·9 (1·4)	9·1 (1·5)	9·6 (1·1)	9·2 (1·2)	9·2 (1·3)
Range	7–11	7–11	7–11	7–11	7–11
Sex					
Boys	16/21 (76%)	8/19 (42%)	13/20 (65%)	11/19 (58%)	48/79 (61%)
Girls	5/21 (24%)	11/19 (58%)	7/20 (35%)	8/19 (42%)	31/79 (39%)
Mean disease duration, days	114·6 (77·4)	106·6 (49·5)	135·8 (109·2)	105·5 (69·2)	115·8 (79·1)
Median	78·0 (55·0–177·0)	107·0 (62·0–146·0)	101·5 (71·5–169·5)	78·0 (66·0–129·0)	90·0 (60·0–151·0)
History of previous major depressive episode	2/21 (10%)	3/19 (16%)	0	4/19 (21%)	9/79 (11%)
Mean number of previous episodes*	1·5 (0·7)	1·3 (0·6)	..	1·3 (0·5)	1·3 (0·5)
Range	1–2	1–2	..	1–2	1–2

Data are n/N (%), mean (SD), or median (IQR). *From the first occurrence until current episode. †Data are for the modified randomised set.

Table 1: **Baseline characteristics of the full analysis set**

size considerations are included in the appendix (p 5). For inferential analyses, missing data were handled using a last observation carried forward approach. This approach was used to provide a conservative estimate of the treatment effect in the context of this trial, in which the condition is expected to improve spontaneously over time.[24]

The modified randomised set comprised all included and randomly assigned patients. The full analysis set comprised all patients from the modified randomised set who had received at least one dose of investigational medicinal product and had a recorded baseline value and at least one post-baseline value for the primary efficacy

	Agomelatine 10 mg/day	Agomelatine 25 mg/day	Placebo	Fluoxetine
Overall population, full analysis set (n=396)				
Mean baseline CDRS-R score	64·3 (8·3)	65·5 (8·3)	67·5 (8·6)	65·0 (8·0)
Mean score at final follow-up, week 0 to week 12	43·4 (14·2)	43·0 (13·4)	47·9 (15·4)	43·3 (12·6)
Mean score at final follow-up minus baseline score	−20·9 (14·0)	−22·5 (15·2)	−19·7 (14·4)	−21·7 (14·1)
Median score	−21·5 (−29·0 to −10·0)	−21·0 (−32·0 to −9·0)	−20·0 (−28·0 to −8·0)	−21·0 (−32·0 to −10·0)
Estimate*	3·18 (1·81)	4·22 (1·83)	..	3·74 (1·81)
95% CI	−0·37 to 6·73	0·63 to 7·82	..	0·18 to 7·30
p value†	0·079	0·040	..	0·039
Adolescents, full analysis set (n=317)				
Mean baseline CDRS-R score	64·5 (8·3)	66·1 (8·7)	68·1 (8·8)	65·3 (8·1)
Mean score at final follow-up, week 0 to week 12	43·4 (15·0)	42·2 (13·4)	48·3 (15·1)	43·3 (12·9)
Mean score at final follow-up minus baseline score	−21·1 (14·1)	−23·8 (15·4)	−19·8 (13·4)	−22·0 (14·2)
Median score	−22·0 (−30·0 to −10·0)	−22·0 (−33·0 to −12·0)	−20·0 (−28·0 to −9·0)	−21 (−32·5 to −10·0)
Estimate*	3·18 (2·11)	5·22 (2·13)	..	3·70 (2·10)
95% CI	−0·96 to 7·32	1·03 to 9·40	..	−0·43 to 7·84
p value†	0·13	0·028	..	0·079
Children, full analysis set (n=79)‡				
Mean baseline CDRS-R score	63·3 (8·7)	63·1 (6·3)	65·2 (7·7)	63·6 (7·5)
Mean score at final follow-up, week 0 to week 12	43·3 (11·0)	46·0 (12·9)	46·2 (17·2)	42·9 (11·1)
Mean score at final follow-up minus baseline score	−20 (13·9)	−17·1 (13·3)	−19·0 (18·3)	−20·7 (14·4)
Median score	−18·0 (−29·0 to −8·0)	−11·0 (−27·0 to −6·0)	−12·0 (−38·5 to −5·0)	−22·0 (−30·0 to −8·0)

Data are mean SD, median (IQR) or as specified. Denominators for the data in the overall set are n=102 for agomelatine 10 mg/day, n=94 for agomelatine 25 mg/day, n=101 for placebo, and n=99 for fluoxetine. Denominators for the data in the adolescent set are n=81 for agomelatine 10 mg/day, n=75 for agomelatine 25 mg/day, n=81 for placebo, and n=80 for fluoxetine. Denominators for the data in the child set are n=21 for agomelatine 10 mg/day, n=19 for agomelatine 25 mg/day, n=20 for placebo, and n=19 for fluoxetine. Range of possible scores was 17–113. CDRS-R=Children's Depression Rating Scale–Revised. *Estimate (SE) of the adjusted difference between treatment group means for change from baseline to last post-baseline value: placebo minus each agomelatine dose regimen (or fluoxetine) using an ANCOVA, including the fixed, categorical effects of treatment (including four treatment groups), age subgroup, and country, as well as continuous, fixed covariate of baseline. †p value for significance was 0·05 (step-down Dunnett adjusted p value for agomelatine dose regimen). ‡Statistical analyses were not performed in children due to the small number of patients in each group.

Table 2: **CDRS-R raw total scores in the overall population, adolescents, and children**

endpoint, in accordance with the intention-to-treat principle.[25] To evaluate the primary objective of this trial in the full analysis set, a three-way analysis of covariance (ANCOVA) model was used to assess change from baseline in CDRS-R raw total score at week 12. Analysis included fixed, categorical effect of treatment (including the four treatment groups); age subgroup, and country; and the continuous fixed covariate of baseline. Differences between treatment groups were calculated as placebo minus each active treatment; therefore, a positive treatment difference was in favour of the active treatment. The step-down Dunnett procedure was used to control the family-wise error rate, as both agomelatine doses were compared with placebo. Assay sensitivity was studied using the same analysis to compare fluoxetine with placebo. The estimate of the difference between adjusted treatment group means, associated SEs, two-sided 95% CIs, and Dunnett-adjusted p value were calculated. Details of sensitivity analyses are provided in the appendix (p 5). Analyses of CDRS-R raw total score were also performed in adolescents. Information about statistical analyses for other secondary endpoints can be found in the appendix (p 6).

Analyses were performed on the safety population (patients who received at least one dose of the investigational medicinal product). Adverse events were collected using the Paediatric Adverse Event Rating Scale and spontaneously by clinicians. Suicidal ideation was assessed using the Columbia Suicide Severity Rating Scale for Children. Data regarding Tanner stage and hormonal profile were also collected. A data safety monitoring committee was responsible for periodic monitoring of patient safety data throughout the study to ensure participant safety. This study is registered with EudraCT, 2015-002181-23.

Role of the funding source

The study was co-designed by the funder and the authors; the funder was also responsible for data collection and statistical analysis. The authors (including employees of the sponsor [PFP, UM, VO, and DC]) were responsible for data analysis, data interpretation, and writing of the report, and the funder was responsible for trial execution.

Results

Between Feb 23, 2016, and Jan 14, 2020, 466 patients were screened and 447 patients were enrolled in the trial. After the 3-week run-in period, 400 patients (80 children and 320 adolescents) were included and randomly assigned to one of the four treatment groups. Patient disposition is shown in the figure; the modified randomised set comprised 400 patients, the full analysis set comprised 396 (99%) patients, and the safety population comprised 399 patients. Contributions from individual countries are listed in the appendix (p 8).

Of included patients, 352 (88%) of 400 completed the study up to week 12, with the highest proportion in the agomelatine 10 mg/day group (94 [92%] of 102) and lowest in the placebo group (87 [84%] of 103). Discontinuation rates were 8% (eight of 102) in the agomelatine 10 mg/day group, 12% (11 of 95) in the agomelatine 25 mg/day group, 16% (16 of 103) in the placebo group, and 13% (13 of 100) in the fluoxetine group.

Baseline characteristics in the full analysis set are shown in table 1. Patients were 7–17 years old with a mean age of 13·7 years (SD 2·7). Overall, 247 (62%) of 396 participants were girls and 149 (38%) were boys, with a lower proportion of female patients in the fluoxetine group (56 [57%] of 99) versus the other three groups. Ethnicity was not recorded. Major depressive disorder was diagnosed as moderate in most patients (244 [62%]

of 396) and severe without psychotic features in 152 (38%) of 396 patients, with a lower proportion in the agomelatine 10 mg/day group (28 [27%] of 102) versus the other three groups (41–44%). Overall, 73 (18%) of 396 patients had melancholic features without relevant differences between groups. Median disease duration at inclusion was 94·5 days (IQR 55·0–175·5). The longer duration observed in the agomelatine 10 mg/day group was due to one single patient with a 4-year disease duration. A history of major depressive episodes was recorded in 113 (29%) of 396 patients, with lower proportions in the agomelatine 10 mg/day group (22 [22%] of 102) and 25 mg/day group (24 [26%] of 94).

According to the Columbia Suicide Severity Rating Scale for Children, 92 (23%) of 400 patients in the modified randomised set had experienced suicidal ideation throughout their lifetime, without differences between groups. Suicidal behaviour throughout their lifetime was reported in 14 (4%) of 400 patients, with higher proportions in the agomelatine 25 mg/day group (six [6%] of 95) versus placebo (two [2%] of 103).

On the basis of body-mass index (BMI) classes,[26] 18 (5%) of 400 patients in the modified randomised set were considered underweight, 66 (17%) of 400 were overweight, and 30 (8%) of 400 were obese at baseline. There were more patients who were obese in the agomelatine 10 mg/day group (11 [11%] of 102) versus the other three groups (6–7%). All patients had a CGI-S score of 4 or more (data not shown).

Overall, patient characteristics were in accordance with the targeted population per the study protocol, without major differences in major depressive disorder characteristics, demographic data, or efficacy criteria between groups.

After 12 weeks' treatment, a greater improvement in CDRS-R raw total score was observed in the active treatment groups versus placebo (table 2). Individual items are shown in the appendix (p 9), as is evolution over time (p 13). The estimate of adjusted differences from baseline to week 12 of treatment group means (hereafter referred to as estimate of differences) versus placebo associated with these improvements were 3·18 (95% CI –0·37 to 6·73) for agomelatine 10 mg/day and 4·22 (95% CI 0·63 to 7·82) for agomelatine 25 mg/day, reaching statistical significance only at last dose for 25 mg/day (step-down Dunnett adjusted p=0·040). The assay sensitivity of the trial was established, as the estimated difference between fluoxetine 10–20 mg/day and placebo was 3·74 (95% CI 0·18 to 7·30), also significant (p=0·039; table 2). The Cohen's effect sizes in the overall population were 0·29 for agomelatine 25 mg/day and 0·26 for fluoxetine (data not shown).

The mixed modelling repeated measures (MMRM) sensitivity analysis did not show a significant difference between any active treatment group and placebo (agomelatine 25 mg/day: estimate of differences 3·19 [95% CI –0·55 to 6·94]; step-down Dunnett adjusted p=0·17), but an unplanned MMRM sensitivity analysis adding baseline-by-visit interaction confirmed the results of the primary analysis (p=0·036). The difference between placebo and agomelatine 25 mg/day groups significantly favoured agomelatine 25 mg/day (estimate of differences 4·27 [95% CI 0·69 to 7·85]; step-down Dunnett adjusted p=0·037) and the difference between placebo and agomelatine 10 mg/day was non-significant. The difference

	Agomelatine 10 mg/day (n=102)	Agomelatine 25 mg/day (n=94)	Placebo (n=101)	Fluoxetine (n=99)
CGI-Severity				
Mean baseline score	4·7 (0·6)	4·9 (0·7)	5·0 (0·6)	4·9 (0·6)
Mean score at final follow-up, week 0 to week 12	3·5 (1·1)	3·5 (1·1)	3·8 (1·2)	3·6 (1·0)
Estimate*	0·27 (0·16)	0·28 (0·17)	..	0·18 (0·16)
95% CI	–0·05 to 0·59	–0·05 to 0·62	..	0·14 to 0·49
Student's *t* test p value	0·095	0·094	..	0·27
Mann-Whitney p value	0·035	0·051	..	0·12
CGI-Improvement				
Mean score at final follow-up, week 0 to week 12	2·6 (1·1)	2·5 (1·0)	2·7 (1·1)	2·6 (1·0)
Estimate*	0·15 (0·15)	0·23 (0·15)	..	0·17 (0·15)
95% CI	–0·14 to 0·45	–0·06 to 0·53	..	–0·12 to 0·46
Student's *t* test p value	0·31	0·12	..	0·26
Mann-Whitney p value	0·30	0·18	..	0·34
Response to treatment based on CGI				
Patients with response to treatment at final follow-up	49 (48%)	46 (49%)	45 (45%)	47 (47%)
Estimate*	–3·48 (7·00)	–4·38 (7·14)	..	–2·92 (7·05)
95% CI	–17·19 to 10·23	–18·38 to 9·62	..	–16·73 to 10·89
χ^2 test p value	0·62	0·54	..	0·68
Children's Global Assessment Scale score				
Mean score at final follow-up, week 0 to week 12	13·2 (11·3)	14·4 (13·0)	12·1 (14·0)	13·9 (12·5)
Adolescent Depression Rating Scale total score† (adolescents only)				
Mean baseline score	31·6 (5·6)	32·8 (5·7)	34·6 (6·1)	33·6 (6·0)
Mean score at final follow-up	18·8 (10·1 [n=79])	18·1 (10·6 [n=75])	22·2 (10·7 [n=80])	19·9 (10·3 [n=80])
Estimate*	3·40 (1·65)	4·07 (1·72)	..	2·34 (1·66)
95% CI	0·14 to 6·67	0·68 to 7·46	..	–0·95 to 5·62
Student's *t* test p value	0·041	0·019	..	0·16
Mann-Whitney p value	0·064	0·032	..	0·28

Data are mean (SD), n (%), or as specified. CGI=Clinical Global Impression. *Estimate (SE) of the difference of mean between placebo and each agomelatine dose regimen and between placebo and fluoxetine. †Denominators for these data are n=81 for agomelatine 10 mg/day, n=75 for agomelatine 25 mg/day, n=81 for placebo, and n=80 for fluoxetine.

Table 3: **Secondary efficacy endpoints**

	Agomelatine 10 mg/day			Agomelatine 25 mg/day			Placebo			Fluoxetine		
	All (N=102)	Boys (n=34)	Girls (n=68)	All (N=94)	Boys (n=33)	Girls (n=61)	All (N=103)	Boys (n=39)	Girls (n=64)	All (N=100)	Boys (n=43)	Girls (n=57)
All	62 (61%)	22 (65%)	40 (59%)	60 (64%)	22 (67%)	38 (63%)	63 (61%)	23 (59%)	40 (63%)	57 (57%)	23 (54%)	34 (60%)
Dry mouth	21 (21%)	8 (24%)	13 (19%)	13 (14%)	4 (12%)	9 (15%)	11 (11%)	4 (10%)	7 (11%)	13 (13%)	8 (19%)	5 (9%)
Thirst	16 (16%)	5 (15%)	11 (16%)	13 (14%)	5 (15%)	8 (13%)	10 (10%)	3 (8%)	7 (11%)	15 (15%)	9 (21%)	6 (11%)
Nausea	10 (10%)	3 (9%)	7 (10%)	12 (13%)	3 (9%)	9 (15%)	14 (14%)	3 (8%)	11 (17%)	9 (9%)	3 (7%)	6 (11%)
Headache	16 (16%)	6 (18%)	10 (15%)	11 (12%)	7 (21%)	4 (7%)	14 (14%)	6 (15%)	8 (13%)	11 (11%)	4 (9%)	7 (12%)
Abdominal pain	8 (8%)	4 (12%)	4 (6%)	7 (7%)	3 (9%)	4 (7%)	7 (7%)	1 (3%)	6 (9%)	4 (4%)	3 (7%)	1 (2%)
Increased appetite	7 (7%)	3 (9%)	4 (6%)	6 (6%)	0	6 (10%)	0	0	0	3 (3%)	2 (5%)	1 (2%)
Fatigue	5 (5%)	2 (6%)	3 (4%)	6 (6%)	3 (9%)	3 (5%)	7 (7%)	3 (8%)	4 (6%)	2 (2%)	1 (2%)	1 (2%)
Weight increase	6 (6%)	3 (9%)	3 (4%)	5 (5%)	..	5 (8%)	..	..	..	2 (2%)	2 (5%)	..
Decreased appetite	3 (3%)	2 (6%)	1 (2%)	5 (5%)	1 (3%)	4 (7%)	7 (7%)	4 (10%)	3 (5%)	5 (5%)	4 (9%)	1 (2%)
Nasopharyngitis	3 (3%)	2 (6%)	1 (2%)	5 (5%)	1 (3%)	4 (7%)	3 (3%)	0	3 (5%)	1 (1%)	1 (2%)	0
Dizziness, postural	2 (2%)	1 (3%)	1 (2%)	5 (5%)	3 (9%)	2 (3%)	1 (1%)	0	1 (2%)	2 (2%)	0	2 (4%)
Diarrhoea	6 (6%)	1 (3%)	5 (7%)	4 (4%)	1 (3%)	3 (5%)	6 (6%)	2 (5%)	4 (6%)	8 (8%)	5 (12%)	3 (5%)
Muscular weakness	2 (2%)	1 (3%)	1 (2%)	3 (3%)	1 (3%)	2 (3%)	6 (6%)	3 (8%)	3 (5%)	1 (1%)	1 (2%)	0
Aggression	0	0	0	1 (1%)	1 (3%)	0	1 (1%)	1 (3%)	0	5 (5%)	4 (9%)	1 (2%)

Data are n (%), expressed as number of patients with at least one emergent adverse event and percentages are based on overall N value. Reported in five patients or more in at least one treatment arm.

Table 4: **Most frequently reported treatment-emergent adverse events by preferred term in the safety population**

between placebo and fluoxetine was significant (estimate of differences 3·92 [95% CI 0·37 to 7·47]; p=0·030).

Sensitivity analysis using the same ANCOVA model as the primary analysis on complete cases at week 12 confirmed the results between placebo and each agomelatine dose obtained in the primary analysis. The difference between placebo and agomelatine 25 mg groups significantly favoured agomelatine 25 mg/day (estimate of differences 5·13 [95% CI 1·63–8·64]; p=0·008). Conversely, the differences between placebo and agomelatine 10 mg/day and between placebo and fluoxetine were non-significant.

The findings for change in CDRS-R raw score from week 0 to week 12 with agomelatine 25 mg/day were confirmed in adolescents (n=75, mean 5·22 [95% CI 1·03 to 9·40]; p=0·028). In this subgroup, non-significant trends were observed in favour of agomelatine 10 mg/day (estimate of differences 3·18 [–0·96 to 7·32]; p=0·13) and fluoxetine groups (estimate of differences 3·70 [–0·43 to 7·84]; p=0·079) versus placebo. The Cohen's effect sizes were 0·36 for agomelatine 25 mg/day and 0·27 for fluoxetine. In children, no difference was observed versus placebo, regardless of treatment group (table 2).

Remission (defined as a CDRS-R raw total score of ≤28 at week 12) was observed in 11 (11%) of 101 patients receiving placebo, 14 (14%) of 102 receiving agomelatine 10 mg/day, 15 (16%) of 94 receiving agomelatine 25 mg/day, and 12 (12%) of 99 receiving fluoxetine, without reaching statistical significance versus placebo in any groups (appendix p 14).

Final follow-up CGI-S score was lower for patients receiving agomelatine 10 mg/day (mean 3·5 [SD 1·1]) versus placebo (3·8 [1·2]; p=0·035; table 3). Reductions were also observed with agomelatine 25 mg/day (3·5 [1·1]) and fluoxetine (3·6 [1·0]), although differences were not significantly different from placebo (p=0·051 for agomelatine 25 mg/day and p=0·12 for fluoxetine). Non-significant differences between placebo and treatment groups were observed in the final follow-up CGI-I value (table 3). Results of the parametric Student's *t* test were globally congruent (table 3). The proportion of patients with a treatment response at week 12 was 48% (49 of 102) in the agomelatine 10 mg/day group, 49% (46 of 94) in the agomelatine 25 mg/day group, and 47% (47 of 99) in the fluoxetine group (table 3). These outcomes were not significantly different from the relatively high placebo response (45 [45%] of 101).

In adolescents, the mean ADRS total score decreased significantly in the 25 mg/day agomelatine group versus placebo (estimate of differences 4·07 [95% CI 0·68–7·46]; p=0·032). No significant decrease was observed in the 10 mg/day agomelatine (p=0·064) and fluoxetine groups (p=0·28) versus placebo. The mean Children's Global Assessment Scale score gradually increased at each clinic visit between baseline and week 12 in all trial groups (appendix p 15), resulting in improvements at final follow-up visit in all groups (table 3) with no significant differences between groups.

The safety population included 399 patients; one patient in the agomelatine 25 mg/day group did not take any study drug and was not included in the analysis. Similar

	Agomelatine 10 mg/day			Agomelatine 25 mg/day			Placebo			Fluoxetine		
	All (N=102)	Boys (n=34)	Girls (n=68)	All (N=94)	Boys (n=33)	Girls (n=61)	All (N=103)	Boys (n=39)	Girls (n=64)	All (N=100)	Boys (n=43)	Girls (n=57)
Treatment-related TEAE	30 (29%)	10 (29%)	20 (29%)	35 (37%)	11 (33%)	24 (39%)	28 (27%)	6 (15%)	22 (34%)	29 (29%)	14 (33%)	15 (26%)
Serious TEAE*	6 (6%)	1 (3%)	5 (7%)	3 (3%)	0	3 (5%)	0	0	0	7 (7%)	3 (7%)	4 (7%)
Serious TEAE leading to treatment withdrawal	3 (3%)	1 (3%)	2 (3%)	2 (2%)	0	2 (3%)	0	0	0	2 (2%)	1 (2%)	1 (2%)
Treatment-related serious TEAEs	0	0	0	1 (1%)	0	1 (2%)	0	0	0	2 (2%)	1 (2%)	1 (2%)
Treatment-related serious TEAEs leading to treatment withdrawal	0	0	0	1 (1%)	0	1 (2%)	0	0	0	2 (2%)	1 (2%)	1 (2%)

Data are n (%). TEAE=treatment-emergent adverse event. *All serious adverse events were emergent during the treatment period.

Table 5: **Serious treatment-emergent adverse events leading to withdrawal in the safety population**

rates of treatment-emergent adverse events were observed for all active treatments (table 4).

No influence of agomelatine dose on adverse event severity or frequency was observed.

Among the treatment-emergent adverse events reported in five or more patients, thirst, increased appetite, and weight increase were more frequently reported in both agomelatine groups versus the placebo group. Dry mouth was more frequently reported in the agomelatine 10 mg/day group and postural dizziness was more frequently reported in the agomelatine 25 mg/day group. Thirst, increased appetite, and aggression were also more frequently reported in the fluoxetine group than in the placebo group.

Analysis of BMI by class showed most patients remained in the same class between baseline and final follow-up value during treatment. Among the few patients with changes in BMI class, increases and decreases occurred equally, with no relevant differences observed between groups (data not shown).

Two cases of reversible aminotransferase (alanine or aspartate aminotransferase) increases in concentration to more than three times the upper limit of normal were reported in both of the agomelatine groups, one (1%) of 102 in the 10 mg/day group in a patient with infectious mononucleosis and one (1%) of 94 in the 25 mg/day group. Two (2%) of 100 patients receiving fluoxetine also developed reversible increases in aminotransferase concentration, including one considered a serious treatment-emergent adverse event.

Hormone profile and pubertal status assessed by Tanner stage did not change appreciably and no sexual side-effects were reported during the trial period. Sex-specific analyses can be found in the appendix (p 16).

According to the Columbia Suicide Severity Rating Scale for Children, emergent suicidal ideations were reported in four patients, one per treatment group. Seven patients had worsening of suicidal ideation measured by the Columbia Suicide Severity Rating Scale for Children; two receiving agomelatine 10 mg/day, one receiving agomelatine 25 mg/day, three receiving placebo, and one receiving fluoxetine. The observed differences between groups were not significant. One patient receiving placebo reported emergent self-injurious behaviour without suicidal intent on treatment. Overall, the small differences observed between groups regarding suicidality did not appear to be clinically relevant.

Serious treatment-emergent adverse events were recorded in 16 patients overall (six patients receiving 10 mg agomelatine, three receiving 25 mg agomelatine, and seven receiving fluoxetine; table 5), in line with what would be expected in the study population and the known safety profile of the active treatments, with none reported in the placebo group. Serious treatment-emergent adverse events leading to treatment withdrawal occurred in three patients receiving agomelatine 10 mg/day (anorexia nervosa, alcohol poisoning, and infectious mononucleosis), two patients receiving agomelatine 25 mg/day (intentional self-injury, suicide attempt, somnolence, and intentional overdose in the context of familial conflicts in the same patient; hypothyroidism [considered treatment related] in another patient), and two patients receiving fluoxetine (amino-transferase increase in one patient and suicidal ideation in another patient [both considered treatment related]).

Discussion

Paediatric depression is an important health-care burden, with a persistent unmet need for new therapeutic options because available treatments are scarce and not always effective. The Cochrane meta-analysis from 2021 on newer generation antidepressants for the treatment of children and adolescents reported negligible reductions in depressive symptoms on the CDRS-R scale compared with placebo for many of these treatments.[27] The 12-week, randomised, double-blind, placebo and active comparator-controlled phase 3 trial presented here investigated the

efficacy and safety of two agomelatine doses to treat children and adolescents with major depressive disorder, and showed the superiority of agomelatine 25 mg/day versus placebo based on the change in CDRS-R raw total score from baseline to week 12 in the overall study population. All participants received standardised psychosocial counselling throughout.

Findings in adolescents (representing the majority of the study population) were similar to those in the overall population by CDRS-R. In this subpopulation, improvement of depressive symptoms was confirmed by ADRS scores, with greater improvements in the agomelatine 25 mg/day group.

As expected, fluoxetine was superior to placebo in this trial from week 1 onwards in terms of CDRS in the overall population, with greater changes in CDRS observed during the first few weeks of treatment. However, statistical significance was not reached in adolescents given fluoxetine in terms of CDRS nor ADRS.

Few data are available regarding major depressive disorder treatment in children aged 7–11 years. Although the trial targeted this population, relatively few children were included (n=80), reflecting the established low prevalence of major depressive disorder in this age group. No robust conclusions can be drawn from the small subgroup of children in this study.

Regarding secondary endpoints, numerical improvements (eg, Children's Global Assessment Scale) were seen without reaching statistical or clinical significance, except for ADRS score in adolescents given agomelatine 25 mg/day. The administration of psychosocial counselling probably had a therapeutic role and might have contributed to the observed important placebo response (CGI-I response 45% at week 12). In the active treatment groups, the overall response is a result of the treatment and study design, including the associated psychosocial counselling. Of note, the effects of a combination of treatments rarely result in the summation of the component effects.[28] Efficacy results were significantly better in the agomelatine-treated patients than in the placebo-treated patients, although the general use of structured psychosocial counselling could have increased the placebo response and, potentially, reduced the observed difference between the two treatment groups.

Agomelatine 25 mg/day showed efficacy in both the overall population and adolescents, with an effect size similar to that of fluoxetine, the only antidepressant currently indicated in this population in Europe. These effect sizes are lower than those previously observed or calculated for fluoxetine in paediatric clinical trials (0·4–0·5),[18,19] but similar to those observed in clinical trials with antidepressants in adults (0·3),[29] supporting the clinical significance of these results. Of note, in the present study, the CDRS-R total score decrease was in the expected range for fluoxetine, while it was higher than those previously observed for placebo. This finding explains the observed lower effect sizes, which could be due to study methodology, particularly the psychosocial counselling provided to all patients before and during the study period. This contention is supported by the high percentage of responders by CGI score in the placebo group.

Agomelatine is noted for its relatively low rate of adverse events and manageable safety profile in the adult population.[11] The safety data from this study indicate that agomelatine was well tolerated in the paediatric population. The most frequent adverse events were as reported in adults, with the addition of thirst and dry mouth, which were also reported frequently in the fluoxetine and placebo groups.

In this population, especially adolescents, some adverse events are of particular interest (ie, weight gain and sexual effects), as they might influence treatment compliance in the paediatric population. Suicidality is of particular concern due to risk of suicide attempts. Although increased appetite and weight gain were among the most common and expected adverse events, most patients remained in the same BMI class throughout the trial. Furthermore, a decrease in BMI class was equally observed with agomelatine, confirming an overall neutral effect of agomelatine on weight. Sexual function was not assessed using a specific scale in this trial; however, no sexual side-effects were reported. The incidence or worsening of suicidal ideation did not differ appreciably between placebo and treatment groups. The one instance of suicide attempt in the agomelatine 25 mg/day group was deemed not to have been associated with the treatment.

One safety issue associated with agomelatine treatment is potential increase in liver enzyme concentrations in the blood; alanine or aspartate aminotransferase increases to more than three times the upper limit of normal were previously documented in 1·25% of adult patients receiving agomelatine 25 mg/day.[12] The incidence of reversible aminotransferase concentration more than three times the upper limit of normal in the present trial was approximately 1% in both agomelatine arms versus 2% in the fluoxetine arm, with no cases in the placebo arm. These findings suggest liver damage is no more likely to occur in paediatric patients than adults, and do not suggest a higher risk than treatment with fluoxetine. More data are required to reinforce this conclusion. These data nevertheless highlight the importance of monitoring liver enzyme activity in patients receiving antidepressants, at least during the first 3 months of treatment.

No adverse events indicative of treatment withdrawal symptoms were reported, in line with adult data showing an absence of discontinuation syndrome.[30]

Some limitations should be considered when interpreting the study results, including the clinical significance of the differences in treatment effects between agomelatine 25 mg/day and placebo. Minimal clinically significant difference and effect size can be useful measures to interpret such differences. Regarding

CDRS-R, the minimal clinically significant difference is not well established,[31] but a Cohen effect size of 0·3 is generally considered to be small.[32] The minimal clinically significant difference of the ADRS was established as 5·2 using an anchor-based approach.[17] Observed differences in ADRS in this study represent 78% of this estimated minimal clinically significant difference. The clinical significance of the agomelatine treatment effect, despite being a similar magnitude to that of fluoxetine, can thus be challenged here.

Another limitation comes from the relative weakness of statistical evidence. Overall, statistical results were positive, although one sensitivity analysis did not confirm significance. In addition, the small sample size for children means that no conclusion can be drawn for this population. Similarly, it is not possible to infer differences between male and female paediatric and adolescent patients in the study due to small numbers in these groups.

The psychosocial counselling performed in the study for ethical reasons and to provide psychological support per paediatric patient treatment guidelines, could have contributed to increased placebo response. The wide age range of the patients (7–17 years) and the large number of countries and study sites (with potential for increased variability) are also important methodological limitations.

Finally, some of the exclusion criteria for this study could reduce the generalisability of the results. As this was the first clinical trial of agomelatine in paediatric patients, the study population was strictly defined, thus excluding patients with treatment-resistant depression, patients with psychotic depression, inpatients, patients who did not live with parents or guardians, patients at suicidal risk, and patients presenting major comorbid psychiatric conditions or clinically significant medical conditions requiring medication. Some of these exclusion criteria were applied as it is not usually acceptable to enrol some patients with depression in a placebo-controlled trial.

In this trial, agomelatine 25 mg/day showed superiority over placebo regarding antidepressant efficacy in paediatric patients, mainly driven by the effect observed in adolescents, both for CDRS and ADRS. This finding was supported by the trend observed with the 10 mg/day dose in the general population for CDRS-R and in adolescents for CDRS-R and ADRS. This result was not confirmed by the CGI scale, for which a high placebo response was observed, possibly due to the effect of psychosocial counselling.

Agomelatine was well tolerated, and no unexpected safety concerns were identified. The overall neutral effect of agomelatine on weight was confirmed. No sexual side-effects were reported, and no abnormalities were detected in Tanner stage evaluation; nor suicidality, which are all troubling side-effects, especially in adolescents. No additional risk of hepatotoxicity was observed in this population.

This study presents some limitations, such as restrictions in inclusion and exclusion criteria or the small size of the sample, especially for children, which can increase variability in response. These results should therefore be interpreted with caution in the context of the overall paediatric major depressive disorder population. Altogether, these results provide good evidence that agomelatine 25 mg/day, in addition to psychosocial counselling, could offer a valuable new treatment option for adolescent patients with major depressive disorder.

Contributors

All authors were involved in designing the study, interpretation of the results, and editing and review of the manuscript. VO, P-FP, UM, and DC verified the underlying data. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CA has been a consultant to or has received honoraria or grants from Acadia, Angelini, Boehringer Ingelheim, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion, and Takeda. JKB has, in the past 3 years, been a speaker for Takeda/Shire, Medice, and Janssen; on advisory boards for Roche, Medice, Angelini, and Servier; and has been a consultant for Servier. He is not an employee or a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. JMF has for the past 3 years been a consultant only to federal and state ministries and agencies and the EU. VO, P-FP, UM, and DC are employees of Servier. BF has been a consultant for Eli Lilly, BMS, Servier, Sanofi, GSK, HRA, Roche, Boehringer Ingelheim, Bayer, Almirall, Allergan, Stallergene, Genzyme, Pierre Fabre, AstraZeneca, Novartis, Janssen, Astellas, Biotronik, Daiichi- Sankyo, Gilead, MSD, Lundbeck, Stallergene, Actelion, UCB, Otsuka, Grunenthal, and ViiV.

Data sharing

Anonymised patient-level, study-level clinical trial data (including clinical study report) and study protocol, underlying the results reported in this article will be shared in agreement with the Servier Data Sharing Policy. Access to data will be granted to researchers identified in the research proposal directed to the data request portal, to achieve the aims described in this proposal, and provided its approval by a dedicated committee and signature of data sharing agreement by requestor.

For **Servier data sharing policy** see https://clinicaltrials.servier.com/clinical-trials-transparency/

For **data request portal** see https://clinicaltrials.servier.com/data-request-portal/

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