30 May 2024
EMA/281144/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Valdoxan

International non-proprietary name: Agomelatine

Procedure No. EMEA/H/C/000915/II/0051

Marketing authorisation holder (MAH) Les Laboratoires Servier

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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List of abbreviations

ADRS	Adolescent Depression Rating Scale
Ago	Agomelatine
ALP	Alkaline Phosphatase
ALT	Alanine (Amino)Transferase
ANCOVA	Analysis of covariance
AST	Aspartate (Amino)Transferase
ASSE	Selection Visit
AUC	Area under the concentration-time curve from time zero (time of drug administration) to infinity
BMI	Body Mass Index
CDRS-R	Children's Depression Rating Scale-Revised
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression
CGI-I	Improvement item of CGI
CGI-S	Severity of illness item of CGI
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum observed plasma Concentration
CRO	Contract Research Organisation
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CPT	Continuous Performance Task
DB	Double-blind
DESS	Discontinuation Emergent Signs and Symptoms
DMC	Data Monitoring Committee
DSM-IV / DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition/ Text Revised
e.g.	*exempli gratia* (for example)
EAE	Emergent Adverse Event
ECG	Electrocardiogram
EEA	European Economic Area
EEG	Electroencephalogram
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
Fluox	Fluoxetine
FSH	Follicle stimulating hormone
GAD	General Anxiety Disorder
GGT	Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HR	Hazard Ratio
i.e.	*id est* (that is to say)
IMP	Investigational Medicinal Product
I.R.I.S.	Institut de Recherches Internationales Servier
IRS	Interactive Response System
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Drug
K-SADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version
LC-MS/MS	Liquid Chromatography coupled with tandem Mass Spectrometry
LH	Luteinizing hormone
LOCF	Last Observation Carried Forward
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MPC	Manualized Psychosocial Counselling
MRS	Modified Randomised Set
MT	Melatonin
Paed	Paediatric

PAERS	Paediatric Adverse Event Rating Scale
PASS	Post Authorisation Safety Study
PC	Placebo-controlled
PCSA	Potentially Clinically Significant Abnormal value
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PopPK	Population Pharmacokinetics
REM	Rapid Eye Movement
RMP	Risk Management Plan
RSI	Reference Safety Information
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SEAE	Serious Emergent Adverse Event
SmPC	Summary of Product Characteristics
SNRI	Selective Noradrenalin Reuptake Inhibitor
SS	Safety Set
SSRI	Selective Serotonin Reuptake Inhibitor
T_{max}	Time at which C_{max} occurs
TME	Targeted Medical Events
TMS	Transcranial Magnetic Stimulation
ULN	Upper Limit of Normal range
vs.	*Versus*
W	Week

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Les Laboratoires Servier submitted to the European Medicines Agency on 28 September 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include new therapeutic indication in adolescents aged 12 to 17 years for the treatment of moderate to severe major depressive episodes, if depression is unresponsive to psychological therapy alone, for Valdoxan, further to the results of the phase 2 (CL2-20098-075) and phase 3 (CL3-20098-076) paediatric clinical studies included in the Paediatric Investigation Plan number EMEA-001181-PIP-11. As a consequence, the sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated.
The Package Leaflet is updated accordingly.
The updated RMP version 25.1 has also been submitted.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

However, during the procedure and in view of the CHMP data assessment, the marketing authorisation holder revised the scope of the variation and, without applying for change in the indication, proposed to update sections 4.2, 4.4, 4.8, 5.1 5.2 of the SmPC to reflect the results of the phase 2 (CL2-20098-075) and phase 3 (CL3-20098-076) paediatric clinical studies. The PL has been updated accordingly. In addition, section 6.6 of the SmPC was updated to reflect the Safety Working Party position.

These changes fall under the category C.1.4 of the variation classification Guideline.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0115/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0115/2021 was completed.

The PDCO issued an opinion on full compliance for the PIP P/0115/2021 in October 2022.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Eva Skovlund Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	28 September 2022
Start of procedure:	29 October 2022
CHMP Rapporteur Assessment Report	21 December 2022
PRAC Rapporteur Assessment Report	21 December 2022
PRAC members comments	5 January 2023
Updated PRAC Rapporteur Assessment Report	12 January 2023
PRAC Outcome	12 January 2023
CHMP members comments	16 January 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 January 2023
Request for supplementary information (RSI)	26 January 2023
CHMP Rapporteur Assessment Report	23 May 2023
PRAC Rapporteur Assessment Report	23 May 2023
PRAC members comments	31 May 2023
PRAC Outcome	8 June 2023
CHMP members comments	9 June 2023
Updated CHMP Rapporteur Assessment Report	15 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	14 November 2023
PRAC Rapporteur Assessment Report	14 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	4 December 2023
Updated CHMP Rapporteur Assessment Report	7 December 2023
Request for supplementary information (RSI)	14 December 2023
CHMP Rapporteur Assessment Report	20 February 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur Assessment Report	n/a (PAR=UAR)
CHMP Opinion	30 May 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This application originally concerned the following extension of the indication: "*Valdoxan is indicated in adolescents aged 12 to 17 years for the treatment of moderate to severe major depressive episodes, if depression is unresponsive to psychological therapy alone. Antidepressant medication should be offered to an adolescent with moderate to severe depression only in combination with concurrent psychological therapy*."

Disease or condition

Major Depressive Disorder (MDD) is a leading cause of disability around the world and contributes greatly to the global burden of disease. The effects of depression can be long-lasting or recurrent and dramatically affect a person's ability to function and live a rewarding life. The causes include complex interactions between social, psychological, and biological factors (WHO Factsheet, September 2021).

Depressive disorders are classified in various classification systems, e.g., currently DSM IV-TR and ICD-10, and are also described in children (from the age of 7-8 years old) and adolescents.

Younger children (below 8 years of age) and infants can present depressive symptomatology, termed "emotional problems", which do not correspond to MDD criteria. ICD-10 and DSM-IV define depression similarly, although DSM-IV makes one exception for children and adolescents, whereby irritable rather than depressed mood is allowed as a core diagnostic symptom.

According to DSM IV-TR, depression in children/adolescents is diagnosed on the basis of:

- Depressed mood or irritability, markedly diminished interest, or pleasure in most or all activities, significant weight loss (or poor appetite) or weight gain, or failure to gain appropriate weight, insomnia or hypersomnia, psychomotor retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, or indecisiveness, recurrent thoughts of death (not just fear of dying), or suicidal ideation, plan, or attempt.

Furthermore, an episode of major depression is characterised by 5 or more of these symptoms (with at least one of the symptoms noted as depressed and/or irritable mood or having reduced interests or little pleasure) that have lasted for ≥ 2 weeks. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. These symptoms are not caused by medication, drug abuse, or alcohol and are not the result of another medical or mental illness (no manic or hypomanic behaviour).

Signs and symptoms of MDD in the adolescent population are often described as being similar to the adult population; however differential diagnosis in this population is difficult particularly with dysthymic disorder or bipolar disorder. Despite having nearly identical diagnostic criteria to adults, there may be some phenomenological differences between adolescent and adult depression, with adolescents more frequently experiencing neurovegetative and somatic symptoms compared with adults, and less commonly reporting anhedonia or concentration difficulties (Nardi, Francesconi, Catena-Dell'osso, & Bellantuono, 2013; Rice *et al*., 2019). There may also be significant biological differences between paediatric and adult-onset MDD (Kaufman, Martin, King, & Charney, 2001). There is also evidence for substantial heterogeneity in

depression which has raised concerns about whether it represents one etiologically distinct entity (Stringaris, 2017).

Depression in adolescents is more often missed than it is in adults (Mullen, 2018), possibly because of the prominence of irritability, mood reactivity, and fluctuating symptoms in adolescents. Depression can also be missed if the primary presenting problems are unexplained physical symptoms, eating disorders, anxiety, refusal to attend school, decline in academic performance, substance misuse, or behavioural problems.

Epidemiology

Depression is a common mental disorder. More than 6% (6.4%) of Europeans suffer from depression according to a population-based study comprising over 250 000 individuals living in 27 European countries (Arias-de la Torre *et al*, Lancet, 2021).

The prevalence of MDD in Europe is approximately 0.5% to 2.5% in children and increases with puberty, with a rate rising to approximately 8% in adolescents (INSERM, 2002; Calles, 2007; Shorey *et al*, 2021), but sometimes much higher in some countries or under special circumstances such as during the coronavirus disease (Covid 19) pandemic (Balazs *et al*, 2012; Racine *et al*, 2021). Depression in childhood affects as many boys as girls, but twice as many girls during adolescence (Birmaher and Brent, 2007).

Globally, depression is the fourth leading cause of illness and disability among adolescents aged 15-19 years, and fifteenth for those aged 10-14 years (WHO 2020). Suicide is the second leading cause of death among adolescents in the European region (WHO 2018) and depression is a main risk factor for suicidal behaviour (Joint Action on Mental Health and Well-being 2015 by the European Commission).

Management

Current treatments used as standard of care of MDD in children and adolescents are psychotherapies and antidepressant drugs. According to clinical trials data, the efficacy of these treatments is modest, with less consistent results in children compared to adolescents, and with potential safety/tolerability issues for some antidepressant drugs. In the EU, currently, only one antidepressant, fluoxetine, has been granted an extension of the indication to include treatment of major depressive episodes in children and adolescents aged 8 to 17 years (EMEA/CHMP/46089/2006/EN):" *Children and adolescents aged 8 years and above: Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy*."

In the US also escitalopram (under the brand name Lexapro) is approved by the FDA for the acute and maintenance treatment of Major Depressive Disorder (MDD) in adults and adolescents aged 12-17 years.

Treatment guidelines recommend starting with a psychotherapy first-line, then using antidepressants as second-line treatment in addition to psychotherapy (NICE, 2019; HAS, 2014). In regards to management of moderate to severe depression, NICE (2019) recommends offering 12-18-year-olds individual cognitive behavioural therapy for at least 3 months. It is also stated in this guideline that following multidisciplinary review, fluoxetine should be offered if moderate to severe depression in a young person (12–18 years) is unresponsive to a specific psychological therapy after 4 to 6 sessions. It is underlined that antidepressant medication should not be offered to a child or young person with moderate to severe depression except in combination with a concurrent psychological therapy. However, patients' access to psychological care might not be optimal in all countries or regions, and antidepressants are occasionally prescribed as first-line treatment. The prescription data report antidepressant use, especially in adolescents with selective serotonin reuptake inhibitors (SSRIs) being the most commonly prescribed drugs (Lee *et al*, 2012; Schröder

et al, 2017a and 2017b). However, approved paediatric medical treatment options for the treatment of depression are currently scarce. Considering that, as already mentioned above, only one SSRI (fluoxetine) is, at present, approved in the EU for use in children/adolescents, presumably many of these prescriptions would be "off label". Further studies on efficacy and safety of antidepressants in the paediatric population are thus needed. Taking this into account, a novel antidepressant treatment in paediatric Major Depressive Episodes (MDE) would fulfil a therapeutic need.

2.1.2. About the product

Agomelatine is an antidepressant medicinal product that possesses pharmacological activity by combining melatonin receptor agonism (at MT1 and MT2 receptors) with serotonin 2C receptor (5-HT2C) antagonism properties. This combination of melatonin agonist and 5-HT2C antagonist properties of agomelatine is thought to explain its antidepressant activity. Binding studies indicated that agomelatine has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors. Agomelatine resynchronises circadian rhythms in animal models of circadian rhythm disruption. It increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin. The lack of effect of agomelatine on monoamine uptake and particularly serotonin distinguishes agomelatine from SSRI and selective noradrenaline reuptake inhibitors (SNRI) (Millan *et al*, 2005).

Valdoxan (agomelatine) is currently approved in the EU (since February 2009) for the treatment of major depressive episodes in adults.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

A complete Paediatric Investigation Plan (PIP) was approved by EMA on May 30th 2012 with two conditions (EMA/230119/2012 dated 30th May 2012): one in children (from 7 to less than 12 years old) and in adolescents (from 12 to less than 18 years old) suffering from MDE, and one in these same age subsets (children from 7 to less than 12 years old and adolescents from 12 to less than 18 years old) suffering from Generalised Anxiety Disorder (GAD) including the following elements:

- The oral film-coated tablet formulation to be used, as it offered a better profile in terms of expected palatability, safety, compliance and efficacy, in comparison with alternative formulations of agomelatine (e.g., liquid formulation, microgranule, orodispersible formulation for mucosal absorption).
- A 10-week toxicity Good Laboratory Practice study in juvenile rats, already assessed and updated accordingly in section 5.3 of the SmPC.

The conduct of the following clinical trials:

- An open-labelled pharmacokinetics (PK) and safety phase II study (**CL2-075**), already assessed through the Paediatric article 46 (EMEA/H/C/000915/P46/027 dated December 2015).

- Two double-blind randomised placebo-controlled phase III short-term efficacy and safety studies, one in MDE patients (**CL3-076**) and one in GAD patients (**CL3-077**), both of these studies being followed by an open-labelled extension long-term safety study.

- Two phase III double-blind randomised placebo-controlled relapse prevention studies, one in MDE patients (**CL3-090**) and one in GAD patients **(CL3-091**).

A waiver in the condition treatment of MDE was granted and applied to:

- All subsets of the paediatric population from birth to less than seven years of age.
- For film-coated tablet, oral use.
- On the grounds that the disease or condition for which the specific medicinal product is intended does not occur in children from birth to less than 24 months of age.
- On the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible in children from 2 years to less than 7 years of age.

The GAD condition was removed during the procedure EMEA-001181-PIP01-11-M03 and deleted from the agreed PIP (EMA decision P/0191/2016 dated on 15 July 2016). Therefore, the concerned paediatric studies **CL3-077** and **CL3-091** in GAD condition were removed from the agreed PIP and not started.

Regarding the relapse prevention study **CL3-090** in the MDE condition, the MAH proposed its removal from the agreed PIP during the procedure EMEA-001181-PIP01-11-M06. The MAH argued that sufficient short-term and long-term data were available to assess the interest of agomelatine MDD treatment in the paediatric population and that extrapolation of long-term efficacy from adults, and especially young adults, to adolescents was, in their opinion, adequate and acceptable.

2.1.4. General comments on compliance with GCP

The MAH confirms that the clinical trials included in this submission were performed in accordance with the principles of Good Clinical Practice, as defined by the International Conference on Harmonization (ICH, E6. CHMP/ICH/135/95), the Declaration of Helsinki applicable at the time of the study, and according to the local regulations in each participating country. Furthermore, it is stated that the clinical trials carried out outside the European Union also meet the ethical requirements of Directive 2001/20/EC.

Audits were performed during Study CL3-076 at 5 investigation sites, at one centre in each of the following countries (double-blind period): Russian Federation (September 2017), Hungary (October 2017), Poland (January 2019), Romania (February 2019) and Ukraine (February 2020). In addition, one audit was performed at the CRO in charge of the IRS in March 2017. During the open-label extension period, 1 additional audit was performed in one centre in South Africa in June 2021. Audit certificates have been submitted.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

A justification for not updating the approved ERA was submitted:

-In the original ERA assessment, the default Fpen was used to calculate the PEC, covering all populations, including the paediatric population.

- A phase II was performed, concluding that agomelatine is unlikely to present a risk to the environment.

The justification is accepted.

2.2.2. Conclusion on the non-clinical aspects

Based on the justification submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of agomelatine.

Agomelatine is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Tabular listing of clinical studies

Type of Study	Number of Study Centers; Countries; Study Dates	Study Design & Objectives	Study Drug Dose(s) & Regimen(s) Route of Administration	Treatment Duration	Healthy Subjects or Diagnosis	Number of Subjects
Study CL2-20098-075: Pharmacokinetics and safety of agomelatine in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) wi Anxiety Disorder						
PK & Safety	10 centers 4 countries (FIN, EST, HUN, ROU) 23 Aug. 2013 - 14 Mar. 2015	Open-label, MC, three-dose level, noncomparative study ***Primary:*** to evaluate the PK of 3 doses of agomelatine ***Secondary:*** to provide safety data, to evaluate vigilance/sedation & tablet acceptability	Agomelatine 5, 10, 25 mg Oral tablet	Single dose 3 days	Children and adolescents (7 to less than 18 years) with Major Depressive Disorder	51 patients (24 children and 27 adolescents)
Study CL3-20098-076: Efficacy and Safety of 2 doses of Agomelatine (10 mg, 25 mg) given orally in children and adolescents with moderate to severe MDD						
Efficacy & Safety	***Period 1:*** 46 centres 9 countries (RUS, HUN, UKR, ROU, POL, ZAF, SRB, BGR, FIN) 23 Feb. 2016 - 14 Jan. 2020 ***Period 2:*** until 27 Oct 2021	***Period 1:*** I, MC, DB, R, PG, PC ***Period 2:*** Open, optional extension period ***Primary:*** demonstrate short-term efficacy of at least one of the two doses of agomelatine vs placebo **Secondary:** - long-term efficacy of agomelatine (10mg, 25mg) - short- and long-term safety of agomelatine (10mg, 25mg) - evaluate efficacy and safety in children and adolescents separately	Agomelatine 10, 25 mg, Placebo, Fluoxetine 10-20 mg Oral dose	Single dose 3 months 26 months	Children and adolescents (7 to less than 18 years) with moderate to severe Major Depressive Disorder	400 patients (320 adolescents and 80 children)

PK: pharmacokinetics, I: international, MC: multicentre, DB: double blind, R: randomized, PG: parallel groups, PC: placebo controlled

2.3.2. Pharmacokinetics

The key clinical pharmacokinetic (PK) characteristics of agomelatine established in previous procedures based on adult data is shown in Table 2.

Table 2. Brief overview of key PK characteristics of agomelatine (adult data)

Absorption	• Absolute bioavailability: not determined, but estimated to <5% • Tmax 0.75-1.5 hours • Not significantly affected by concomitant food, but variability is increased
Distribution	• 90-94% protein bound in human plasma (albumin and α1-acid glycoprotein) • Vss of 32-37 L • Plasma to blood concentration ratio of 1.45 • A linear correlation (r2 = 0.915) was observed between the plasma and saliva concentrations and saliva concentrations of agomelatine were found to represent ~3% of the plasma concentrations
Elimination	• Primarily metabolic • Excretion is mainly urinary (80%) in the form of metabolites • Total plasma clearance is high, about 1100 mL/min • T1/2 = 1-2 hours
Metabolism	• Primary metabolic pathway: CYP1A2 (metabolites are not active) • Secondary metabolic pathways: glucuronidation • Minor pathway of oxidative metabolism: CYP2C9, CYP2C19
Dose proportionality	• Roughly proportional within the therapeutic dose range • At higher doses, a saturation of the first-pass effect occurs
Pharmacokinetic variability	• Inter- and intra-individual variability in oral bioavailability is high and was estimated to 160% and 104%, respectively
Sources of variability	• The bioavailability is increased in women compared to men, increased by intake of oral contraceptives and reduced by smoking

Paediatric PK data from two phase 2 studies (CL2-20098-75 (abbreviated to **CL2-075**), n=51) and (CL2-20098-044 (abbreviated to **CL2-044**), n=9) was previously submitted in a P46 procedure (EMEA/H/C/000915/P46/027). Patients were distributed as follows: 30 children in age subset 6-11 years and 30 adolescents in age subset 12-18 years. Plasma PK samples were collected in study **CL2-044**, while saliva PK samples were collected in study **CL2-075**. In addition, one plasma sample was collected in study **CL2-075** to determine the saliva to plasma ratio of agomelatine. Please find further details on study design and PK sampling schemes below and in section 5.4.1.

In the current application to extend the MDD indication to adolescents aged 12 to 17 years, data from the phase 3 study (CL3-20098-076, abbreviated to **CL3-076**) has been submitted, including saliva PK data from 175 patients treated with 10 mg or 25 mg agomelatine daily. Among them, 36 were of child age (from 7 to less than 12 years of age) and 139 were of adolescent age (from 12 to less than 18 years of age).

The proposed dose for the treatment of MDD in adolescents is 25 mg taken orally once daily, which is identical to the adult starting dose. For the paediatric development, the marketed film-coated tablets dedicated to adults with the 25 mg strength was used, as agomelatine tablets shape and size were acceptable for the targeted age-range.

Methods

- **Analytical methods**

Bioanalytical method for the determination of concentrations of agomelatine in human plasma is based on 96-well plate solid phase extraction and liquid chromatography with tandem mass spectrometry detection (LC-MS/MS). A calibration range from 0.0250 to 50.0 ng/mL was employed, using 250 µL of plasma for work-up and S 40706-1 (agomelatine-d5) as internal standard. The short-term and long-term stability of agomelatine in human Li-heparin plasma samples was assessed.

Analytical method for the determination of agomelatine in human saliva samples is based on liquid-liquid extraction and liquid chromatography with tandem mass spectrometry detection (LC-MS/MS). Method is validated in calibration range from 0.0100 to 10.0 ng/mL, using 100 µL of saliva and agomelatine-d5 internal standard. The short-term and long-term stability of agomelatine in human saliva samples was also assessed.

- **Pharmacokinetic data analysis**

A population PK (popPK) approach was used to analyse saliva PK data from studies **CL2-075** and **CL3-076**. The saliva to plasma ratio of agomelatine based on the observed time-matched concentrations in study **CL2-075** was estimated by linear regression without intercept.

- **Evaluation and Qualification of models**

Previous model

A previously developed popPK model based on paediatric data (report number CL2-20098-075 dated July 2015) was submitted in procedure EMEA/H/C/000915/P46/027. Data were included from 51 patients from study **CL2-075** and 9 patients from study **CL2-044**. The final model was a one compartment model parameterised in terms of CL/F, V/F and Ka and was applied to describe both saliva and plasma concentrations of agomelatine. A saliva to plasma ratio (S/P) of agomelatine was also part of the model structure. Interindividual variability (IIV) on Frel and inter-occasion variability (IOV) on V/F and Frel was estimated. No covariates were identified. The final model parameter estimates are shown in Table 3.

Table 3. Parameter estimates for fixed and random effects (and their coefficients of variation (CV)), standard errors (SE) and relative standard errors (RSE) for the previously developed popPK model in paediatric patients. Source: PK report number CL2-20098-075, July 2015.

Parameter (unit)	Value	SE	RSE(%)
Ka (1/h)	8 fixed	-	-
CL/F (L/h)	1070	168	15.7
V/F (L)	2170	392	18.1
S/P ratio	0.0304	0.00476	15.7
σ Plasma add (ng/mL)	0.01 fixed	-	-
σ Plasma prop (%)	38.2	3.67	9.61
σ Saliva add (ng/mL)	0.0031	0.000586	18.9
σ Saliva prop (%)	39.5	2.82	7.14

Parameter	CV(%)	Value	SE	RSE(%)
IIV_Frel	93.3	0.871	0.363	41.7
IOV_Frel	47	0.221	0.0924	41.8
IOV_V	65	0.423	0.113	26.7

Current application

To support the current application, the MAH has submitted a population PK modelling and simulation report based on saliva PK data from studies **CL2-075** and **CL3-076**. The objectives of this analysis were to:

- describe the population PK characteristics of agomelatine with its associated interindividual variability in children and adolescents patients from 7 to less than 18 years of age with MDD
- compare derived PK parameters to adult values

A prospectively written modelling analysis plan was provided (ANA-1-SER-S20098-PMX-1, dated 22 November 2019).

PopPK model (CL3-20098-076, dated 24 June 2020)

Methods

Software and estimation method

Plasma concentration-time data were analysed using a nonlinear mixed-effects modelling approach using NONMEM version 7.3.0 and the first-order conditional estimation method with interaction (FOCEI).

Database

A total of 226 subjects were included in the PK dataset; 51 from the study CL2-075 and 175 from the study CL3-076 (see section 5.4 for study details). Among them, 24 and 36 were children (from 7 to less than 12 years of age), and 27 and 139 were adolescents (from 12 to less than 18 years of age) in **CL2-075** and **CL3-076** respectively.

In study **CL2-075**, PK saliva samples were taken on D1, D2, D3, 30 min before dosing, then 30 min, 1h, 2h, 3h and 4h post-dose, then every hour until bedtime, then at the patient's awakening the following morning and finally at run-out visit. A single blood sample was taken on D3, 1h after oral administration of agomelatine 25 mg. This study contributed 554 agomelatine saliva concentrations (Table 4) and 49 agomelatine plasma concentrations to the analysis data set.

In study **CL3-076**, PK saliva samples were collected at home one evening between W001 and W002, 30 min before tablet intake, then 10 min, 30 min, 1 h, 3 h post-dose and 2 samples between 4 and 8 hours (with at least 1 hour interval between both samples) post-dose. This study contributed 734 agomelatine saliva concentrations to the analysis data set (Table 4).

In total, 1288 saliva agomelatine concentrations were included in the popPK data analysis set.

Table 4. Number of individuals with agomelatine saliva observations and number of agomelatine saliva observations in the derived data file

Study / Dose[a]		Agomelatine saliva conc.[c]							
	Number of subjects	Above LLOQ[b]	Before first dose	Below LLOQ[b]	CWRES>5	Trough>Post-dose	Duplic.	Unpl.	Total
CL2-20098-075									
5 mg/10 mg	2	12	2	11	0	0	0	0	25
5 mg/10 mg/25 mg	49	542	49	494	2	0	0	0	1 087
CL3-20098-076									
10 mg	96	351	0	296	0	2	1	1	651
25 mg	93	383	0	243	0	2	0	0	628
All									
All	240	1 288	51	1 044	2	4	1	1	2 391

[a] list of unique doses given to each subject. [b] LLOQ is lower limit of quantification (0.01 ng/mL in both studies).
[c] Samples below the LLOQ, before first dose, with CWRES>5, with trough > to post-dose samples in a same ID, duplicates and unplanned samples are not included in the analysis data set. CWRES is conditional weighted residuals; Duplic.: duplicate; conc.: concentration; Unpl.: unplanned.

Data handling (BLQs, missing data, outliers)

During the analysis, BLQ observations, samples collected before the first dose, duplicate, unplanned samples as well as trough samples under QD regimen that were higher than any of subject's post-dose samples were excluded to avoid undue influence of outliers (Table 4).

The plasma concentrations, although considered as part of the analysis data set, were excluded from model-based analysis and evaluation, and merely used for the saliva to plasma ratio estimation.

Covariates

The majority of patients from studies **CL2-75** and **CL3-76** who provided PK data were adolescents ≥12 years (73.5%). The overall mean body weight and age of the subjects was 51.5 kg (range 21-104) and 13.3 years (range 7-17). The overall percentage of boys, pre pubertal girls and post pubertal girls in the two studies was 37%, 16% and 47%, respectively. Only 4 % of patients in the two studies had smoking habits (≥5 cigarettes daily), and only 2 % were co-administered oestrogen during the study.

Methodology

Structural model: The starting model was a one compartment model with a first-order absorption process (current model of agomelatine in children and adolescents). In addition, weight impacted CL/F (with a fixed coefficient of 0.75) and apparent central volume of distribution (Vc/F) (with a fixed coefficient of 1) and was considered as structural covariates in this analysis. Early in the model building a two compartments model was also considered and based on the high IIV observed, the allometric scaling of weight on CL/F and Vc/F was challenged.

Statistical model: During the course of model development, inter-individual variability was tested on all parameters of the model that are likely to vary between individuals. IIV parameters were included in an exponential manner. Inter-occasion variability was tested on Vc/F and F. IOV was considered after IIV was explored and was included in an exponential manner. Additive (homoscedastic), log-additive (exponential), proportional (heteroscedastic) or combined additive and proportional error models were considered. A starting point was the combined error model. Log-transformation of both sides was also investigated, as it worked well with the wide range of the PK data.

Covariate model: When estimating covariate effects, the screening value of the covariate (or the value at the first dose if the screening value is missing) was used for time independent covariates. Continuous covariate-parameter relationships were implemented as power models and categorical covariate-parameter relationships as a fractional difference to the most common category. Non-structural covariates were tested using the stepwise covariate model building procedure (SCM) approach. Covariates were included in the forward stage if they were significant at the $p<0.01$ level but were only retained in the final covariate model if significant at the $p<0.001$ level. All covariate-parameter pairs taken into consideration are listed in Table 5.

Table 5. Covariates tested in the SCM

Parameter	Covariate
F, CL/F	age*, sex**, pubertal status, WT
V_c/F	age*, sex**, WT

WT is the body weight, F is the relative bioavailability. *As available samples were sparse, age will be considered as a surrogate of the maturation function (MF) in this analysis. ** Gender was also split in different categories such as child or adolescent male, adolescent female and child female in pubertal status.

Model evaluation included graphical analysis of goodness of fit plots, assessment of relative standard errors (RSEs) and visual predictive checks (VPCs). Stratifications, e.g., dose, study, age and weight group, were used to ensure that the models perform adequately across important sub-groups of the data. Diagnostics and other procedures that rely on empirical Bayes estimates of the ηs were used with caution if shrinkage was high.

The discrimination between models were mainly made based on the inspection of graphical diagnostics and changes in the objective function value provided by NONMEM. For a more complicated model to be retained it had to provide a significant improvement over the contending model ($p < 0.05$ hierarchical models) and provide plausible parameter estimates that were not associated with excessively high RSEs. Preferably it should also demonstrate improvements in the graphical diagnostics and not lead to a high (> 1,000) condition number.

Results

Exploratory analysis

Plots of dose-normalised agomelatine saliva concentrations versus time in the analysis data set, stratified by dose and study are presented up to 10 h post-dose in Figure 1. Similar plots stratified by age and body weight were also submitted.

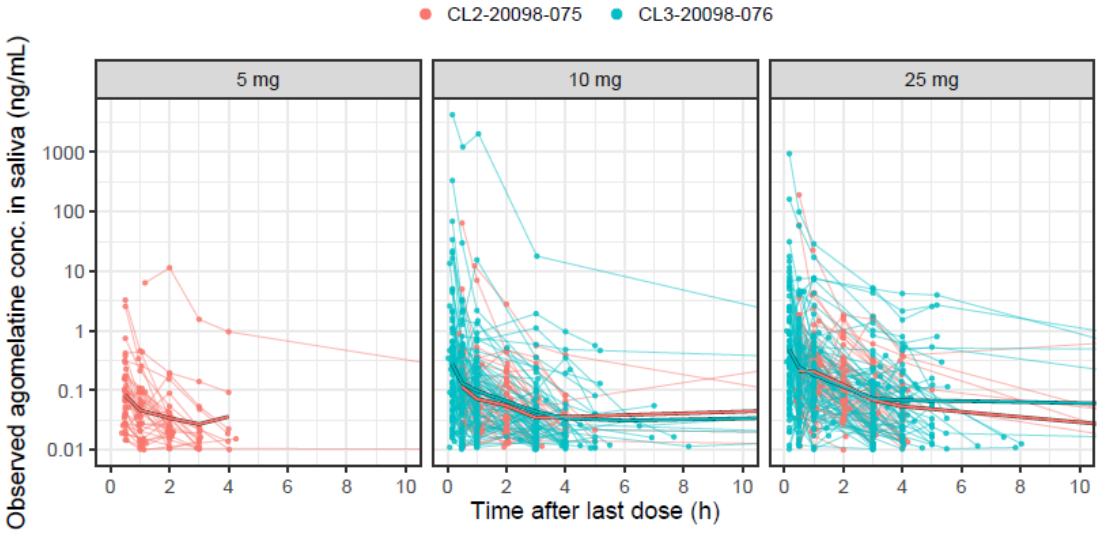


Figure 1. Observed saliva concentrations versus time after last dose in the analysis data set, stratified by dose and coloured by study. The thick line displays the geometric mean (when more than 3 samples are present).

Saliva to plasma ratio

Individual agomelatine saliva concentrations versus agomelatine plasma concentrations are presented in Figure 2. The estimated saliva to plasma ratio for agomelatine was 0.0333.

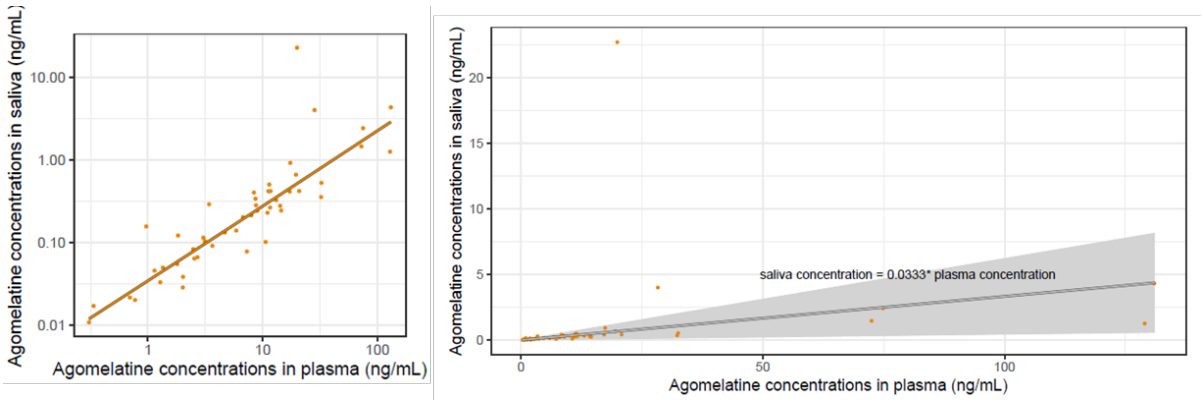


Figure 2. Observed agomelatine saliva concentrations versus plasma concentrations in the analysis data set on logarithmic (left) and linear (right) scales. Each point is colored by the

last dose given. Samples are merged based on theoretical time after first dose. A regression line (using the function lm in R) with its 95% CI is added to the data (right).

Model development

The key steps in the development of the population PK model for agomelatine is presented in Table 6.

Table 6. Summary of key NONMEM runs for the agomelatine PK models

Run #[a]	Ref #[b]	OFV	ΔOFV	Cond.[c]	Minimization	Covariance step	Description
1	First run	2425.75		11.7	Successful	Successful	log-log transformation both side, additive RUV, exclude BLQ data
2	1	2329.14	-96.61	12.3	Successful	Successful	exclude trough>post-dose, duplicate, unplanned
3	2	2275.21	-53.94	11.1	Successful	Successful	exclusion of samples with CWRES>5
4	3	2079.48	-195.72				apply a 2 compts model
6	4	2074.86	-4.63	25.2	Successful	Successful	no allometric scaling
10	6	2049.96	-24.90	46.2	Successful	Successful	estimate KA
49	10	2019.92	-30.04	1068.0	Successful	Successful	estimate IOV on V but fix IIV to 0
127	**49**	**2004.62**	**-15.30**	**33.7**	**Successful**	**Successful**	**estimate different RUV for each study. (Base Model)**
136	127	2046.27	41.65				include BLQ except predose and use M3
134	127	2008.55	3.93				add MF on F
147[d]	**127**	**1974.83**	**-29.79**	**605.3**	**Successful**	**Successful**	**add block between CL and F. (Final Model)**
148	147	1944.65	-30.18				add block between CL and F and V
170	147	1957.88	-16.95		Successful		estimate IIV on VP
171	147	1946.07	-28.76		Successful		estimate IOV on F
172	147	1961.01	-13.82				estimate IIV on KA
173	147	1959.00	-15.83				estimate IIV on RUV
174	147	1977.06	2.24	520.2	Successful	Successful	add MF on F
175	147	2005.83	31.01				include BLQ except predose and use M3
176	147	1973.45	-1.37				estimate IIV on Q
177	147	2000.01	25.18	1116.9	Successful	Successful	estimate IIV on Q (same as CL)

[a]Run number
[b]Reference run number
[c]Condition number
[d]Final model

Base model

The base model for agomelatine was a two-compartment model with first-order absorption and a first-order elimination. IIV terms were supported on F as well as IOV on Vc/F. The RUV for agomelatine was described by a proportional error model but parameterized as an additive RUV on the log-transformed scale of separate magnitude for each of the two studies. The ka was estimated to an high value but data were considered as supportive.

Covariate analysis

Among the tested covariates (sex, age, WT and pubertal status) none of them impacted significantly at the $p<0.01$ level Vc/F, CL/F or F.

Final model

The final model for agomelatine was a two-compartment model with first-order absorption and a first-order elimination. IIV on F and the correlation between F and CL/F were estimated. The estimation of IOV was possible on Vc/F. The RUV for agomelatine was described by a proportional error model but parameterized as an additive RUV on the log-transformed scale of separate magnitude for each of the two studies. The ka was estimated to a high value, but data were considered as supportive. No IIV could be estimated on ka with successful convergence. The population PK model parameter estimates of the final model for agomelatine are presented in Table 7.

Table 7. Parameter estimates of the base model (left) and final model (right) for agomelatine

	Base model for agomelatine
Run	127
OFV	2004.62
Condition number	33.69

	Unit	Base model for agomelatine Value	RSE (%)	SHR (%)
V_c/F	10^3.L	58.6	11.5	
CL/F	10^3.L/h	22.7	9.00	
V_p/F	10^3.L	70.1	39.6	
Q/F	10^3.L/h	9.92	38.9	
k_a	h^{-1}	30.3	10.1	
IIV F	CV	1.20	13.1	9.90
IOV V_c/F^a	CV	1.10	13.4	25.3
Add. RUV, study CL2-20098-075 (log scale)	CV	0.874	5.85	16.0
Add. RUV, study CL3-20098-076 (log scale)	CV	1.07	6.35	16.0

The RSE for IIV and IOV parameters are reported on the approximate CV scale. F is the relative F.
[a]Same variance for the three occasions (see Section 4.3.2.2 for more details).
CL/F: apparent clearance; k_a: first-order absorption rate constant; Q/F: apparent inter-compartmental clearance; V_c/F: apparent central volume of distribution; V_p/F: apparent peripheral volume of distribution; CV: coefficient of variation; IIV: interindividual variability; IOV: interoccasion variability;
OFV: objective function value; RSE: relative standard error; RUV: residual unexplained variability; SHR: shrinkage;

	Final model for agomelatine
Run	147
OFV	1974.8
Condition number	605.2

	Unit	Final model for agomelatine Value	RSE (%)	SHR (%)
V_c/F	10^3.L	55.7	14.3	
CL/F	10^3.L/h	19.3	9.76	
V_p/F	10^3.L	123	43.3	
Q/F	10^3.L/h	14.2	25.7	
k_a	h^{-1}	29.5	24.6	
IIV CL/F	CV	0.552	20.0	27.5
Correlation CL/F-F	CV	0.835	16.3	
IIV F	CV	1.60	14.3	8.32
IOV V_c/F^a	CV	1.13	11.3	26.9
Add. RUV, study CL2-20098-075 (log scale)	CV	0.852	5.31	16.8
Add. RUV, study CL3-20098-076 (log scale)	CV	1.01	5.77	16.8

The RSE for IIV and IOV parameters are reported on the approximate CV scale. F is the relative F.
[a]Same variance for the three occasions (see Section 4.3.2.2 for more details).
CL/F: apparent clearance; k_a: first-order absorption rate constant; V_p/F: apparent peripheral volume of distribution; Q/F: apparent inter-compartmental clearance; V_c/F: apparent central volume of distribution; CV: coefficient of variation; IIV: interindividual variability; IOV: interoccasion variability;
OFV: objective function value; RSE: relative standard error; RUV: residual unexplained variability; SHR: shrinkage;

Model evaluation

Different goodness of fit plots were performed to assess the final model, and are presented in Figure 3. The eta plots of CL/F and F versus covariates weight, age, study, sex, pubertal status, and dose for the final model indicated no clear trends (not shown). Individual model fits were also provided (not shown). There are small trends for an over-prediction of the model at early time points which were deemed to be acceptable considering other model diagnostics.

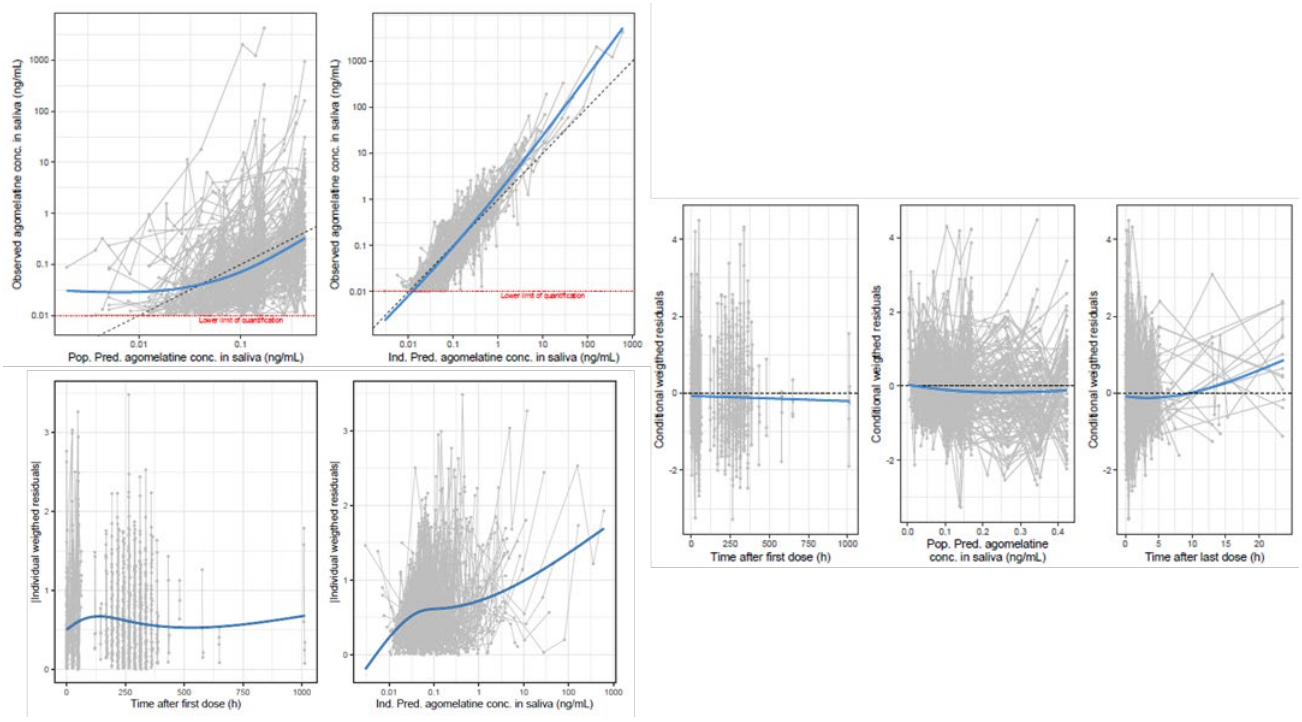


Figure 3. Goodness of fit plots for the final model. Top left: Observed agomelatine saliva concentrations versus population (left) and individual (right) predictions. Bottom left: Absolute IWRES versus time after first dose (left) and versus individual predictions of

agomelatine saliva concentrations (right). Right: CWRES versus time after first dose (left), time after last dose (right) and versus population predictions (middle).

Prediction-corrected visual predictive checks (pcVPCs) of the final model applied to the analysis data set combined with BLQ observations are presented in Figure 4. These figures showed overall adequate agreement between the simulations and the observed agomelatine concentrations. On the overall pcVPC, the model tends to overpredict the observed concentrations from 1.5 to 5 hours post dose. When stratified by age, the medians are generally well captured and within the 95% confidence interval but tend to overestimate the profile in older subjects. Based on those findings, the model was considered as acceptable.

VPCs stratified by study and dose were also submitted (not shown).

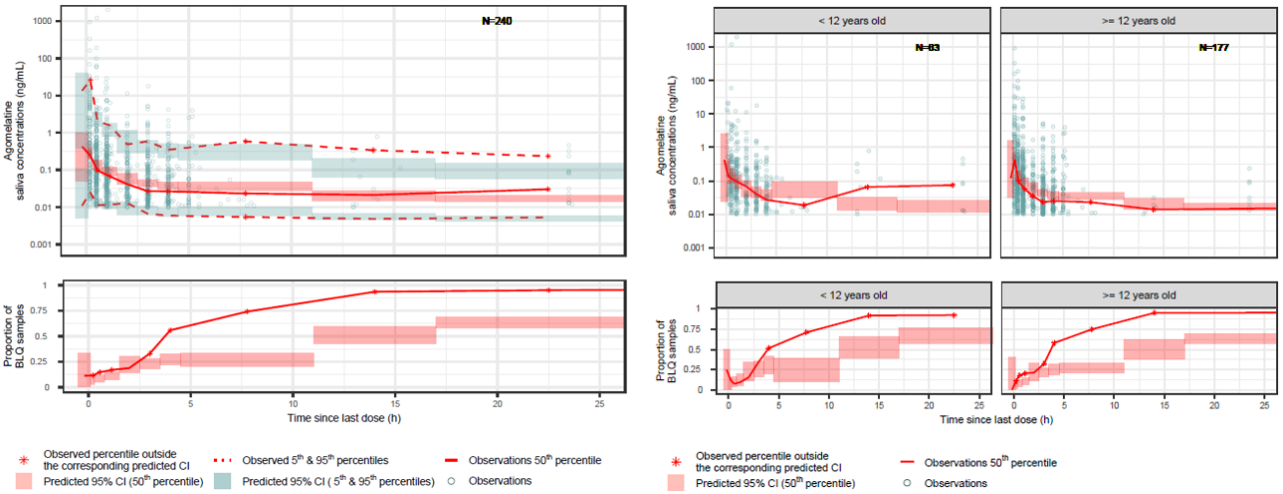


Figure 4. pc-VPCs of agomelatine concentrations in saliva versus time since last dose of the final model applied to the analysis data set and BLQ observations, overall (left) and stratified by age group (right)

Sensitivity analysis using the "M3 method" to handle BLQ observations

The MAH conducted an additional analysis in which the population PK parameters were estimated using the final model but with inclusion of the BLQ observations and applying the "M3 method". This model did not converge, and RSE of parameter estimates were calculated based on 1000 bootstrap samples. Compared to the final model with application of the M1 method, parameter estimates were considered similar and pcVPCs indicated that the M3 method did not provide a better fit to the data.

Special populations

Paediatrics

Comparison of observed plasma and saliva agomelatine concentrations in adult and paediatric patients

Paediatric agomelatine plasma PK data was available from studies **CL2-044** and **CL2-075**. In study **CL2-044**, plasma PK samples were obtained from 6 children and 3 adolescents receiving a dose of 1 mg or 5 mg agomelatine. PK data were available from all 9 patients following the first administration and from 8 patients at 6 months (trough, 1h, 2h, 4h, 8h, 12h post-dose). A total of 58 plasma concentrations and 17 PK profiles were available. In study **CL2-075**, PK samples were obtained from 24 children and 27 adolescents. One plasma sample was collected on D3 1h after administration of 25 mg agomelatine for a total of 49 patients. The adult plasma PK data used for comparison was derived from 17 studies including only data for doses of 25 or 50 mg.

Overall, the visual comparison shows a good overlap of agomelatine concentrations in both plasma and saliva samples between the 3 paediatric studies and the pool of the 20 adult studies (Figure 5).

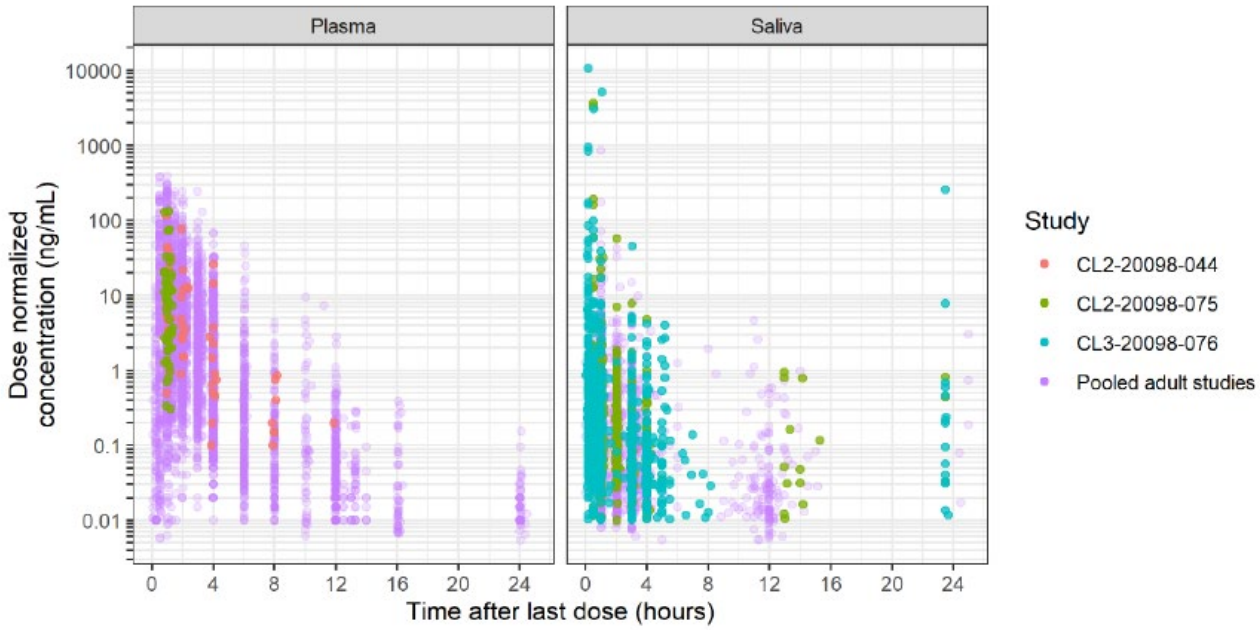
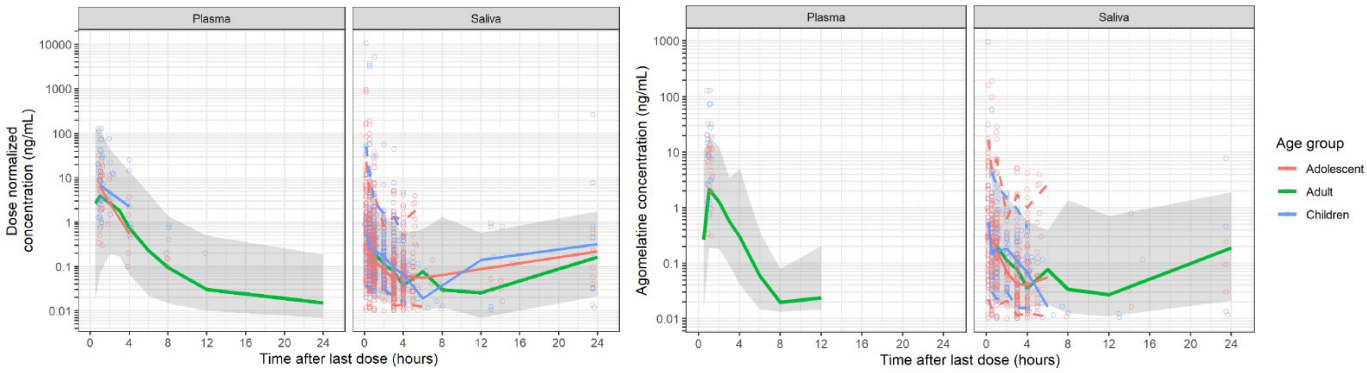


Figure 5. Individual plasma and saliva dose normalized concentrations after oral administration of agomelatine 25 and 50 mg (Pool of 20 adult studies) and 1, 5, 10 and 25 mg (paediatric studies CL2-044, CL2-075 and CL3-076). Source: Response to RSI April 2023.

In plasma, most of the individual dose normalized concentrations in children and adolescents from studies **CL2-044** and **CL2-075** (at 1h post-dose) are within the 90% interval of the dose normalized concentrations in adults. Despite a limited number of children and adolescents with plasma concentrations, there is a good agreement between the median of concentrations in adolescents and adults. More disparities are observed between the median of concentrations in children and adults, that may be the consequence of the limited sample size of children in the study **CL2-044** (that provides data for timepoints later than 1h post dose) (Figure 6, left). In the plot including only 25 mg data, most of the individual concentrations in children and adolescents from study **CL2-075** at 1h post-dose are within the 90% interval of the concentrations in adults (Figure 6, right).

In saliva, most of the individual concentrations in children and adolescents from studies **CL2-075** and **CL3-076** are within the 90% interval of the concentrations in adults. Also, there is a good agreement between the median, the 5th and 95th percentiles of concentrations in children, adolescents and adults (represented when the number of observations was considered sufficient) (Figure 6).



Dots: individual concentrations
Solid line: median (represented when at least 6 observations were available)
Dashed line: 5th/95th percentiles (represented when at least 20 observations were available)
Grey shaded area: 90% of adults data

Figure 6. Individual plasma and saliva agomelatine stratified by age group. Left: dose normalized data after oral administration of agomelatine 25 and 50 mg (pool of adult studies) and 1, 5, 10 and 25 mg (paediatric studies CL2-044, CL2-075 and CL3-076. Right: oral administration of agomelatine 25 mg in a pool of adult studies and in paediatric studies CL2-075 and CL3-076. Source: Response to RSI April 2023.

Comparison of saliva/plasma ratios of agomelatine in adult and paediatric patients

Paired plasma and saliva samples were obtained from 40 adults throughout a dosing interval at Day 1 and 8 following an agomelatine dose of 25 mg in study PKH-20098-010. The S/P ratio was consistent over the range of agomelatine concentrations and was overall similar to the ratios observed in paediatric study **CL2-075**. The mean S/P ratio in adults was also consistent with time (data not shown here), but there is substantial variability.

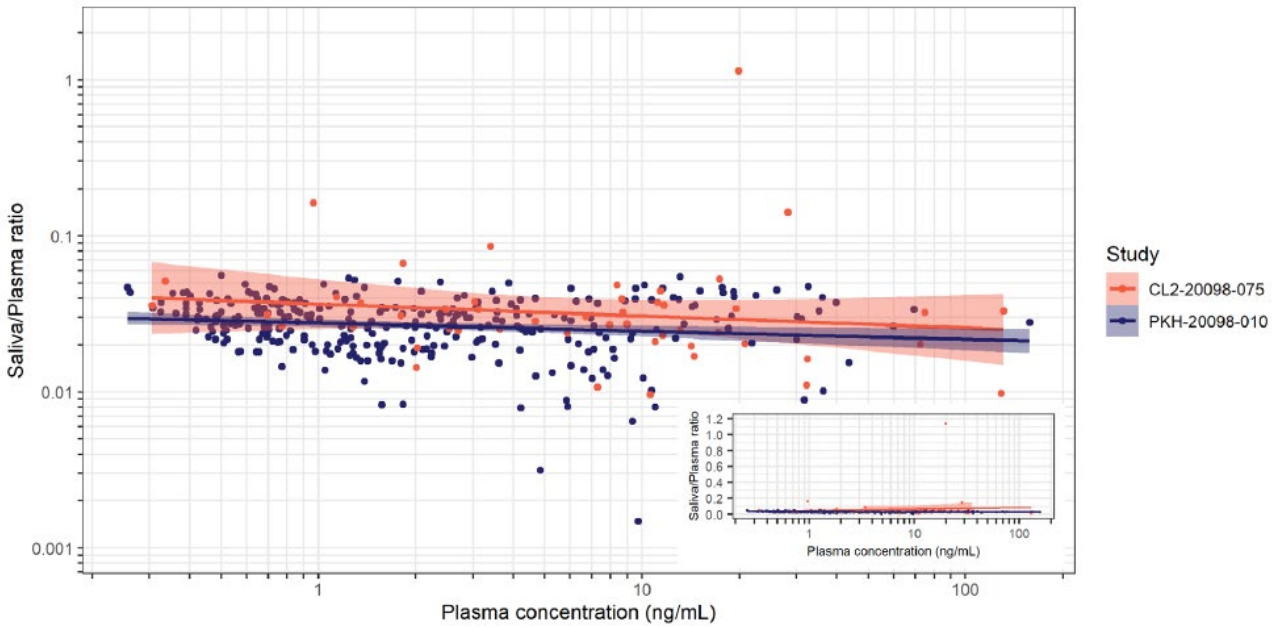


Figure 7. Linear regression of agomelatine S/P ratio versus plasma concentrations after oral administration of agomelatine 25 mg in adults (PKH-20098-010) and children and adolescents (CL2-075). Source: Response to RSI April 2023.

Comparison of individual estimated saliva agomelatine exposure metrics in adult and paediatric patients

Derived saliva exposure variables in children and adolescents in study **CL2-075** and **CL3-076** based on the final agomelatine model are shown in Table 8 and Table 9.

Table 8. Summary of derived PK parameters based on the final model for agomelatine – Pool of children and adolescents from CL2-20098-075 study

Statistics	AUC_{tau} (ng.h/mL)			Cmax (ng/mL)			Tmax (h)		
	5 mg	10 mg	25 mg	5 mg	10 mg	25 mg	5 mg	10 mg	25 mg
N	50	51	49	50	51	49	50	51	49
5th percentile	0.105	0.208	0.521	0.0211	0.0314	0.0526	0.106	0.0998	0.101
Median	0.208	0.414	0.965	0.0682	0.0986	0.378	0.136	0.146	0.133
95th percentile	1.1	2.17	5.58	0.526	1.47	2.9	0.167	0.183	0.187
Mean	0.666	1.31	3.35	0.254	1.11	5.36	0.136	0.142	0.14
Geometric mean	0.265	0.519	1.29	0.0807	0.135	0.359	0.134	0.139	0.136

In this table, each subject of the analysis data set has contributed with one set of PK parameters per dose level received. AUCt: AUC for the dosing interval of 24h; Cmax: maximum concentration; Tmax: time to maximum concentration

Table 9. Summary of derived PK parameters based on the final model for agomelatine – Pool of children and adolescents from CL3-076 study

Statistics	AUCtau (ng.h/mL)		Cmax (ng/mL)		Tmax (h)	
	10 mg	25 mg	10 mg	25 mg	10 mg	25 mg
N	91	84	91	84	91	84
5th percentile	0.182	0.35	0.0262	0.0519	0.08	0.0738
Median	0.427	0.982	0.168	0.336	0.131	0.135
95th percentile	4.35	7.61	4.84	7.19	0.162	0.167
Mean	6.69	3.6	8.16	3.86	0.129	0.129
Geometric mean	0.566	1.17	0.218	0.451	0.126	0.124

In this table, each subject of the analysis data set has contributed with one set of PK parameters per dose level received. AUCt: AUC for the dosing interval of 24h; Cmax: maximum concentration; Tmax: time to maximum concentration

Comparison of exposure variables in adolescents and adults

Exposure PK parameters in adults (pooled from 24 previous studies) were exported from the most current adult population PK report (NP34210) and were back-computed for the saliva matrix by using the adult saliva to plasma ratio of 0.033.

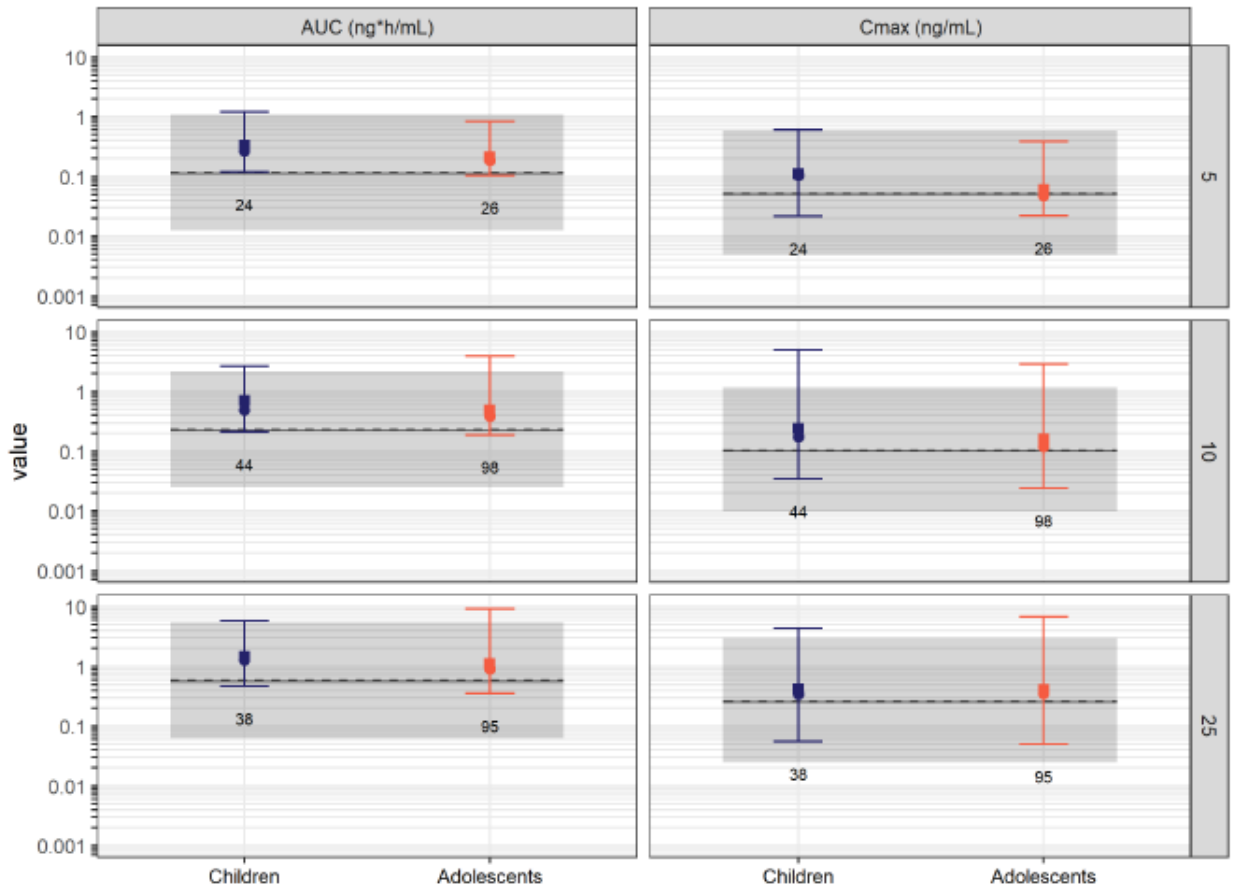
The exposure PK parameters are highly variable within dose levels which is in line with the high IIV in the population PK model estimates for both adult and paediatric populations. It appears that the adolescent population had higher mean and median values for AUC for the dosing interval of 24h than the adults but with a large overlap according to the percentile values (Table 10, Figure 8). The Cmax were similar between the two populations (Table 11, Figure 8) and the adolescents had shorter Tmax (geometric mean of ~0.73 h in adults and ~0.13 h in adolescents). The shorter Tmax was a result of the higher estimate of first-order absorption rate constant (ka) in paediatric population (29.5 h-1 versus 8 h-1 in adults).

Table 10. AUC for the dosing interval of 24h (ng.h/mL) in adults and pool of adolescents from studies CL2-075 and CL3-076 after agomelatine 5, 10 or 25 mg

Population	Adults	Adolescents (075+076)	Adults	Adolescents (075+076)	Adults	Adolescents (075+076)
Dose (mg)	5	5	10	10	25	25
N	1667	26	1667	98	1667	95
5th percentile	0.0125	0.104	0.0251	0.188	0.0626	0.353
Median	0.112	0.185	0.224	0.386	0.56	0.917
95th percentile	1.08	0.839	2.16	3.89	5.41	9.2
Mean	0.32	0.353	0.64	0.949	1.6	3.38
Geometric mean	0.116	0.213	0.232	0.491	0.579	1.12

Table 11. Cmax (ng/mL) in adults and pool of adolescents from studies CL2-075 and CL3-076 after agomelatine 5, 10 or 25 mg

Population	Adults	Adolescents (075+076)	Adults	Adolescents (075+076)	Adults	Adolescents (075+076)
Dose (mg)	5	5	10	10	25	25
N	1667	26	1667	98	1667	95
5th percentile	0.00496	0.0219	0.00992	0.0241	0.0248	0.0504
Median	0.0512	0.0481	0.102	0.12	0.256	0.35
95th percentile	0.59	0.386	1.18	2.87	2.95	6.76
Mean	0.192	0.0985	0.383	1.01	0.958	3.56
Geometric mean	0.0518	0.0605	0.104	0.162	0.259	0.414



Dot: median
Square: geometric mean
Bar: 5th-95th percentiles
Solid line: median of adults data
Dashed line: geometric mean of adults data
Grey shaded area: 90% of adults data
Figures indicate the number of subjects (note: in study CL2-20098-075, one subject received different dose levels)

Figure 8. Distribution of individual pharmacokinetic exposure parameters in saliva, AUC for the dosing interval of 24h (left) and Cmax (right), in adults compared to the pool of children and

adolescent patients from CL2-075 and CL3-076 studies after agomelatine 5, 10 or 25 mg. Source: Response to RSI April 2023.

2.3.3. Pharmacodynamics

Mechanism of action

Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist. Binding studies indicate that agomelatine has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors.

Agomelatine resynchronises circadian rhythms in animal models of circadian rhythm disruption. Agomelatine increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin.

2.3.4. Discussion on clinical pharmacology

Results from the phase 3 study **CL3-076** have been submitted to support the current application to extend the MDD indication to adolescent patients, including saliva PK data from 175 patients <18 years treated with 10 mg or 25 mg agomelatine daily. The proposed dose is 25 mg taken orally once daily, which is identical to the adult starting dose.

A popPK analysis was performed using saliva PK data from 60 children and 166 adolescents included in studies **CL2-075** and **CL3-076**. The model was used to describe the population saliva PK characteristics of agomelatine with its associated interindividual variability in children and adolescents, and to investigate the potential influence of covariates. The model has also been used to derive individual post-hoc exposure estimates for adolescent patients from studies **CL2-075** and **CL3-076** for comparison with those previously derived from adult patients.

Diagnostic plots indicated that the final model was a reasonable fit to the observed saliva agomelatine PK data set as a whole, but with overprediction of the central tendency. In accordance with previous findings in adults, the inter-individual variability is high. While several factors have been found to significantly influence agomelatine PK in adults, no covariates were identified in the paediatric popPK analysis. This may in part be due to limitations in the PK database, including the very high proportion of BLQ observations. From a clinical point of view, the large and unpredictable variability is unfavourable because it may imply an unpredictable therapeutic response.

The very limited plasma PK data from the paediatric population could indicate agomelatine concentrations in the higher end of the range of observed adult data. A similar trend is observed when comparing individual paediatric and adult saliva exposure metrics. However, the magnitude of a potential higher mean exposure in paediatric patients compared to adults cannot be quantified based on current data. The comparative analysis of saliva PK variables in adults and adolescents should be interpreted with caution as the conversion of exposure data across saliva/plasma using a fixed ratio represents a large uncertainty. The very large interindividual variability in agomelatine PK also complicates the comparison. There is not sufficient data to conclude that systemic agomelatine exposure is similar in adults and children/adolescents.

2.3.5. Conclusions on clinical pharmacology

Limited agomelatine plasma PK data is available from the paediatric population, and most PK data derives from saliva concentration measurements. The robustness of extrapolation from saliva exposure to plasma exposure is not established. Therefore, the systemic exposure and plasma pharmacokinetics of agomelatine in children and adolescents is to a large extent uncharacterised. Overall, the available data suggest that the systemic exposure of agomelatine following a 25 mg dose in children and adolescents mostly falls within, possibly in the higher end of, the observed adult exposure range. The variability in the saliva pharmacokinetics of agomelatine in paediatric patients is high and unpredictable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Study CL2-20098-044 (abbreviated to CL2-044)

The CL2-044 study aimed to assess the activity of co-administration of agomelatine (1 mg or 5 mg, according to body weight) and acebutolol (10 mg/kg) given orally once a day to children suffering from Smith-Magenis Syndrome. It was a multicentre, uncontrolled open-labelled Phase II study with a treatment duration of 6 months (M0-M6), followed by extension periods of treatment up to 4 years.

Nine children aged between 6 and 18 years were included. Four patients who weighed ≤30 kg received 1 mg agomelatine daily, while 5 patients who weighed >30 kg received 5 mg agomelatine daily. Plasma PK samples were collected on M0 D1 and on M6 D1, 15 minutes before administration and 1 h, 2 h, 4 h, 8 h and 12 h after administration of agomelatine.

Pharmacokinetic results showed a wide variability on AUC and Cmax, as for adults. Parameters calculated in this study, when adjusted to the dose of 25 mg, were overall in the same range as those observed in the adult population after administration of the 25 mg dose (non-smoker and evening drug administration in healthy volunteers and patients), concluding that no dose adaptation based on weight would be needed in paediatric studies.

Study CL2-20098-075 (abbreviated to CL2-075)

The CL2-075 study aimed to evaluate the PK and safety of agomelatine in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) with depressive or anxiety disorder.

It was a phase 2, open-labelled, multicentre, three-dose level (with intra-subject dose escalation), non-comparative study (Figure 9). All included patients received agomelatine 5 mg on Day 1 (D1), then agomelatine 10 mg on Day 2 (D2), then agomelatine 25 mg on Day 3 (D3). The dose was taken between 6.00 p.m. and 7.00 p.m. each evening, to allow PK sampling before bedtime.

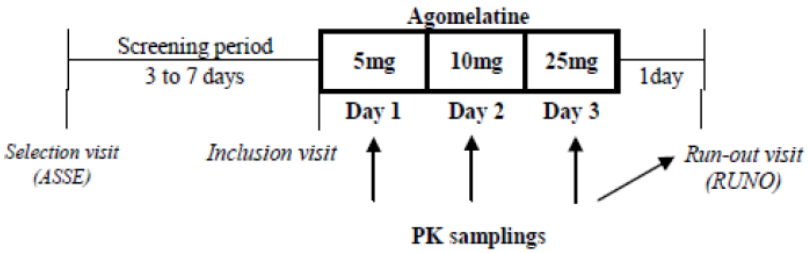


Figure 9. Study plan for study CL2-075

The primary objective was to evaluate the PK characteristics of 3 doses of agomelatine (5, 10 and 25 mg) in children and adolescents. Saliva samples were collected for evaluating the agomelatine PK (sampling scheme described in section 5.3.2). Only one PK blood sample was drawn per patient in order to check the correlation and ratio between plasma and saliva agomelatine concentrations. The secondary objective was to provide safety data for the 3 agomelatine doses.

A total of 51 patients were IIed (27 adolescents and 24 children).

Results indicated that agomelatine pharmacokinetic parameters at 5 mg, 10 mg and 25 mg in paediatric population were in the same range as in the adult population. As in adults, a high variability on PK parameters was observed. However, contrary to adults, no covariate influencing agomelatine PK was identified in paediatric patients. No new safety signals could be detected, but the safety results of the study were limited due to the rather low number of patients (51) who were exposed to 3 increasing single oral doses of agomelatine (5, 10 and 25 mg) over 3 consecutive days.

The 10 mg dose was effective in a specific dose-response study in adults suffering from MDD (Kennedy *et al*, 2014) and 25 mg is the recommended dose for treating MDD adult patients. The dose of 5 mg was not effective in a placebo-controlled dose range study in adult patients with MDD (Loo, 2002). As exposure in the adult and paediatric populations was similar, and based on the assumption that the exposure/efficacy relationship is the same, the doses of 10 mg and 25 mg were chosen for the phase III study CL3-076.

2.4.2. Main study

Study CL3-20098-076 – abbreviated to CL3-076

This is a Phase 3, 12-week, multicentre, randomised, double-blind, parallel groups and placebo-controlled study comparing two doses (10 mg and 25 mg) of agomelatine in children (from 7 to < 12 years) and adolescent patients (from 12 years to 17 years) suffering from moderate to severe MDE. In order to ensure assay sensitivity one group of patients was randomised to receive fluoxetine 10-20 mg.

At W012 visit, all patients who were deemed to benefit from a continuation of a treatment with agomelatine were offered to enter an open-labelled 21-month extension period at a flexible dose of agomelatine 10 or 25 mg.

Primary endpoint of the 12-week double-blind period was to demonstrate superiority of at least one dose of agomelatine (10 mg or 25 mg) as compared to placebo on the Children's Depression Rating Scale – Revised (CDRS-R) raw total score expressed in terms of change from baseline to W012.

The study was divided into 4 periods:

1. A run-in period of 3 weeks (± 5 days) between selection (ASSE) and inclusion (W000) visits without any Investigational Medicinal Drug (IMP) treatment. According to the study protocol the patients were to have three sessions (or at least two) of Manualized Psychosocial

Counselling (Spröber *et al*, 2015). Each session was to last around 45 minutes and involve the patient and his/her family. These sessions were organised with a minimum of 3 days between each session. The last session was to take place at least 1 day before inclusion. Only patients who were considered non-responders to the Manualized Psychosocial Counselling, according to the investigator judgment, would be eligible for inclusion.

2. Double-blind treatment period of 12 weeks (from W000 to W012):

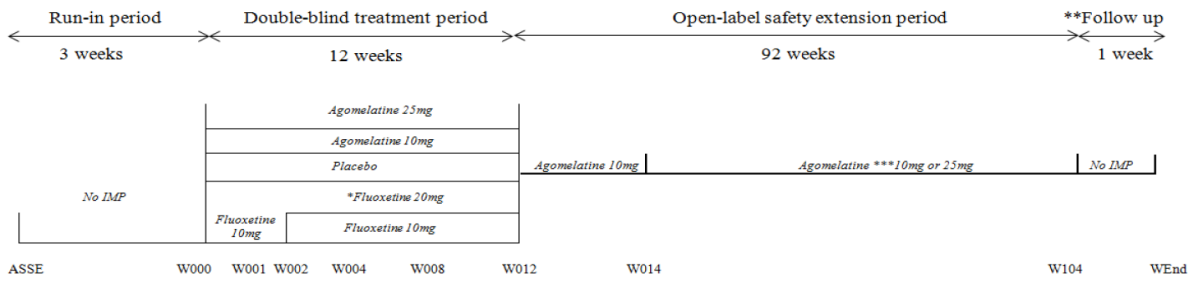
   At inclusion (W000), patients were randomised to one of four groups: Agomelatine 10 mg/day, Agomelatine 25 mg/day, Placebo or Fluoxetine 10 mg/day (with a possible increase to 20 mg/day at W002). According to the study protocol Manualized Psychosocial Counselling was to be performed once a month in this period (i.e., W004, W008 and W012).

3. An optional open-label safety extension period of 21 months (from W012 to W104) for patients who could benefit from a continuation of a treatment with agomelatine.

   From W012 to W014, each patient received agomelatine 10 mg. From W014 to W104, the dose could be adjusted at each visit (flexible dose, either to increase to 25 mg or decrease again to 10 mg). According to the study protocol, Manualized Psychosocial Counselling was to be continued in the extension period with one session at each visit in the period W018-W104.

4. A follow-up period of 1 week on average (5 to 7 days) without any IMP after the last IMP intake (after W012, W104 or in case of premature withdrawal from the study at any moment).

A schema over the study design is provided in Figure 10 below.



The following visits were performed between W014 and W104: W018, W024, W032, W040, W048, W052, W060, W068, W077, W086, W095.

*If no improvement at W002, 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.
*** During the extension period the dose could be adjusted at each visit (flexible dose, either to increase to 25 mg or decrease again to 10 mg) by the investigator based on the clinical picture of patient.

Figure 10. Study plan for Study CL3-076

2.4.3. Methods

Considering the target population of patients, a Data Monitoring Committee (DMC) was set up and was responsible for reviewing the safety on a regular basis and providing written recommendations to the sponsor regarding the conduct of the study (modification or termination). Their recommendations were to

be forwarded to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities only if relevant for the safety of patients.

Of note, there were several criteria leading to a mandatory withdrawal from the study. These included (non-exhaustive list):

Worsening of depression based on the investigator's clinical judgment or a CGI-S = 7; any suicide attempt (whatever its severity); high suicidal risk, according to investigator's judgment and or with a suicidal ideation of 4 or 5 on Columbia-Suicide Severity Rating Scale (C-SSRS); AST and/or ALT value > 3 ULN confirmed by a re-test; any symptoms or signs of potential liver injury; occurrence of seizures, psychotic features, and/or manic reactions; occurrence of a new psychiatric condition needing a concomitant medication or likely to interfere with the conduct of the study.

2.4.4. Study participants

Main inclusion criteria:

Demographic criteria

1. Male or female.

2. In-or-out patients (hospitalisation was not required for this study).

3. Aged from 7 to less than 12 years of age (ICH E11 children age sub-set, 2001) or from 12 to less than 18 years of age (ICH E11 children age sub-set, 2001).

4. Living with their parents/close relatives (sister or brother if they were adults, grandparent, step- parent) or legally authorised representative(s).

5. Informed consent/assent obtained from the parents or legally authorised representative(s)/patient: to be defined according to patient's age and corresponding regulatory requirements in the concerned countries.

Medical and therapeutic criteria

6. Primary diagnosis of Major Depressive Disorder, single or recurrent episode, of moderate to severe intensity, as per Diagnostic Criteria for Major Depressive Episode, 4th edition, Text Revision (DSM-IV-TR). The diagnosis of MDD according to DSM-IV-TR criteria was made using a validated semi-structured interview, the Schedule for Affective Disorders and Schizophrenia for School-age Children, Present and Lifetime version (KSADS-PL, Birmaher *et al*, 2009).

7. Single or recurrent episode, of moderate or severe intensity according to DSM-IV TR criteria:

- with or without melancholic features;
- with or without seasonal pattern;
- with or without chronic features;
- with or without catatonic features;
- with or without atypical features;
- without psychotic features;
- without post-partum onset for the current episode.

8. Current episode ≥ 4 weeks.

9. Children's Depression Rating Scale – Revised: CDRS-R Raw score ≥ 45 (Poznanski and Mokros, 1996).

10. Clinical Global Impression -Severity (CGI-S) rating score ≥ 4 (Guy, 1976).

11. Considered as non-responder to Manualized Psychosocial Counselling according to the investigator judgment.

Main exclusion criteria

1. Post-pubertal (i.e., who already have had menarche), and sexually active females without an effective contraception method (oral contraceptive pill, contraceptive implant, patch, intra uterine contraceptive device, or condom).
2. Pregnant or breastfeeding females.
3. Patients participating in another study at the same time or having participated in another study within the 3 months prior to inclusion (patients participating to data collection register could be selected).
4. Patients with MDD currently improved on current antidepressant treatment or other medical care.

   Medical and therapeutic criteria

   Related to other depressive disorders

5. Current diagnosis of Major Depressive Disorder of mild intensity according to DSM-IV-TR criteria.
6. All types of Depression other than MDE such as Depressive Disorder Not Other Specified, Dysthymic Disorder, Bipolar Disorder I and II, Schizoaffective Depressive Disorder or Bipolar type, according to DSM-IV-TR criteria and confirmed by MINI-Kid (Mini International Neuropsychiatric Interview for Children and Adolescents).
7. Patient who had a current suicide risk according to the investigator (based on the information obtained during the evaluation of the Columbia-Suicide Severity Rating Scale Children version (C-SSRS-C: Baseline/Screening: "suicidal ideation" part, item 4 or 5 is "yes" in "6 months" part).
8. Patients having a high suicidal risk according to the investigator based on the MINI-Kid or having suicide attempt in the previous 3 months based on information obtained during the investigator interview.

   Related to other psychiatric conditions

9. Diagnosis of Mental Retardation according to the investigator.
10. Diagnosis of Pervasive Developmental Disorder according to the investigator.
11. Current Bulimia according to DSM-IV TR confirmed by MINI-Kid.
12. Patients fulfilling DSM-IV TR criteria for substance or alcohol dependence in the past 12 months confirmed by MINI-Kid.
13. Current or previous diagnosis of Psychotic Disorder according to DSM-IV TR confirmed by MINI-Kid.
14. Any other psychiatric co-morbidity requiring the use of a concomitant psychotropic medication (except attention deficit hyperactivity disorder [ADHD]).
15. Current or previous diagnosis of any other psychiatric co-morbidity likely to interfere with the conduct of the study (e.g., oppositional, conduct disorder).

16. Patient with comorbid ADHD when not stabilised for at least 12 weeks of treatment with methylphenidate or amphetamine derivate.

Related to miscellaneous conditions

17. Any severe, uncontrolled or chronic condition incompatible with study treatment or likely to interfere with the conduct of the study (e.g., neoplasic, cardiovascular, pulmonary, metabolic and digestive disorders, unstabilised diabetes of type I or II).
18. Current infectious mononucleosis.
19. Any current diagnosis of neurological disorders (such as migraine, epilepsy).
20. Prominent and severe neurological symptoms e.g., seizures.
21. Patients with a weight less than 20 kilogram (kg) at screening.
22. Transaminases values (AST and/or ALT) ≥ 2 times the upper limit of normal range (ULN).
23. Total bilirubin ≥ 1.5 times ULN and/or free bilirubin ≥ 2 times ULN.
24. Transaminases (AST and/or ALT) and total bilirubin values > upper reference value.
25. Alkaline phosphatase (ALP) ≥ 3 times ULN and both ALP and gamma-glutamyl transferase (GGT) > 1 time ULN.
26. Creatinine Clearance ≤ 30 mL/min.
27. Abnormal thyroid function (if TSH was out of range, then thyroxine [T4] was automatically tested. Patient could not be included if T4 parameter showed a result out of range).
28. Known hypersensitivity to agomelatine and/or fluoxetine and/or any of the excipients.
29. Patients having risk of acute angle-closure glaucoma or raised intra ocular pressure.
30. Patients having a history of bleeding disorders/ of known haemostasis abnormality.

Related to previous and concomitant treatments

31. Structured psychotherapy for MDE started or continued within the previous 3 months before selection.
32. Electroconvulsive therapies and transcranial magnetic stimulation (TMS); hormone replacement therapy initiated or discontinued within the previous 3 months.
33. Concomitant use of several other treatments was contraindicated, such as potent cytochrome (CYP) P450 1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin), all types of monoamine oxidase inhibitors (MAOIs), treatment with oral anticoagulant, hormone therapy initiated or discontinued within the previous 3 months, anxiolytics/hypnotics, antiepileptics/mood stabilisers, treatments likely to interfere with fluoxetine, treatments prone to interfere with CNS (e.g., systemic corticosteroids, exogenous melatonin, methyldopa, opiates except codeine derivates), other psychotropic drugs (e.g., neuroleptics).
34. Any treatment with β-blockers if started, stopped or modified within the 4 weeks prior to inclusion was forbidden.
35. Patients previously non responders to fluoxetine for the current episode.

Patients treated with fluoxetine for the current period could not be selected in the study.

2.4.5. Treatments

During the double-blind treatment period, the patient took daily 2.5 mL or 5 mL of an oral solution according to the doctor's prescription in the morning at wake-up and 1 oral tablet in the evening at bedtime.

From week 0 to week 2:

- For agomelatine 10 mg group: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 10 mg in the evening at bedtime.
- For agomelatine 25 mg group: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of agomelatine 25 mg in the evening at bedtime.
- For fluoxetine 10 mg group: 2.5 mL (10 mg) of oral solution of fluoxetine in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.
- For placebo group: 2.5 mL of oral solution of placebo in the morning at wake-up, 1 tablet of placebo in the evening at bedtime.

On the day of saliva collection, the oral tablet intake had to be brought forward to 6 p.m. to facilitate the repeated saliva sampling collection according to its planned time schedule.

From week 2 to week 12:

At W002, in case of insufficient improvement according to the investigator's clinical judgement, the volume of oral solution could double, leading potentially to an increased dose of fluoxetine to 20 mg/day. Patients with a sufficient improvement remained on the initial dose until W012.

Patients took daily 1 oral tablet and 2.5 ml or 5 ml of oral solution depending on the dose decided by the investigator. Patients with no dose increase received the same treatment as that of week 0 to week 2.

During the *open-label extension period*, the patient took daily one oral tablet in the evening at bedtime.

From week 12 to week 14:

All patients entering the extension period took 1 tablet of agomelatine 10 mg orally per day in the evening at bedtime.

From week 14 to week 104:

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

2.4.6. Objectives

The primary objective was to demonstrate superiority of at least one dose of agomelatine as compared to placebo on the Children's Depression Rating Scale – Revised (CDRS-R) raw total score expressed in terms of change from baseline to W012.

Secondary objectives were to:

- assess the short-term (10 mg, 25 mg) and long-term safety of agomelatine (10 mg and 25 mg) pooled)
- evaluate the long-term efficacy of agomelatine (10 mg and 25 mg pooled)
- explore efficacy and safety in children and adolescents separately

2.4.7. Outcomes/endpoints

Primary efficacy endpoint:

Change from baseline to W012 in the Children's Depression Rating Scale – Revised (CDRS-R) raw total score.

- *Primary analysis*: superiority of at least one dose of agomelatine as compared to placebo on antidepressant efficacy after a 12-week treatment period, from the CDRS-R raw total score expressed in terms of an adjusted difference from baseline to W012, using a three-way analysis of covariance (ANCOVA) model.

Secondary efficacy endpoints:

- Clinical Global Impression – Severity of Illness (CGI-S) and Improvement (CGI-I) scales:
  - difference between placebo and each active treatment group on the value of these scores at W012
- Response to treatment based on CGI-I score 1 ("very much improved") or 2 ("much improved"):
  - difference between placebo and each active treatment group in proportion of patients with response to treatment at W012
- Adolescent Depression Rating Scale (ADRS) total score (only for adolescents):
  - difference between placebo and each active treatment group on the value of this score at W012
- Children's Global Assessment Scale (CGAS) total score:
  - expressed as value at baseline and at each post-baseline visit as well as change from baseline to each post-baseline visit.

Additionally, in supplementary analyses the proportion of remitters at W012 and at each visit were examined in both the total population and in adolescents. Remission was defined as a CDRS-R raw total score ≤ 28.

Measurement tools:

Several specific scales were used for this study. According to the MAH, a mandatory training was performed for investigators before the start of the study. The aim of these sessions was to provide training on the diagnosis and on the assessment of the main efficacy evaluation of the study in order to minimize biases related to individual rating variability. Instruction manuals were also given to the investigators.

The primary efficacy endpoint chosen for this study was the *Children's Depression Rating Scale – Revised* (CDRS-R) (Poznanski and Mokros, 1996). This scale is a semi-structured 17-item clinician-rated instrument which has been initially designed for assessing the severity of symptoms commonly associated with depression in children aged 6 to 12 years: in this age-set the scales reportedly showed high inter-rater reliability (ICC=0.92), good test-retest reliability (ICC = 0.80) and quite good internal consistency (alpha=0.85). Each of the items can be rated within the ranges of 1-5 or 1-7. Total scores range from 17 to 113, with higher numbers reflecting worsening of depression. CDRS-R is widely used in adolescents as well and has also reportedly showed good reliability and validity with this age group (Mayes *et al*, 2010, Gunlicks-Stoessel *et al*, 2020).

The rater had to complete the rating scale during 2 separate interviews: 1 with the patient and 1 with the parent(s)/legally authorised representative(s).

The CDRS-R was performed at the selection visit, at inclusion (W000) and thereafter at each visit (i.e., in the double-blind period: W001, W002, W004, W008 and W012). It was also rated at all visits in the open-label extension period.

The *Clinical Global Impression scale* (CGI, Guy, 1976) was used as a secondary efficacy endpoint assessed by the investigator.

The CGI scale rates:

- the severity of the illness with Severity of Illness (CGI-S) score. The severity is rated on a 1-7 scale, with (1) representing normal symptoms, meaning the patient is not ill. The highest on the scale, (7), represents patients among the most severely ill. Right in the middle (4), a patient will be defined as moderately ill.
- the global improvement or worsening in comparison with patient's condition at inclusion with Global Improvement (CGI-I) score. The 7-point CGI-I scale rates improvement with a (1) representing a 'very much improved' patient and (7) representing a patient who has become 'very much worse' due to treatment. The rating (4) represents a patient displaying no change from the treatment.

Only CGI-S was performed at the selection visit and at inclusion (W000) and thereafter both CGI-S and CGI-I were performed at each visit (i.e., in the double-blind period: W001, W002, W004, W008 and W012). They were also rated at all visits in the open-label extension period.

The *Adolescent Specific Rating Scale* (ADRS), designed to specifically evaluate adolescent depression (Revah-Levy *et al*, 2007) was used as a secondary efficacy endpoint. In the framework of this study the clinician reported version was used. The scale consists of 10 items and maximum score of each item is 6.

The *Children's Global Assessment Scale* (CGAS) (Schaffer, 1983) is a clinician rated scale that measures the overall functioning of children and adolescents. Scores ranges from 1 to 100 with "1 to 10" indicating "needs constant supervision" and "91 to 100" indicating "superior functioning".

The two scales ADRS and CGAS were performed only at inclusion (W000) and thereafter at W004, W008 and W012 in the double-blind period. These scales were not used during the open-label extension period.

Analysis sets

Modified Randomised Set (MRS):

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

Full Analysis Set (FAS):

All patients of the MRS having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value for the primary efficacy endpoint. All efficacy analyses were carried out in the FAS.

Safety Set for double blind period (SS):

All patients having taken at least one dose of IMP.

2.4.8. Sample size

Initially, the sample size has been estimated on the CDRS-R raw total score change from baseline to W012 for a difference research between at least one dose of agomelatine and placebo in patients of the FAS, based on a two-sided Student's t-test for independent sample and using a Bonferroni correction (conservative procedure) in order to maintain the experiment-wise type I error at 5% (bilateral situation).

Finally, after the amendment n° 2, overall, at least 390 patients with at least 312 adolescents (divided in each treatment group) were estimated to be enough to allow to conclude that at least one dose of agomelatine was superior to placebo with a power of 89% in the overall population and a power of 80% in the subgroup of adolescents, assuming an effect size of 0.50.

2.4.9. Randomisation

The treatment (agomelatine 10 mg, agomelatine 25 mg, placebo, fluoxetine) was assigned at inclusion (W000) by balanced (non-adaptative) randomisation. It was done using an Interactive Response System (IRS). The data were stratified by country and children/adolescents age set (children from 7 to less than 12 at selection; adolescents from 12 to less than 18 at selection).

2.4.10. Blinding (masking)

The 12-week period of the study was conducted in double-blind conditions. Each treatment dispensed throughout this period was similar (same appearance for tablets [active treatment (agomelatine) and its placebo (A)] and same appearance for oral solution [active control (fluoxetine) and its placebo (B)]), please also refer to "Treatments" above.

The blind for any study patient had to be broken by the investigator or authorised person only under circumstances such as any serious adverse event (SAE) or any severe medical condition if it was absolutely necessary to ascertain the type of treatment given for the follow-up of the patient.

The DMC could ask in specific cases, as far as the safety of patients was concerned, for decoding.

2.4.11. Statistical methods

First, in the Full Analysis Set (N=396) in which the main analysis was performed, the descriptive analysis did not show clinically relevant differences between the treatment groups at the study entry regarding most of demographic data nor for other main baseline characteristics.

The randomization process could be thus considered as validated and the following model could be used.

The superiority of at least one dose of Agomelatine as compared to placebo on antidepressant efficacy after a 12-week treatment period was assessed in the FAS, from the CDRS-R raw total score expressed in terms of change from baseline to W012 using an analysis of covariance (ANCOVA) model. Missing data were imputed using Last Observation Carried Forward (LOCF) method and step-down Dunnett's procedure was used in order to consider multiplicity issues.

To study the superiority of at least one dose (Agomelatine 10mg and 25mg versus placebo) on a quantitative criterion (change from baseline to W012 of CDRS-R raw total score), the following ANCOVA model was used:

Y = Treatment Age-class Country Baseline with "Treatment", "Age-class" and "Country" introduced as a fixed class effect and "Baseline" as a continuous quantitative effect.

The following null hypothesis was tested associated to the main analysis:

H0: "μA = μP" ⇔ H0: "μP – μA = 0"

H1: "μA ≠ μP" ⇔ H1: "μP – μA ≠ 0"

where μA and μP were the true adjusted means of change from baseline to W012 of the CDRS-R raw total score in Agomelatine and placebo groups respectively.

The GLIMMIX procedure of SAS® software was used and the denominator degrees of freedom for the test of fixed effect was computed using Satterthwaite method. The type I error was set at α = 5% (bilateral situation), which was consistent with the objective of demonstrating superiority of at least one dose of Agomelatine versus placebo (unilateral situation at 2.5%).

Since two Agomelatine dose regimens were compared to placebo, step down Dunnett's procedure was used to adjust for multiplicity in the main analysis. The conclusion of the test of the null hypotheses was based on Dunnett's adjusted p-values.

For the validation of the model, the following points were studied:

- Existence of a linear relationship between the change from baseline to W012 and baseline value

- Parallelism of straight lines between treatment groups

- Normality and homoscedasticity of residuals

- Detection of outliers.

In case of assumptions judged satisfactory, the model chosen to analyze the primary endpoint will be considered as consistent.

Existence of a linear relationship

In order to justify the introduction of the CDRS-R raw total score at baseline as a continuous quantitative covariate in the main analysis model, the objective of this section was to show the existence of a linear relationship between the change from baseline to W012 and the baseline value of this score.

The validation of this assumption was based on the test of baseline covariate (Table 12) in the main analysis model:

Y= Treatment Age-class Country Baseline

The significance of this test was expected.

Type III Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRT01PN	3	382	2.20	0.0877
BASE	1	382	46.04	<.0001
AGEGR1	1	382	0.01	0.9209
COUNTRYC	8	382	8.00	<.0001

Table 12. Test of Baseline covariate in the model Y= Treatment Age-class Country Baseline - Full Analysis Set (N=396)

The baseline covariate was statistically significant (p<0.0001). The assumption of a linear relationship between the change from baseline to W012 and the baseline value of CDRS-R raw total score was acceptable. Consequently, a model with baseline as covariate was justified.

Parallelism of straight lines between treatment groups

In order to justify the use of a model with a common slope for baseline values as a quantitative continuous covariate, the objective of this section was to show that the linear relationship between the change from baseline to W012 and the baseline value of CDRS-R raw total score was independent of the treatment group.

The validation of this assumption was based on the test of the treatment-by-baseline interaction in the model:

Y= Treatment Age-class Country Baseline Baseline x Treatment.

The non-significance of this test was expected, indicating a common slope for the baseline terms among all treatment groups. The parallelism of straight lines between treatment groups was also checked graphically.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRT01PN	3	379	2.00	0.1141
BASE	1	379	49.46	<.0001
BASE*TRT01PN	3	379	2.50	0.0591
AGEGR1	1	379	0.01	0.9277
COUNTRYC	8	379	7.68	<.0001

Table 13. Test of Baseline x Treatment interaction in the model Y= Treatment Age-class Country Baseline Baseline x Treatment - Full Analysis Set (N=396)

The treatment-by-baseline interaction tested in the model was not statistically significant (p=0.0591). The slopes were not significantly different between treatment groups even if the parallelism of straight lines was not observed on Figure 11 thereafter.

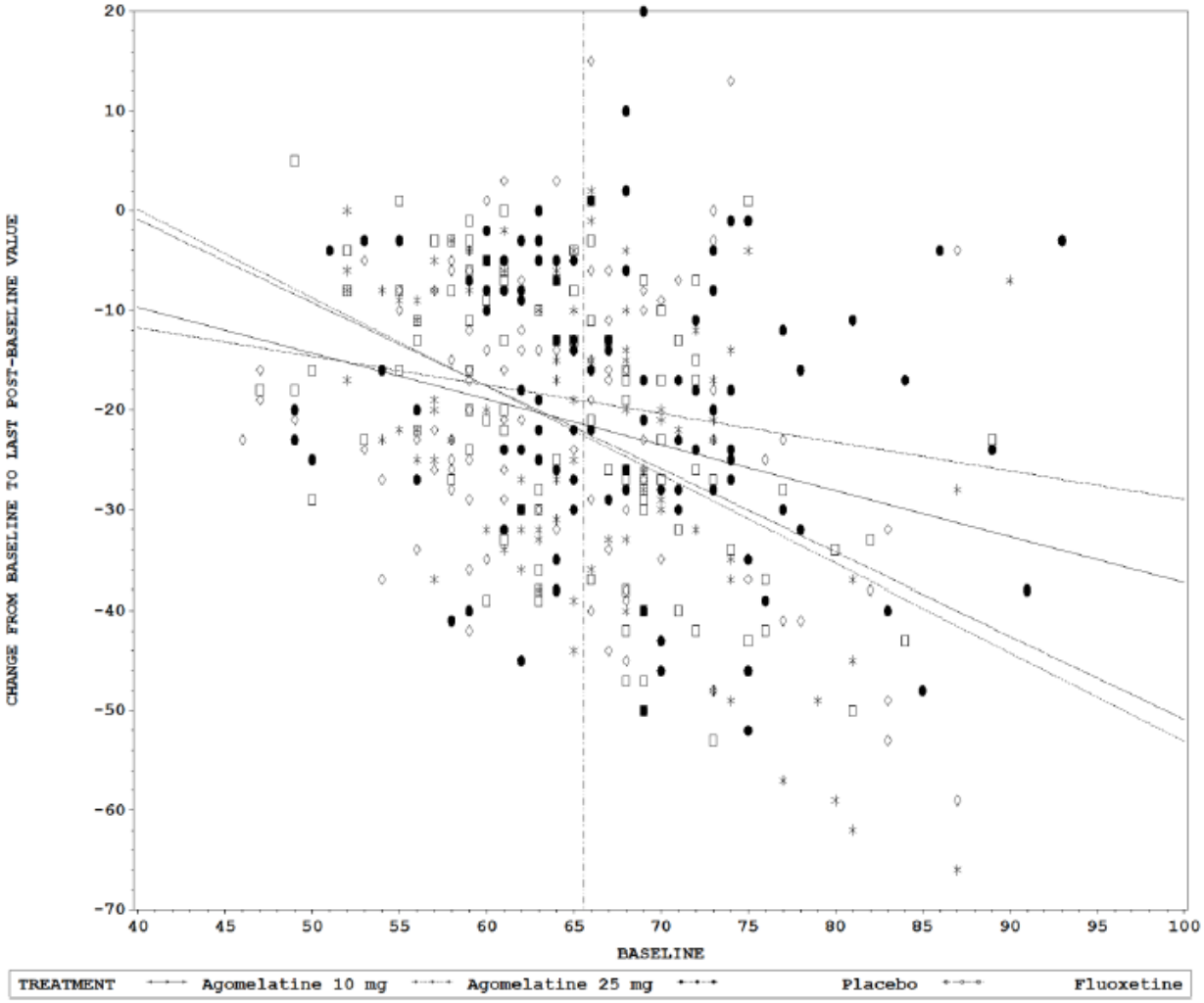


Figure 11. Change from baseline to W012 versus baseline value of CDRS-R raw total score by treatment group – Full Analysis Set (N=396)

Even if crossing trend from the parallelism assumption is observed on Figure 1, the treatment-by-baseline interaction, tested in the model ***Y=Treatment Age-class Country Baseline Baseline x Treatment*** was not statistically significant. Therefore, a model with a common slope for baseline covariate could be used to model the data.

Normality and homoscedasticity of residuals

The objectives of this section were to check the assumptions of normality and homoscedasticity of residuals underlying the main analysis model using graphs and descriptive statistics.

According to the fitting density plot (see Figure 12) and the normal probability plot (see Figure 13), the residuals normality assumption seemed acceptable. Mean of residuals was estimated to 0.

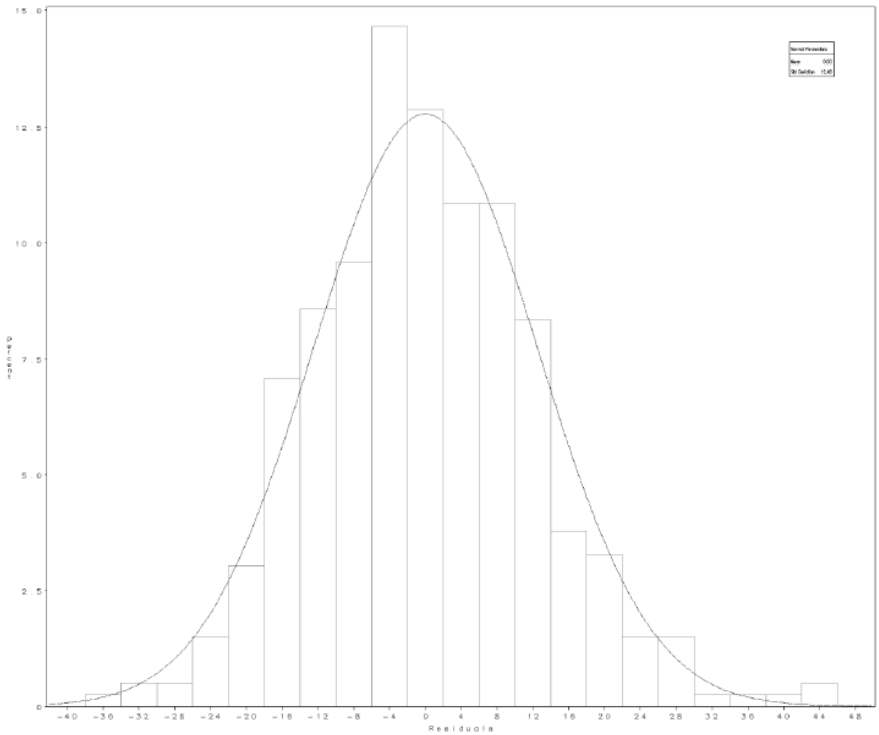


Figure 12. Residuals normality examination: fitting density plot – All treatment groups pooled – Change from baseline to W012 – Full Analysis Set (N=396)

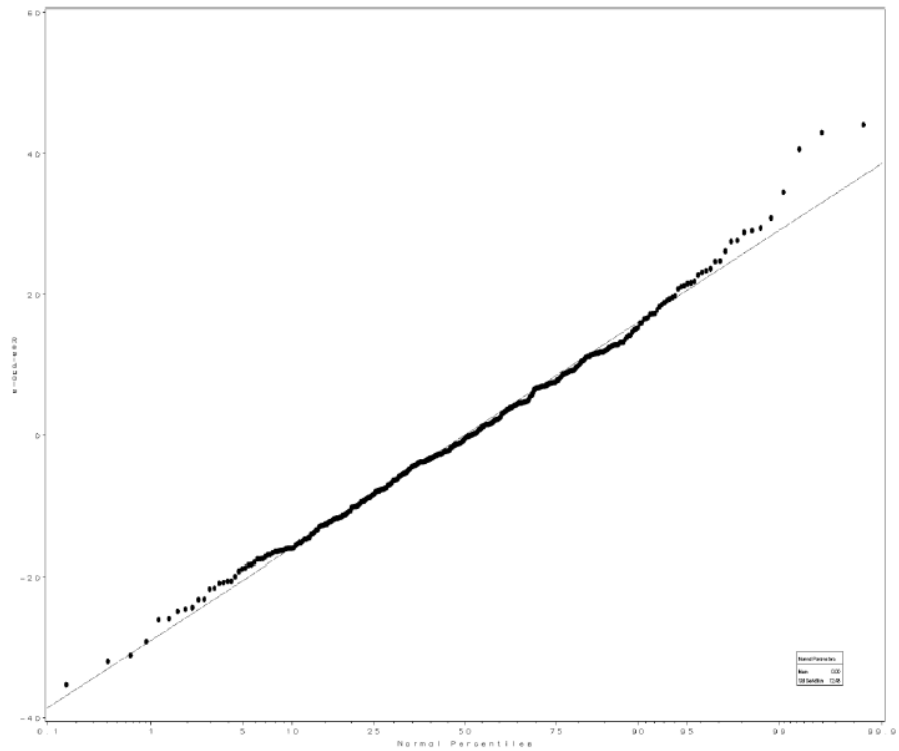


Figure 13. Residuals normality examination: normal probability plot – All treatment groups pooled – Change from baseline to W012 – Full Analysis Set (N=396)

The normality of residuals was also confirmed (Table 14), since less than 5% (17/396 to be verified) of studentized residuals values were outside the [-2 ; 2] interval.

Analysis Variable : RESID Residual	
Planned Treatment for Period 01	Std Dev
Agomelatine 10 mg	12.28
Agomelatine 25 mg	12.61
Fluoxetine	11.50
Placebo	13.64

Table 14. Residuals normality and homoscedasticity examination: Standard deviation per treatment group - Full Analysis Set (N=396)

The homogeneity of variances was also checked using descriptive statistics: the standard deviations of the residuals were quite similar. The assumptions of normality and homoscedasticity of residuals were thus validated for the main analysis model.

Detection of outliers

The objective of this section was to detect potential outliers to detect potential outlying patients. According to the plot of studentized residuals versus predicted values, 3 patients could be considered as outliers, since their values were outside [-3; 3] interval.

The following Table 15 present result of the analysis excluding these patients from the main analysis:

Among these 3 outliers patients, 2 belonged to Agomelatine 10mg group and 1 belonged to Placebo group.

	Statistical model	Placebo minus Agomelatine 10 mg	Placebo minus Agomelatine 25 mg	Placebo minus Fluoxetine
MAIN	ANCOVA model with LOCF approach to handle missing data	E (SE) [(1)] = 3.18 (1.81)	E (SE) [(1)] = 4.22 (1.83)	E (SE) [(1)] = 3.74 (1.81)
Without outlier	ANCOVA model with LOCF approach to handle missing data	E (SE) [(1)] = 3.71 (1.74)	E (SE) [(1)] = 3.81 (1.75)	E (SE) [(1)] = 3.38 (1.73)

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

Table 15. Results of the main analysis in the Full Analysis Set (N=396) and in the FAS without outliers (N=393)

All these patients had a score increase after W002 particularly the Placebo patient (+20 at W012). So by removing these patients the estimates of difference in change from baseline to last post baseline value between treatment group means were slightly different compare to the main analysis:

- Due to one degraded placebo patient less in the analysis, the estimates of the difference in means of Agomelatine 25mg and Fluoxetine were slightly lower.

- Due to two degraded Agomelatine 10mg patients less in the analysis the estimate according to the Placebo was slightly higher.

The model without outliers conducted to estimates and variability softly affected but remained in the same range. Thus, the results of the main analysis were considered validated.

Sensitivity analyses to the missing data handling methods

To assess the robustness of the primary analysis results, several sensitivity analyses were performed:

Mixed Model for Repeated Measurements (MMRM)

First, a Mixed-effects Model for Repeated Measures (MMRM), including the fixed, categorical effects of treatment, age subgroup, country, visit and treatment-by-visit interactions well as the continuous, fixed covariate of baseline was performed.

Type III Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
TRT01PN	3	371.5	4.17	0.0064
BASE	1	394.1	54.46	<.0001
AGEGR1	1	380.1	0.43	0.5122
COUNTRYC	8	380.1	16.48	<.0001
AVISIT	4	375.4	2.56	0.0386
TRT01PN*AVISIT	12	640.8	1.75	0.0525
BASE*AVISIT	4	375.3	11.54	<.0001

Since this MMRM model did not fit correctly data another MMRM including the fixed, categorical effects of treatment, age subgroup, country, visit, treatment-by-visit and baseline by-visit interaction as well as the continuous, fixed covariate of baseline was performed (Table 16).

The baseline-by-visit interaction tested in the model was statistically significant (p<0.0001).

Table 16. Test of Baseline*Visit interaction in the model Y= Treatment Age-class Country Visit Baseline Treatment x Baseline Baseline*Visit - Full Analysis Set (N=396)

Fit statistics	MMRM without baseline-by-visit interaction	MMRM with baseline-by-visit interaction
AIC (smaller is better)	12312.68	12287.45
AICC (smaller is better)	12312.93	12287.71
BIC (smaller is better)	12372.40	12347.17

Table 17. Fit statistics of both Mixed Model for Repeated Measurements

Fit statistics (Table 17) also shown that baseline-by-visit interaction had to be kept in the model. Results of the MMRM including the fixed, categorical effects of treatment, age subgroup, country, visit and treatment-by-visit interaction as well as the continuous, fixed covariate of baseline were presented but considered by the applicant as not relevant. Only the results from the MMRM with the baseline-by-visit interaction added were considered relevant by the applicant, as argued above.

Then, the same ANCOVA as for the primary analysis was performed in patients having a value of CDRS-R raw total score at W012. Multiple imputation with fixed categorical effects of treatment, age subgroup, country, visit: the same ANCOVA as for the primary analysis was also performed on each of the 100 imputed datasets.

The following sensitivity analyses were repeated for the primary efficacy endpoint in adolescent patients of the Full Analysis Set:

- A Mixed-effects Model for Repeated Measures (MMRM), including the fixed, categorical effects of treatment, age subgroup, country, visit, treatment-by-visit and baseline-by-visit interaction as well as the continuous, fixed covariate of baseline.

- A Complete Cases analysis: the same ANCOVA as for the primary analysis was performed in patients having a value of CDRS-R raw total score at W012.

- Multiple imputation with fixed categorical effects of treatment, age subgroup, country, visit: the same ANCOVA as for the primary analysis was performed on each of the 100 imputed datasets.

Multiplicity issues

At W012, the step-down Dunnett's procedure was used to control the familywise error rate, since 2 doses of agomelatine will be compared to placebo. The principle of the stepdown Dunnett's procedure consists in examining the ordered test statistics starting with the most significant one. Here, in the case of 2 comparisons:

- if the most significant test statistic t(2) ≤ c2 (Dunnett critical value for 2 comparisons) then both two null hypotheses were not rejected,

- otherwise the hypothesis H0(2) corresponding to t(2) was rejected and the lowest significant test statistic t(1) was compared to c1 (Dunnett critical value for 1 comparison).

- if t(1) ≤ c1, H0(1) was not rejected otherwise H0(1) was rejected.

Supplementary analyses

The difference between placebo and each agomelatine dose and between placebo and fluoxetine was studied on remission (derived from CDRS-R Raw total score) at W012 using a Chi-Square test. Missing data at W012 were imputed with the LOCF approach.

For these comparisons the following elements was provided in a summary table:

- Estimate (Standard Error) of the difference between the proportions of patients.
- Two-sided 95% CI of the estimate.
- P-value from Chi-2 test (to be compared to 0.05).

Secondary endpoints:

Clinical Global Impression (CGI)

This endpoint was defined as the value at W012 in Severity of Illness (CGI-S) and Global Improvement (CGI-I). The difference between placebo and each agomelatine dose and between placebo and fluoxetine was studied at W012 using a two-sided Student's t-test for independent samples and a Mann-Whitney test. In addition, descriptive statistics at baseline and at each post-baseline visit by treatment group will be provided. Missing data was imputed with the LOCF approach.

For these comparisons the following elements were provided in a summary table:

Estimate (standard error) of the difference between treatment group means, two- sided 95% CI of the estimate, P-value from two-sided Student's t-test for independent (to be compared to 0.05), P-value from Mann-Whitney test (to be compared to 0.05).

Response to treatment

This endpoint was defined as the value at W012 in the response to treatment (based on CGI-I). Missing data was imputed with the LOCF approach. The difference between placebo and each agomelatine dose and between placebo and fluoxetine was studied at W012 using a Chi-Square test. In addition, descriptive statistics at baseline and at each post-baseline visit by treatment group were provided as well as the following elements in a summary table: Estimate (Standard Error) of the difference between the proportions of patients, two-sided 95% CI of the estimate, P- value from Chi-2 test (to be compared to 0.05).

Children's Global Assessment Scale (CGAS)

CGAS total score, was expressed as value at baseline and at each post-baseline visit as well as change from baseline to each post-baseline visit.

Subgroups analysis

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

Children (from 7 to less than 12 at selection),

Adolescents (from 12 to less than 18 at selection).

Comparison tests were computed only in adolescents group, the children group being too small to perform test.

Subgroups analyses were carried out on: The primary endpoint: CDRS-R raw total score, The difference between placebo and each agomelatine dose and between placebo and fluoxetine on depressive symptoms will be studied at W012 by age subgroup, using a two-way ANCOVA model in each subgroup on CDRS-R raw total score, expressed in terms of change from baseline to W012.

Analysis included the fixed, categorical effects of treatment (including the four treatment groups), and country, as well as the continuous, fixed covariate of baseline. Missing data was imputed with the LOCF approach.

Multiplicity was handled in the same way as in the primary analysis. In order to explore the homogeneity of treatment effect among age subgroups on antidepressant efficacy, graphical display (Forest plot) of the overall results and each age subgroup result was provided on the primary endpoint in the FAS.

The secondary endpoints:

CGI-I score

The difference between placebo and each agomelatine dose and between placebo and fluoxetine on global improvement was studied at W012 in the subgroup of adolescents, using a two-sided Student's t-test for independent samples and a Mann-Whitney test in each subgroup on CGI-I score. Missing data was imputed with the LOCF approach.

In order to explore the homogeneity of treatment effect among age subgroups on global improvement, graphical display (Forest plot) of the results of each age subgroup was provided on CGI-I score in the FAS.

Adolescent Depression Rating Scale (ADRS)

The difference between placebo and each agomelatine dose and between placebo and fluoxetine was studied in the subgroup of adolescents at W012 on ADRS total score, using a two-sided Student's t-test for independent samples and a Mann-Whitney test. Missing data at W012 will be imputed with the LOCF approach.

Moreover, description at baseline and at each post-baseline visit as well as change from baseline to each post-baseline visit was provided.

Results

2.4.12. Participant flow

The participant flow in Study CL3-076 is shown in Figure 14 below:

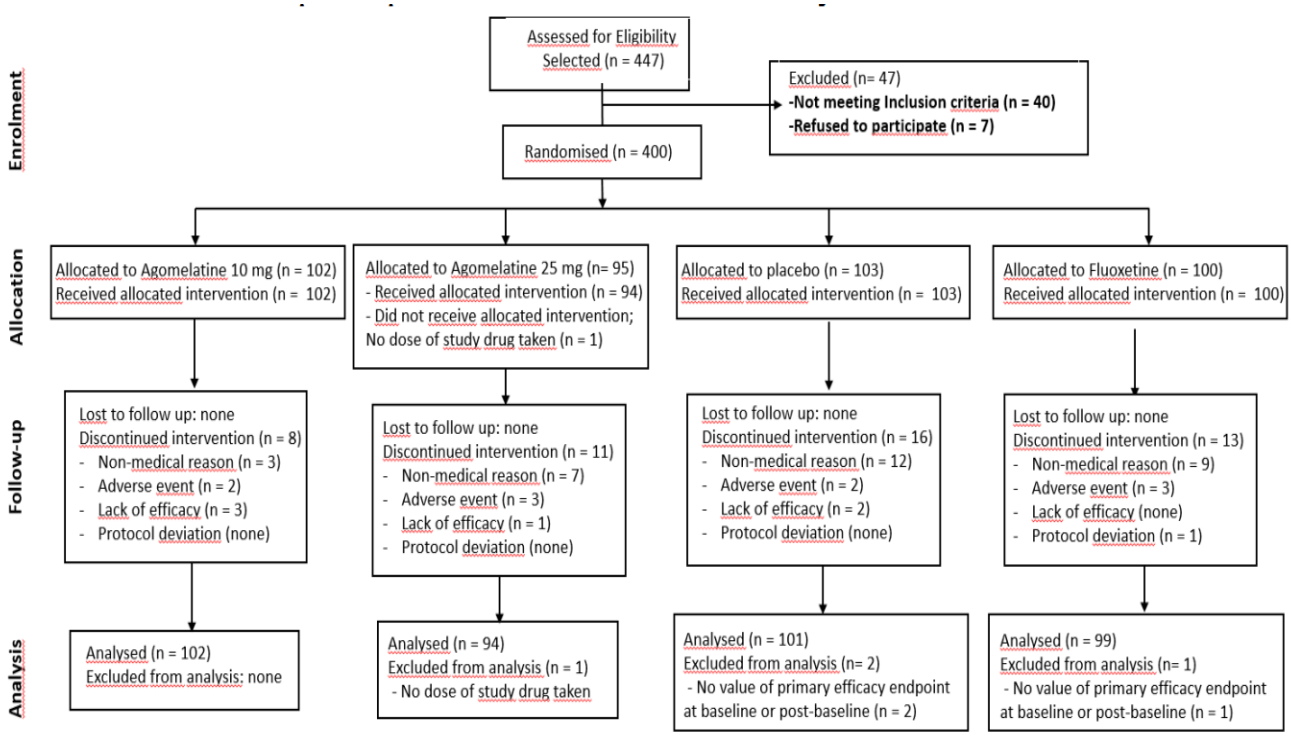


Figure 14. Participant flow in Study CL3-076

Table 18. Patient disposition – Screened patients (N=466)

Status		ALL
SCREENED	**n**	**466**
Selected	n	447
Not Selected	n	19
SELECTED	**n**	**447**
Included	n	400
Excluded	n	47

Table 19. Disposition of included patients by group

Status		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 95)	Placebo (N = 103)	Fluoxetine (N = 100)	ALL (N = 400)
Included	**n**	**102**	**95**	**103**	**100**	**400**
in compliance with the protocol	n (%)	79 (77.5)	63 (66.3)	69 (67.0)	73 (73.0)	284 (71.0)
with a protocol deviation before or at inclusion	n (%)	23 (22.5)	32 (33.7)	34 (33.0)	27 (27.0)	116 (29.0)
Withdrawn due to	**n (%)**	**8 (7.8)**	**11 (11.6)**	**16 (15.5)**	**13 (13.0)**	**48 (12.0)**
non-medical reason	n (%)	3 (2.9)	7 (7.4)	12 (11.7)	9 (9.0)	31 (7.8)
adverse event	n (%)	2 (2.0)	3 (3.2)	2 (1.9)	3 (3.0)	10 (2.5)
lack of efficacy	n (%)	3 (2.9)	1 (1.1)	2 (1.9)	-	6 (1.5)
protocol deviation	n (%)	-	-	-	1 (1.0)	1 (0.3)
Completed	**n (%)**	**94 (92.2)**	**84 (88.4)**	**87 (84.5)**	**87 (87.0)**	**352 (88.0)**
in compliance with the protocol	n (%)	55 (53.9)	54 (56.8)	47 (45.6)	57 (57.0)	213 (53.3)
with a protocol deviation after inclusion	n (%)	39 (38.2)	30 (31.6)	40 (38.8)	30 (30.0)	139 (34.8)

N: number of patients by group
n: number of patients
Percentages are based on n

The patient disposition by visit is shown in Table 20 below:

Table 20. Patient disposition by visit – Modified Randomised Set (N=400)

Visit / Status			Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 95)	Placebo (N = 103)	Fluoxetine (N = 100)	ALL (N = 400)
W000	**INCLUDED**	**n**	**102**	**95**	**103**	**100**	**400**
W001	**WITHDRAWN DUE TO**	**n**	**1**	**1**	-	**1**	**3**
	Adverse event	n	-	-	-	1	1
	Withdrawal non medical reason	n	1	1	-	-	2
	ON-GOING	n	101	94	103	99	397
W002	**WITHDRAWN DUE TO**	**n**	-	**2**	**4**	**4**	**10**
	Adverse event	n	-	-	1	-	1
	Withdrawal non medical reason	n	-	2	3	4	9
	ON-GOING	n	101	92	99	95	387
W004	**WITHDRAWN DUE TO**	**n**	**1**	**3**	**1**	**2**	**7**
	Adverse event	n	1	1	1	-	3
	Withdrawal non medical reason	n	-	2	-	2	4
	ON-GOING	n	100	89	98	93	380
W008	**WITHDRAWN DUE TO**	**n**	**6**	**3**	**7**	**3**	**19**
	Adverse event	n	1	2	-	1	4
	Lack of efficacy	n	3	1	1	-	5
	Withdrawal non medical reason	n	2	-	6	2	10
	ON-GOING	n	94	86	91	90	361
W012	**WITHDRAWN DUE TO**	**n**	-	**2**	**4**	**3**	**9**
	Adverse event	n	-	-	-	1	1
	Lack of efficacy	n	-	-	1	-	1
	Withdrawal non medical reason	n	-	2	3	1	6
	Protocol violation	n	-	-	-	1	1
	COMPLETED	n	94	84	87	87	352

Table 21. Disposition of adolescents of the Modified Randomised Set, by group

Status		Agomelatine 10 mg (N = 81)	Agomelatine 25 mg (N = 76)	Placebo (N = 82)	Fluoxetine (N = 81)	ALL (N = 320)
Included	**n**	**81**	**76**	**82**	**81**	**320**
in compliance with the protocol	n (%)	62 (76.5)	50 (65.8)	54 (65.9)	57 (70.4)	223 (69.7)
with a protocol deviation before or at inclusion	n (%)	19 (23.5)	26 (34.2)	28 (34.1)	24 (29.6)	97 (30.3)
Withdrawn due to	**n (%)**	**8 (9.9)**	**8 (10.5)**	**11 (13.4)**	**10 (12.3)**	**37 (11.6)**
non-medical reason	n (%)	3 (3.7)	5 (6.6)	8 (9.8)	6 (7.4)	22 (6.9)
adverse event	n (%)	2 (2.5)	2 (2.6)	1 (1.2)	3 (3.7)	8 (2.5)
lack of efficacy	n (%)	3 (3.7)	1 (1.3)	2 (2.4)	-	6 (1.9)
protocol deviation	n (%)	-	-	-	1 (1.2)	1 (0.3)
Completed	**n (%)**	**73 (90.1)**	**68 (89.5)**	**71 (86.6)**	**71 (87.7)**	**283 (88.4)**
in compliance with the protocol	n (%)	43 (53.1)	43 (56.6)	40 (48.8)	46 (56.8)	172 (53.8)
with a protocol deviation after inclusion	n (%)	30 (37.0)	25 (32.9)	31 (37.8)	25 (30.9)	111 (34.7)

N: number of patients by group
n: number of patients
Percentages are based on n

2.4.13. Recruitment

The study was initiated 23 February 2016 (first visit first patient) and the 12-week double-blind period was completed 14 January 2020. The completion date of the open extension-phase was 27 October 2021 (last visit last patient).

Database lock:

Double-blind period date: 25 February 2020

Open-label period date: 29 November 2021

In all, 46 centres in 9 countries included 400 patients: 120 patients in Russia (8 centres), 74 patients in Hungary (5 centres), 72 patients in Ukraine (10 centres), 61 patients in Romania (6 centres), 31 patients in Poland (4 centres), 17 patients in South Africa (4 centres), 10 patients in Serbia (4 centres), 9 patients in Bulgaria (3 centres) and 6 patients in Finland (2 centres).

2.4.14. Conduct of the study

Protocol amendments

Two substantial amendments of the protocol were issued for this study:

Amendment No. 1, dated 19 September 2016, was applicable in all centres and countries, for patients already enrolled in the study and for new patients. It mainly concerned:

- Supplementary non-inclusion criteria for liver function:
  - Free bilirubin ≥ 2 ULN, to exclude patients with Gilbert-syndrome who could present unpredictable timing and level of free bilirubin levels.
  - ALP and GGT > 1 ULN, to exclude patients in normal growth but with potential hepatic enzyme alterations.

- In the inclusion criteria: the selection criteria on scale scores which had to be still fulfilled were specified in the text (i.e., CDRS-R Raw score ≥ 45 and CGI-Severity rating score ≥ 4).

Measures concerning liver function tests:

- Liver function tests (AST, ALT, total bilirubin, free bilirubin, conjugated bilirubin, ALP, GGT) were added during double-blind period (W004) and during open label extension period (W014, W048 and W068).
    - Close monitoring through blood samplings re-tests in case of abnormalities observed on ALT/AST, bilirubin, ALP or GGT was defined as a monitoring every two weeks.
    - In case of ALT/AST > 2 ULN under study treatment, a monitoring was organised every two weeks until values return to normal/baseline values.
    - Additional investigations which were to be performed in case of AST and/or ALT > 3 ULN were described in detail.
- PAERS (Paediatric Adverse Event Rating Scale) was added as individual safety assessment in addition to AEs.

Amendment No. 2, dated 13 December 2019, was applicable in all centres and countries, for all patients already enrolled in the study. It mainly concerned:

- Integration of agreed modifications on the Paediatric Investigation Plan by EMA:
    - decreased sample size (at least 390 patients instead of 484) and adapted statistical analysis including the modifications of subgroup analyses of primary endpoint and the update of statistical patient sets (at least 312 adolescents, with no requirement on children population).
- Update of the total number of centres (63 instead of 67) and the list of participating countries (deletion of Germany and addition of Serbia).

Protocol deviations

Protocol deviations before, at and after inclusion were summarised and reviewed.

2.4.15. Baseline data

Table 22. Main demographic data in the Modified Randomised Set

			Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 95)	Placebo (N = 103)	Fluoxetine (N = 100)	ALL (N = 400)
Age (years)		n	102	95	103	100	400
		Mean ± SD	13.6 ± 2.9	13.4 ± 2.7	13.8 ± 2.6	13.8 ± 2.7	13.7 ± 2.7
		Median	14.0	14.0	15.0	14.0	14.0
		Min ; Max	7 ; 17	7 ; 17	7 ; 17	7 ; 17	7 ; 17
	Children	n	21	19	21	19	80
	Adolescents	n	81	76	82	81	320
Gender	Women	n (%)	68 (66.7)	61 (64.2)	64 (62.1)	57 (57.0)	250 (62.5)
	Men	n (%)	34 (33.3)	34 (35.8)	39 (37.9)	43 (43.0)	150 (37.5)
Number of years of school education		n	102	95	103	100	400
		Mean ± SD	7.2 ± 2.9	7.0 ± 2.7	7.4 ± 2.7	7.4 ± 2.7	7.3 ± 2.7
		Median	8.0	8.0	8.0	8.0	8.0
		Min ; Max	0 ; 11	0 ; 12	0 ; 12	1 ; 12	0 ; 12
Weight, before current depressive episode (kg)		n	101	89	99	93	382
		Mean ± SD	52.49 ± 15.41	53.27 ± 14.39	53.39 ± 15.82	54.07 ± 15.47	53.29 ± 15.25
		Median	51.30	54.60	54.00	55.00	54.00
		Min ; Max	21.0 ; 106.0	22.0 ; 90.0	25.00; 100.0	21.0 ; 100.0	21.0 ; 106.0
Current Weight (kg)		n	102	95	103	100	400
		Mean ± SD	52.65 ± 15.68	52.79 ± 13.90	53.32 ± 16.95	53.49 ± 15.54	53.07 ± 15.53
		Median	51.95	54.00	53.60	54.55	53.00
		Min ; Max	21.00; 103.0	22.0 ; 87.0	23.00; 116.0	21.00; 104.0	21.0 ; 116.0
Height (cm)		n	102	95	103	100	400
		Mean ± SD	159.4 ± 13.7	159.6 ± 13.3	159.8 ± 14.1	160.0 ± 13.8	159.7 ± 13.7
		Median	163.0	163.0	163.0	163.0	163.0
		Min ; Max	122 ; 185	124 ; 196	127 ; 186	119 ; 186	119 ; 196
BMI (kg/m²)		n	102	95	103	100	400
		Mean ± SD	20.35 ± 4.22	20.46 ± 3.97	20.40 ± 4.31	20.50 ± 3.89	20.42 ± 4.09
		Median	19.00	20.20	19.90	20.10	19.85
		Min ; Max	13.9 ; 34.4	12.3 ; 36.7	12.8 ; 35.0	13.8 ; 35.0	12.3 ; 36.7
BMI (kg/m²) in classes*		n	102	95	103	100	400
Underweight (< -2SD)		n (%)	5 (4.9)	5 (5.3)	4 (3.9)	4 (4.0)	18 (4.5)
Normal range ([-2SD ; +1SD])		n (%)	72 (70.6)	67 (70.5)	75 (72.8)	72 (72.0)	286 (71.5)
Overweight (]+1SD ; +2SD])		n (%)	14 (13.7)	17 (17.9)	17 (16.5)	18 (18.0)	66 (16.5)
Obese (> +2SD)		n (%)	11 (10.8)	6 (6.3)	7 (6.8)	6 (6.0)	30 (7.5)

** The BMI classes were defined using the WHO Standards (2017) according to the sex and the age in months.*

Table 23. Main demographic data in the adolescents of the Modified Randomised Set

			Agomelatine 10 mg (N = 81)	Agomelatine 25 mg (N = 76)	Placebo (N = 82)	Fluoxetine (N = 81)	ALL (N = 320)
Age (years)		n	81	76	82	81	320
		Mean ± SD	14.8 ± 1.6	14.5 ± 1.5	14.9 ± 1.5	14.9 ± 1.6	14.8 ± 1.6
		Median	15.0	15.0	15.0	15.0	15.0
		Min ; Max	12 ; 17	12 ; 17	12 ; 17	12 ; 17	12 ; 17
Gender	Women	n (%)	63 (77.8)	50 (65.8)	56 (68.3)	49 (60.5)	218 (68.1)
	Men	n (%)	18 (22.2)	26 (34.2)	26 (31.7)	32 (39.5)	102 (31.9)
Number of years of school education		n	81	76	82	81	320
		Mean ± SD	8.4 ± 1.6	8.1 ± 1.7	8.5 ± 1.6	8.4 ± 1.8	8.4 ± 1.7
		Median	9.0	8.0	9.0	9.0	9.0
		Min ; Max	5 ; 11	4 ; 12	5 ; 12	4 ; 12	4 ; 12
Weight, before current depressive episode (kg)		n	81	71	80	75	307
		Mean ± SD	57.09 ± 13.00	58.33 ± 10.97	58.79 ± 12.36	59.05 ± 12.44	58.30 ± 12.21
		Median	55.00	58.00	56.00	56.40	56.00
		Min ; Max	37.5 ; 106.0	38.30 ; 90.0	35.30 ; 100.0	30.00 ; 100.0	30.0 ; 106.0
Current Weight (kg)		n	81	76	82	81	320
		Mean ± SD	57.34 ± 13.28	57.31 ± 11.01	59.07 ± 13.82	58.19 ± 12.88	57.99 ± 12.78
		Median	53.00	55.70	56.15	56.40	55.45
		Min ; Max	36.5 ; 103.0	36.5 ; 87.0	35.0 ; 116.0	31.9 ; 104.0	31.9 ; 116.0
Height (cm)		n	81	76	82	81	320
		Mean ± SD	165.1 ± 7.6	164.7 ± 8.3	165.5 ± 8.7	165.2 ± 8.1	165.2 ± 8.2
		Median	165.0	164.0	165.0	165.0	165.0
		Min ; Max	146 ; 185	146 ; 196	143 ; 186	140 ; 186	140 ; 196
BMI (kg/m²)		n	81	76	82	81	320
		Mean ± SD	20.95 ± 4.18	21.13 ± 3.87	21.44 ± 4.07	21.19 ± 3.79	21.18 ± 3.97
		Median	19.30	20.50	20.85	20.30	20.35
		Min ; Max	14.7 ; 34.4	15.6 ; 36.7	14.7 ; 35.0	15.5 ; 35.0	14.7 ; 36.7
BMI (kg/m²) in classes*		n	81	76	82	81	320
Underweight (< -2SD)		n (%)	5 (6.2)	4 (5.3)	2 (2.4)	3 (3.7)	14 (4.4)
Normal range ([-2SD ; +1SD])		n (%)	58 (71.6)	56 (73.7)	61 (74.4)	61 (75.3)	236 (73.8)
Overweight (]+1SD ; +2SD])		n (%)	10 (12.3)	12 (15.8)	12 (14.6)	12 (14.8)	46 (14.4)
Obese (> +2SD)		n (%)	8 (9.9)	4 (5.3)	7 (8.5)	5 (6.2)	24 (7.5)

** The BMI classes were defined using the WHO Standards (2017) according to the sex and the age in months.*

Table 24. Main baseline data on history of major depression disorder in the Modified Randomised Set

		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 95)	Placebo (N = 103)	Fluoxetine (N = 100)	ALL (N = 400)
Current episode duration [a] (days)	n	102	95	103	100	400
	Mean ± SD	181.2 ± 210.0	129.1 ± 138.0	137.0 ± 130.5	125.2 ± 109.2	143.4 ± 153.2
	Median	116.5	90.0	91.0	90.5	96.0
	Min ; Max	30 ; 1463	29 ; 961	30 ; 882	35 ; 705	29 ; 1463
Patients with history of previous MDE	n (%)	22 (21.6)	24 (25.3)	37 (35.9)	31 (31.0)	114 (28.5)
Number of MDE [b] (before the current one)	Mean ± SD	1.3 ± 0.5	1.5 ± 0.7	1.4 ± 0.8	1.4 ± 0.7	1.4 ± 0.7
	Median	1.0	1.0	1.0	1.0	1.0
	Min ; Max	1 ; 2	1 ; 3	1 ; 5	1 ; 4	1 ; 5
Duration between previous and current episode [c] (days)	Mean ± SD	402.2 ± 427.9	288.6 ± 275.9	541.9 ± 454.5	421.6 ± 349.9	428.9 ± 395.4
	Median	210.5	190.5	395.0	318.0	306.0
	Min ; Max	75 ; 1571	39 ; 1081	24 ; 1817	40 ; 1342	24 ; 1817
Duration of last episode [d] (days)	Mean ± SD	177.7 ± 222.6	137.1 ± 132.0	174.3 ± 167.4	114.6 ± 93.5	150.9 ± 157.2
	Median	111.0	101.5	115.0	89.0	100.0
	Min ; Max	24 ; 852	1 ; 639	21 ; 783	1 ; 367	1 ; 852
Patients' first-degree relatives mood disorders experimentation	n (%)	20 (19.6)	18 (18.9)	20 (19.4)	14 (14.0)	72 (18.0)
Diagnosis according to DSM-IV-TR criteria						
Single episode	n (%)	80 (78.4)	71 (74.7)	66 (64.1)	69 (69.0)	286 (71.5)
Recurrent episode	n (%)	22 (21.6)	24 (25.3)	37 (35.9)	31 (31.0)	114 (28.5)
Criteria of Severity						
Moderate	n (%)	74 (72.5)	56 (58.9)	58 (56.3)	59 (59.0)	247 (61.8)
Severe Without Psychotic Features	n (%)	28 (27.5)	39 (41.1)	45 (43.7)	41 (41.0)	153 (38.3)
Chronic specifier	n (%)	4 (3.9)	3 (3.2)	1 (1.0)	-	8 (2.0)
Catatonic features specifier	n (%)	-	-	1 (1.0)	-	1 (0.3)
Melancholic features specifier	n (%)	18 (17.6)	15 (15.8)	20 (19.4)	20 (20.0)	73 (18.3)
Atypical features specifier	n (%)	2 (2.0)	-	2 (1.9)	1 (1.0)	5 (1.3)
Post partum onset specifier	n (%)	-	-	-	-	-
Seasonal pattern specifier	n (%)	2 (2.0)	2 (2.1)	3 (2.9)	1 (1.0)	8 (2.0)
Diagnosis criteria for dysthymic disorder	n (%)	1 (1.0)	-	1 (1.0)	-	2 (0.5)
Columbia-suicide severity rating scale for children						
Actual suicide attempt	n (%)	4 (3.9)	5 (5.3)	2 (1.9)	2 (2.0)	13 (3.3)
Preparatory actions toward imminent suicidal behaviour	n (%)	1 (1.0)	4 (4.2)	1 (1.0)	1 (1.0)	7 (1.8)
Suicidal ideation or behaviour	n (%)	26 (25.5)	21 (22.1)	22 (21.4)	23 (23.0)	92 (23.0)
Suicidal ideation	n (%)	26 (25.5)	21 (22.1)	22 (21.4)	23 (23.0)	92 (23.0)
Suicidal behaviour	n (%)	4 (3.9)	6 (6.3)	2 (1.9)	2 (2.0)	14 (3.5)
Self-injurious behaviour without suicidal intent	n (%)	12 (11.8)	9 (9.5)	10 (9.7)	14 (14.0)	45 (11.3)

[a] *Date of selection visit - Date of diagnosis of the current Major Depressive Episode +1*
[b] *From the first occurrence until current episode*
[c] *Duration between the previous episode end and the current episode start (days)*
[d] *Before current episode (days)*

According to the diagnosis M.I.N.I-KID the most common psychiatric comorbidities at baseline were (Modified Randomised Set):

- Suicidality (current [past month]): in total 124/400, 31.0%, and this was fairly balanced between the 4 treatment groups. Of patients with suicidality, 39/124 (31.0%) was characterised as moderate (lowest number in the agomelatine 10 mg group, 6/95, 21.4%).
- Social phobia (Separation Anxiety Disorder) (current [past month]): in total 36/400 (9.0%), highest in the agomelatine 25 mg group (13/95, 13.7%).
- Specific phobia (current [past month]): in total 21/400, 5.3%, highest in the agomelatine 10 mg and 25 groups (8/102, 7.8% vs. 7/95, 7.4%, respectively).
- Generalised anxiety disorder (current [past 6 months]): in total 23/400, 5.8%, highest in the agomelatine 10 mg and 25 mg groups (9/102, 8.8% vs. 7/95, 7.4%, respectively).
- Agoraphobia (current): in total 16/400, 4.0%, highest in the agomelatine 25 mg group (8/95, 8.4%).
- ADHD combined (past 6 months): in total 15/400, 3.8%, highest in the agomelatine 25 mg group (6/95, 6.3%).

Table 25. Main baseline data on history of major depressive disorder in the adolescents of the Modified Randomised Set

		Agomelatine 10 mg (N = 81)	Agomelatine 25 mg (N = 76)	Placebo (N = 82)	Fluoxetine (N = 81)	ALL (N = 320)
Current episode duration [a] (days)	n	81	76	82	81	320
	Mean ± SD	198.5 ± 229.6	134.7 ± 152.1	137.3 ± 136.5	129.8 ± 116.5	150.3 ± 166.1
	Median	121.0	84.5	89.0	97.0	97.0
	Min ; Max	30 ; 1463	29 ; 961	30 ; 882	35 ; 705	29 ; 1463
Patients with history of previous MDE	n (%)	20 (24.7)	21 (27.6)	37 (45.1)	27 (33.3)	105 (32.8)
Number of MDE [b] (before the current one)	Mean ± SD	1.3 ± 0.5	1.5 ± 0.7	1.4 ± 0.8	1.4 ± 0.7	1.4 ± 0.7
	Median	1.0	1.0	1.0	1.0	1.0
	Min ; Max	1 ; 2	1 ; 3	1 ; 5	1 ; 4	1 ; 5
Duration between previous and current episode [c] (days)	Mean ± SD	424.5 ± 442.2	262.8 ± 264.5	541.9 ± 454.5	396.6 ± 354.5	426.4 ± 403.1
	Median	210.5	182.0	395.0	274.0	280.0
	Min ; Max	75 ; 1571	39 ; 1081	24 ; 1817	40 ; 1342	24 ; 1817
Duration of last episode [d] (days)	Mean ± SD	190.2 ± 230.1	111.6 ± 81.9	174.3 ± 167.4	100.4 ± 89.9	145.8 ± 155.3
	Median	119.0	91.0	115.0	62.0	93.0
	Min ; Max	24 ; 852	1 ; 274	21 ; 783	1 ; 367	1 ; 852
Patients' first degree relatives mood disorders experimentation	n (%)	17 (21.0)	15 (19.7)	15 (18.3)	7 (8.6)	54 (16.9)
Diagnosis according to DSM-IV-TR criteria						
Single episode	n (%)	61 (75.3)	55 (72.4)	45 (54.9)	54 (66.7)	215 (67.2)
Recurrent episode	n (%)	20 (24.7)	21 (27.6)	37 (45.1)	27 (33.3)	105 (32.8)
Criteria of Severity						
Moderate	n (%)	56 (69.1)	42 (55.3)	44 (53.7)	45 (55.6)	187 (58.4)
Severe Without Psychotic Features	n (%)	25 (30.9)	34 (44.7)	38 (46.3)	36 (44.4)	133 (41.6)
Chronic specifier	n (%)	4 (4.9)	3 (3.9)	1 (1.2)	-	8 (2.5)
Catatonic features specifier	n (%)	-	-	1 (1.2)	-	1 (0.3)
Melancholic features specifier	n (%)	18 (22.2)	14 (18.4)	17 (20.7)	18 (22.2)	67 (20.9)
Atypical features specifier	n (%)	2 (2.5)	-	1 (1.2)	1 (1.2)	4 (1.3)
Post partum onset specifier	n (%)	-	-	-	-	-
Seasonal pattern specifier	n (%)	2 (2.5)	2 (2.6)	3 (3.7)	1 (1.2)	8 (2.5)
Diagnosis criteria for dysthymic disorder	n (%)	1 (1.2)	-	1 (1.2)	-	2 (0.6)
Columbia-suicide severity rating scale for children						
Actual suicide attempt	n (%)	4 (4.9)	5 (6.6)	2 (2.4)	2 (2.5)	13 (4.1)
Preparatory actions toward imminent suicidal behaviour	n (%)	1 (1.2)	4 (5.3)	1 (1.2)	1 (1.2)	7 (2.2)
Suicidal ideation or behaviour	n (%)	22 (27.2)	18 (23.7)	18 (22.0)	22 (27.2)	80 (25.0)
Suicidal ideation	n (%)	22 (27.2)	18 (23.7)	18 (22.0)	22 (27.2)	80 (25.0)
Suicidal behaviour	n (%)	4 (4.9)	6 (7.9)	2 (2.4)	2 (2.5)	14 (4.4)
Self-injurious behaviour without suicidal intent	n (%)	12 (14.8)	8 (10.5)	9 (11.0)	14 (17.3)	43 (13.4)

[a] *Date of selection visit - Date of diagnosis of the current Major Depressive Episode +1;* [b] *From the first occurrence until current episode*
[c] *Duration between the previous episode end and the current episode start (days);* [d] *Before current episode (days)*

Smoking

At the time of the study, 24 patients (6.0%) of the MRS were current smokers for an average ± SD of 1.6 ± 1.0 years (range from 0 to 5 years) with a median tobacco consumption of 5 cigarettes/day (range

from 1 to 40 cigarettes/day). The mean consumption of cigarettes/day was highest in the placebo group, i.e., 14.1 ± 13.5 and with a range of 3 to 40 cigarettes.

Table 26. Baseline scores of rating scales in the Modified Randomised Set

		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 95)	Placebo (N = 103)	Fluoxetine (N = 100)	ALL (N = 400)
CDRS-R raw total score	n	102	95	103	100	400
	Mean ± SD	64.3 ± 8.3	65.3 ± 8.3	67.4 ± 8.6	64.9 ± 7.9	65.5 ± 8.4
	Median	63.5	65.0	66.0	65.0	65.0
	Min ; Max	46 ; 87	52 ; 90	49 ; 93	47 ; 89	46 ; 93
CGI-S score	n	102	95	103	100	400
	Mean ± SD	4.7 ± 0.6	4.8 ± 0.7	5.0 ± 0.6	4.9 ± 0.6	4.9 ± 0.6
	Median	5.0	5.0	5.0	5.0	5.0
	Min ; Max	4 ; 6	4 ; 6	4 ; 6	4 ; 6	4 ; 6
CGAS score	n	102	95	103	100	400
	Mean ± SD	47.5 ± 7.8	45.9 ± 9.1	45.4 ± 7.8	47.2 ± 7.9	46.5 ± 8.2
	Median	48.0	45.0	45.0	47.0	46.0
	Min ; Max	30 ; 66	25 ; 66	23 ; 68	31 ; 67	23 ; 68

Table 27. Baseline scores of rating scales in the adolescents of the Modified Randomised Set

		Agomelatine 10 mg (N = 81)	Agomelatine 25 mg (N = 76)	Placebo (N = 82)	Fluoxetine (N = 81)	ALL (N = 320)
CDRS-R raw total score	n	81	76	82	81	320
	Mean ± SD	64.5 ± 8.3	65.9 ± 8.7	68.1 ± 8.7	65.2 ± 8.1	65.9 ± 8.5
	Median	64.0	65.0	68.0	65.0	65.0
	Min ; Max	46 ; 87	52 ; 90	49 ; 93	47 ; 89	46 ; 93
CGI-S score	n	81	76	82	81	320
	Mean ± SD	4.8 ± 0.6	4.9 ± 0.7	5.0 ± 0.7	4.9 ± 0.6	4.9 ± 0.6
	Median	5.0	5.0	5.0	5.0	5.0
	Min ; Max	4 ; 6	4 ; 6	4 ; 6	4 ; 6	4 ; 6
CGAS score	n	81	76	82	81	320
	Mean ± SD	46.8 ± 7.3	44.8 ± 8.4	45.5 ± 7.8	47.0 ± 7.8	46.0 ± 7.8
	Median	48.0	45.0	45.0	46.0	45.0
	Min ; Max	31 ; 66	25 ; 65	23 ; 68	31 ; 61	23 ; 68
ADRS total score	n	81	76	82	81	320
	Mean ± SD	31.6 ± 5.6	32.6 ± 6.0	34.6 ± 6.1	33.5 ± 6.0	33.1 ± 6.0
	Median	32.0	33.0	34.0	34.0	33.0
	Min ; Max	20 ; 52	16 ; 48	22 ; 48	14 ; 46	14 ; 52

Previous treatments

A total of 123 patients (30.8%) had received at least one previous treatment. These treatments mainly concerned:

- Psychoanaleptics (19.8% of patients), mostly antidepressants (18.3%), with a lower rate in the active treatment groups (15.7% to 18.0%) than in the placebo group (22.3%).
    - Of the antidepressants, SSRIs were most commonly used (in total 16.5%; 14.7% in the two agomelatine groups vs. 20.4% in the placebo group and 16.0% in the fluoxetine group). Sertraline was most frequently used (12.8% in the agomelatine 10 mg group, 11.6% in the agomelatine 25 mg, 14.6% in the placebo group and 10.0% in the fluoxetine group). Fluoxetine had only been used by 1 patient in each of the groups agomelatine 10 mg and 25 mg vs. 2 patients in the fluoxetine group.
- Psycholeptics (16.8%) with a lower rate in the agomelatine 10 mg group (11.8%) than in the other 3 groups (between 16.0% and 21.4%, according to treatment group).
    - Anxiolytics (11.5%) and antipsychotics (7.5%) were the most frequently reported treatments in this pharmacological class.

A total of 28 patients had previously received at least one kind of psychotherapy (cognitive behaviour, group therapy, supportive therapy and other) with a lower number in the agomelatine groups (4 and 5 patients in the 10 mg and 25 mg groups, respectively) than in the placebo group (9 patients). The number of patients with previous psychotherapy was similar in fluoxetine and placebo group.

Concomitant treatments

Psychotropic concomitant treatments during the treatment period

A total of 12 patients of the MRS (3.0%) received psychotropic concomitant treatments during the treatment period, mainly methylphenidate (8 patients [2.0%]) without relevant difference between groups.

Concomitant psychotherapies during the treatment period

At inclusion, 3 patients received at least one concomitant psychotherapy for more than 3 months and these 3 patients continued this treatment during the double-blind period.

Referral to the study

A psychiatrist referred more than half of the patients of the MRS (54.3%) or spontaneously in 29.5% of patients. General practitioner/other specialist as well as psychologist referred 7.5% of patients, each. Only 1.3% of patients were referred following advertisement. A total of 115 patients (28.8%) had previously been treated by investigator with a higher frequency in the agomelatine 25 mg group (34.7%) as compared to the other 3 groups (between 25.0% and 28.2% according to treatment group).

Psychosocial counselling

Table *28* below presents the number and rate of patients participating in the Manualized Psychosocial Counselling session at each visit. At W000, all patients had participated in one session. Patients had to be considered as non-responders to be included in the study.

Table 28. Manualised Psychosocial Counselling session at each visit in the Modified Randomised Set

			Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 95)	Placebo (N = 103)	Fluoxetine (N = 100)	ALL (N = 400)
W000		n	102	95	103	100	400
	No	n (%)	-	-	-	-	-
	Yes	n (%)	102 (100.0)	95 (100.0)	103 (100.0)	100 (100.0)	400 (100.0)
W004		n	101	92	99	95	387
	No	n (%)	2 (2.0)	3 (3.3)	2 (2.0)	1 (1.1)	8 (2.1)
	Yes	n (%)	99 (98.0)	89 (96.7)	97 (98.0)	94 (98.9)	379 (97.9)
W008		n	100	89	98	93	380
	No	n (%)	5 (5.0)	2 (2.2)	7 (7.1)	2 (2.2)	16 (4.2)
	Yes	n (%)	95 (95.0)	87 (97.8)	91 (92.9)	91 (97.8)	364 (95.8)
W012		n	94	86	91	90	361
	No	n (%)	-	2 (2.3)	1 (1.1)	3 (3.3)	6 (1.7)
	Yes	n (%)	94 (100.0)	84 (97.7)	90 (98.9)	87 (96.7)	355 (98.3)

2.4.16. Numbers analysed

Table 29. Patients disposition

Double blinded period (12 weeks)						
		Agomelatine 10 mg	**Agomelatine 25 mg**	**Placebo**	**Fluoxetine 10-20 mg**	**ALL**
Included						
Overall paediatric population [adolescents]	**n [n']**	**102 [81]**	**95 [76]**	**103 [82]**	**100 [81]**	**400 [320]**
Withdrawn due to	**n (%)[a]**	**8 (7.8)**	**11 (11.6)**	**16 (15.5)**	**13 (13.0)**	**48 (12.0)**
- non-medical reason	n (%)[a]	3 (2.9)	7 (7.4)	12 (11.7)	9 (9.0)	31 (7.8)
- adverse event	n (%)[a]	2 (2.0)	3 (3.2)	2 (1.9)	3 (3.0)	10 (2.5)
- lack of efficacy	n (%)[a]	3 (2.9)	1 (1.1)	2 (1.9)	-	6 (1.5)
- protocol deviation	n (%)[a]	-	-	-	1 (1.0)	1 (0.3)
Completed	**n (%)[a]**	**94 (92.2)**	**84 (88.4)**	**87 (84.5)**	**87 (87.0)**	**352 (88.0)**
Modified Randomised Set	**n (%)**	**102 (25.5)[b]**	**95 (23.8)[b]**	**103 (25.8)[b]**	**100 (25.0)[b]**	**400 (100%)**
Full Analysis Set	**n (%)**	**102 (25.8)[b]**	**94 (23.7)[b]**	**101 (25.5)[b]**	**99 (25.0)[b]**	**396 (99.0)[c]**
Safety set (SS)	**n (%)**	**102 (25.6)[b]**	**94 (23.6)[b]**	**103 (25.8)[b]**	**100 (25.1)[b]**	**399 (99.8)[c]**

Treatment duration and compliance

Table 30. Treatment duration (days) in the Safety Set

			Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 103)	Fluoxetine (N = 100)	ALL (N = 399)
Treatment duration (days)	n		102	94	102	99	397
	Mean ± SD		81.7 ± 14.2	80.5 ± 15.6	79.7 ± 16.1	79.0 ± 18.0	80.2 ± 16.0
	Median		85.0	85.0	85.0	85.0	85.0
	Min ; Max		10 ; 97	14 ; 92	14 ; 95	6 ; 91	6 ; 97
	< 80 days	n (%)	10 (9.8)	9 (9.6)	13 (12.7)	13 (13.1)	45 (11.3)
	[80 - 88[days	n (%)	81 (79.4)	79 (84.0)	84 (82.4)	82 (82.8)	326 (82.1)
	> 88 days	n (%)	11 (10.8)	6 (6.4)	5 (4.9)	4 (4.0)	26 (6.5)

Treatment duration (days): Date of the last IMP intake on the concerned period - Date of the first IMP intake +1

In the Safety Set (SS), the tablet compliance was on average of 95.7 ± 10.6% and ranged from 16.6% to 104.7%. Overall, 96.6% of patients had a tablet compliance between 70% and 130%. In the SS, the oral solution compliance was on average of 96.4 ± 13.8% and ranged from 16.6% to 175.6%. In the total population, 94.5% of patients had an oral solution compliance between 70% and 130%. No relevant difference between groups was observed for these parameters.

The same pattern as reported for the total population, in regards to both treatment duration and compliance, was also observed for the adolescent subset.

2.4.17. Outcomes and estimation

Primary endpoint

Results of the primary analysis on CDRS-R total score expressed in terms of adjusted difference (by using an ANCOVA model) from baseline to last post-baseline value (W012) in the FAS are presented by treatment group in Table 31 below.

Table 31. CDRS-R raw total score – Comparison between groups – Main analysis: change from baseline to last post-baseline value – FAS

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

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

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

(2) 95% Confidence interval of the estimate

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

Change in CDRS-R from baseline to each post-baseline visit and last post baseline visit is given in Table 32 below.

Table 32. CDRS-R raw total score – FAS – Change from baseline to each post baseline visit and last post baseline visit

		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 101)	Fluoxetine (N = 99)
W001 - BASELINE	n	102	93	100	99
	Mean ± SD	-4.7 ± 6.8	-5.2 ± 6.6	-4.2 ± 5.7	-5.8 ± 7.6
	Median	-2.5	-3.0	-3.0	-3.0
	Q1 ; Q3	-6.0 ; -1.0	-8.0 ; -1.0	-6.0 ; -1.0	-9.0 ; -1.0
	Min ; Max	-32 ; 9	-34 ; 4	-27 ; 6	-45 ; 4
W002 - BASELINE	n	100	94	100	98
	Mean ± SD	-8.7 ± 10.1	-10.5 ± 9.5	-7.4 ± 8.2	-10.5 ± 10.1
	Median	-5.0	-9.0	-5.0	-8.0
	Q1 ; Q3	-13.0 ; -2.0	-13.0 ; -3.0	-11.0 ; -2.0	-16.0 ; -3.0
	Min ; Max	-50 ; 3	-45 ; 2	-41 ; 8	-49 ; 7
W004 - BASELINE	n	100	92	99	94
	Mean ± SD	-12.5 ± 11.3	-15.1 ± 11.5	-12.4 ± 10.0	-16.4 ± 12.6
	Median	-10.5	-13.0	-11.0	-13.0
	Q1 ; Q3	-17.0 ; -4.0	-21.0 ; -6.0	-17.0 ; -5.0	-27.0 ; -5.0
	Min ; Max	-56 ; 12	-50 ; 1	-43 ; 6	-48 ; 5
W008 - BASELINE	n	98	89	93	92
	Mean ± SD	-17.8 ± 12.8	-20.1 ± 13.8	-17.2 ± 13.3	-19.0 ± 13.8
	Median	-16.5	-19.0	-15.0	-17.0
	Q1 ; Q3	-25.0 ; -8.0	-28.0 ; -9.0	-25.0 ; -7.0	-27.5 ; -8.0
	Min ; Max	-59 ; 9	-64 ; 2	-52 ; 17	-51 ; 7
W012 - BASELINE	n	94	84	91	89
	Mean ± SD	-21.8 ± 13.9	-24.4 ± 14.8	-21.3 ± 14.1	-22.6 ± 13.9
	Median	-22.0	-22.0	-22.0	-22.0
	Q1 ; Q3	-30.0 ; -12.0	-33.0 ; -14.0	-30.0 ; -11.0	-33.0 ; -11.0
	Min ; Max	-59 ; 15	-66 ; 0	-52 ; 20	-53 ; 5
LAST POST-BASELINE VALUE - BASELINE	n	102	94	101	99
	Mean ± SD	-20.9 ± 14.0	-22.5 ± 15.2	-19.7 ± 14.4	-21.7 ± 14.1
	Median	-21.5	-21.0	-20.0	-21.0
	Q1 ; Q3	-29.0 ; -10.0	-32.0 ; -9.0	-28.0 ; -8.0	-32.0 ; -10.0
	Min ; Max	-59 ; 15	-66 ; 2	-52 ; 20	-53 ; 5

Sensitivity analyses

Two planned sensitivity analyses were performed in the total population of the FAS):

- The first one used a MMRM model including the fixed, categorical effects of treatment, age subgroup, country, visit and treatment-by-visit interaction as well as the continuous, fixed covariate of baseline, see results in Table 33 below:

Table 33. CDRS-R raw total score – Full Analysis Set (N=396) – Comparison between groups – Sensitivity analysis – MMRM – Change from baseline to W012

		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 101)	Fluoxetine (N = 99)
Descriptive Statistics					
Baseline	n	94	84	91	89
	Mean ± SD	63.8 ± 8.0	65.4 ± 8.1	67.8 ± 8.1	65.0 ± 7.6
	Median	63.0	65.0	67.0	65.0
	Q1 ; Q3	59.0 ; 68.0	59.0 ; 70.0	62.0 ; 73.0	60.0 ; 69.0
	Min ; Max	46 ; 87	52 ; 87	49 ; 91	49 ; 89
W012	n	94	84	91	89
	Mean ± SD	42.0 ± 13.1	41.0 ± 11.9	46.5 ± 14.9	42.4 ± 11.9
	Median	42.5	41.0	47.0	43.0
	Q1 ; Q3	32.0 ; 51.0	31.0 ; 50.5	38.0 ; 54.0	33.0 ; 52.0
	Min ; Max	17 ; 87	17 ; 65	17 ; 89	19 ; 66
W012 - Baseline	n	94	84	91	89
	Mean ± SD	-21.8 ± 13.9	-24.4 ± 14.8	-21.3 ± 14.1	-22.6 ± 13.9
	Median	-22.0	-22.0	-22.0	-22.0
	Q1 ; Q3	-30.0 ; -12.0	-33.0 ; -14.0	-30.0 ; -11.0	-33.0 ; -11.0
	Min ; Max	-59 ; 15	-66 ; 0	-52 ; 20	-53 ; 5
Statistical analysis					
	E (SE) (1)	1.55 (1.86)	3.19 (1.90)		2.75 (1.89)
	95% CI (2)	[-2.12 ; 5.22]	[-0.55 ; 6.94]		[-0.96 ; 6.46]
	p-value (3)	0.617	0.167		0.146

LEGEND :
(1) Estimate (Standard Error) of the adjusted difference from baseline to W012 between treatment group means : Placebo minus each Agomelatine dose regimen and Fluoxetine using a Mixed-effects Model for Repeated Measures including terms for the fixed categorical effects of treatment (including the four treatment groups), age subgroup, country, visit and treatment by visit interaction as well as the continuous, fixed covariate of baseline
(2) 95% Confidence interval of the estimate
(3) Step Down Dunnett adjusted p-value for Agomelatine dose regimen and p-value for Fluoxetine (to be compared to 0.05)

The originally planned MMRM model did not include the covariate "baseline-by-visit interaction". Based on model checking criteria, the MAH found that the initial model did not fit study data as well as a MMRM model with this interaction. Thus, the baseline-by-visit interaction was added in the model after unblinding, see results in the table below.

The second sensitivity analysis used the same ANCOVA model as for the primary analysis but on complete cases at W012. The result from this analysis is also presented in Table 34 below.

Table 34. CDRS-R raw total score – Comparison between groups – Sensitivity analyses: MMRM model and model with complete cases – Change from baseline to W012 – FAS

		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 101)	Fluoxetine (N = 99)
Baseline	n	94	84	91	89
	Mean ± SD	63.8 ± 8.0	65.4 ± 8.1	67.8 ± 8.1	65.0 ± 7.6
	Median	63.0	65.0	67.0	65.0
	Min ; Max	46 ; 87	52 ; 87	49 ; 91	49 ; 89
W012	n	94	84	91	89
	Mean ± SD	42.0 ± 13.1	41.0 ± 11.9	46.5 ± 14.9	42.4 ± 11.9
	Median	42.5	41.0	47.0	43.0
	Min ; Max	17 ; 87	17 ; 65	17 ; 89	19 ; 66
W012 - Baseline	n	94	84	91	89
	Mean ± SD	-21.8 ± 13.9	-24.4 ± 14.8	-21.3 ± 14.1	-22.6 ± 13.9
	Median	-22.0	-22.0	-22.0	-22.0
	Min ; Max	-59 ; 15	-66 ; 0	-52 ; 20	-53 ; 5
Statistical analyses					
MMRM model*	E (SE) (1a)	3.27 (1.80)	4.27 (1.82)		3.92 (1.81)
	95% CI (2)	[-0.26 ; 6.80]	[0.69 ; 7.85]		[0.37 ; 7.47]
	p-value (3)	0.069	0.037		0.030
Complete cases	E (SE) (1b)	3.43 (1.76)	5.13 (1.78)		3.45 (1.76)
	95% CI (2)	[-0.02 ; 6.89]	[1.63 ; 8.64]		[-0.01 ; 6.91]
	p-value (3)	0.051	0.008		0.051

(1a) Estimate (Standard Error) of the adjusted difference from baseline to W012 between treatment group means: Placebo minus each Agomelatine dose regimen and Fluoxetine using a Mixed-effects Model for Repeated Measures including terms for the fixed categorical effects of treatment (including the four treatment groups), age subgroup, country, visit, treatment by visit interaction and baseline by visit interaction as well as the continuous, fixed covariate of baseline*

**The baseline-by-visit interaction was added in the model after unblinding as it fitted better to the study data.*

(1b) Estimate (Standard Error) of the adjusted difference from baseline to W012 between treatment group means: Placebo minus each Agomelatine dose regimen and Fluoxetine using an ANCOVA including the fixed, categorical effects of treatment (including the four treatment groups), age subgroup and country, as well as the continuous, fixed covariate of baseline

(2) 95% Confidence interval of the estimate

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

A third unplanned sensitivity analysis was performed using a multiple imputation approach. Results are presented in Table 35 below:

Table 35. CDRS-R raw total score – Comparison between groups – Sensitivity analysis: Multiple imputation approach- Change from baseline to W012 – FAS (unplanned analysis)

		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 101)	Fluoxetine (N = 99)
Baseline	n	102	94	101	99
	Mean ± SD	64.26 ± 8.33	65.46 ± 8.30	67.53 ± 8.62	64.98 ± 7.96
	Median	63.50	65.00	67.00	65.00
	Min ; Max	46.0 ; 87.0	52.0 ; 90.0	49.0 ; 93.0	47.0 ; 89.0
W012	n	102	94	101	99
	Mean ± SD	42.48 ± 13.49	42.11 ± 12.22	46.76 ± 15.37	42.41 ± 12.13
	Median	42.92	43.67	47.22	42.56
	Min ; Max	17.0 ; 87.0	17.0 ; 67.1	17.0 ; 89.8	18.8 ; 68.7
W012 - Baseline	n	102	94	101	99
	Mean ± SD	-21.78 ± 14.00	-23.35 ± 14.74	-20.78 ± 14.15	-22.57 ± 13.97
	Median	-22.04	-21.74	-21.05	-22.09
	Min ; Max	-59.0 ; 15.1	-66.0 ; 2.0	-52.0 ; 20.1	-53.5 ; 5.7
Statistical analysis					
	E (SE) (1)	3.15 (1.76)	4.17 (1.78)		3.65 (1.76)
	95% CI (2)	[-0.30 ; 6.61]	[0.68 ; 7.65]		[0.20 ; 7.10]
	p-value (3)	0.074	0.037		0.038

Multiple imputation: All missing data (at each week and) at W012 are imputed by treatment group, using age subgroup, country and baseline, using MI approach based on the regression method (after a MCMC monotone-data imputation) to generate 100 complete data sets. Descriptive statistics correspond to the mean of statistical parameters of each generated data sets.
Resulting complete datasets are modeled using an ANCOVA including the fixed, categorical effects of treatment (including the four treatment groups), age subgroup and country, as well as the continuous, fixed covariate of baseline.
Corresponding results are combined to produce final inference:
(1) Estimate (Standard Error) of the adjusted difference from baseline to W012 between treatment group means: Placebo minus each Agomelatine dose regimen and Fluoxetine with a multiple imputation approach
(2) 95% Confidence interval of the estimate
(3) Step Down Dunnett adjusted p-value for Agomelatine dose regimen and p-value for Fluoxetine (to be compared to 0.05)

Age subgroup analysis: change from baseline to W012, in adolescents of the FAS

The same model as that for the primary analysis in the FAS was used in the adolescent subgroup of the FAS. Results are presented in Table 36 below.

Table 36. CDRS-R raw total score – Comparison between groups – Change from baseline to last post-baseline value – Adolescents of the FAS

		Agomelatine 10 mg (N = 81)	Agomelatine 25 mg (N = 75)	Placebo (N = 81)	Fluoxetine (N = 80)
Baseline	n	81	75	81	80
	Mean ± SD	64.5 ± 8.3	66.1 ± 8.7	68.1 ± 8.8	65.3 ± 8.1
	Median	64.0	65.0	68.0	65.5
	Min ; Max	46 ; 87	52 ; 90	49 ; 93	47 ; 89
Last post baseline	n	81	75	81	80
	Mean ± SD	43.4 ± 15.0	42.2 ± 13.4	48.3 ± 15.1	43.3 ± 12.9
	Median	43.0	41.0	48.0	43.0
	Min ; Max	17 ; 87	17 ; 83	17 ; 90	19 ; 76
Last post baseline - Baseline	n	81	75	81	80
	Mean ± SD	-21.1 ± 14.1	-23.8 ± 15.4	-19.8 ± 13.4	-22.0 ± 14.2
	Median	-22.0	-22.0	-20.0	-21.0
	Min ; Max	-53 ; 15	-66 ; 2	-50 ; 20	-53 ; 1
Statistical analysis					
	E (SE) (1)	3.18 (2.11)	5.22 (2.13)		3.70 (2.10)
	95% CI (2)	[-0.96 ; 7.32]	[1.03 ; 9.40]		[-0.43 ; 7.84]
	p-value (3)	0.132	0.028		0.079

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

(2) 95% Confidence interval of the estimate

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

Sensitivity analyses (unplanned) performed in adolescents

Three sensitivity analyses were also performed in the adolescents of the FAS, but in this subset they were unplanned. These were the same analyses as in the FAS; the adjusted MMRM model (including the covariate "baseline-by-visit interaction"), the ANCOVA model on complete cases at W012 and the model with the multiple imputation approach to handle missing data.

Results are presented in **Table 37**, Table **38** and Table **39** below.

Table 37. CDRS-R raw total score – Comparison between groups – Sensitivity analyses (unplanned): MMRM model and model with complete cases – Change from baseline to W012 – Adolescents of the FAS

		Agomelatine 10 mg (N = 81)	Agomelatine 25 mg (N = 75)	Placebo (N = 81)	Fluoxetine (N = 80)
Baseline	n	73	68	75	73
	Mean ± SD	64.0 ± 7.9	66.0 ± 8.5	68.1 ± 8.4	65.1 ± 7.7
	Median	64.0	65.5	68.0	64.0
	Min ; Max	46 ; 83	52 ; 87	49 ; 91	49 ; 89
W012	n	73	68	75	73
	Mean ± SD	41.6 ± 13.7	40.4 ± 12.0	47.1 ± 14.3	42.2 ± 12.1
	Median	42.0	40.0	47.0	43.0
	Min ; Max	17 ; 87	17 ; 64	17 ; 89	19 ; 66
W012 - Baseline	n	73	68	75	73
	Mean ± SD	-22.4 ± 14.0	-25.6 ± 14.9	-21.0 ± 13.1	-22.9 ± 13.7
	Median	-23.0	-23.0	-22.0	-23.0
	Min ; Max	-53 ; 15	-66 ; 0	-50 ; 20	-53 ; 1
Statistical analysis					
MMRM model	E (SE) (1a)	3.78 (2.06)	5.45 (2.07)		4.11 (2.05)
	95% CI (2)	[-0.28 ; 7.83]	[1.36 ; 9.53]		[0.08 ; 8.15]
	p-value (3)	0.068	0.018		0.046
Complete cases	E (SE) (1b)	4.00 (2.03)	6.25 (2.04)		3.95 (2.01)
	95% CI (2)	[0.00 ; 8.00]	[2.24 ; 10.26]		[-0.00 ; 7.91]
	p-value (3)	0.050	0.005		0.050

(1a) Estimate (Standard Error) of the adjusted difference from baseline to W012 between treatment group means: Placebo minus each Agomelatine dose regimen and Fluoxetine using a Mixed-effects Model for Repeated Measures including terms for the fixed categorical effects of treatment (including the four treatment groups), country, visit, treatment by visit interaction and baseline by visit interaction as well as the continuous, fixed covariate of baseline

(1b) Estimate (Standard Error) of the adjusted difference from baseline to W012 between treatment group means: Placebo minus each Agomelatine dose regimen and Fluoxetine using an ANCOVA including the fixed, categorical effects of treatment (including the four treatment groups) and country, as well as the continuous, fixed covariate of baseline

(2) 95% Confidence interval of the estimate

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

Table 38. CDRS-R raw total score – Comparison between groups – Sensitivity analysis (unplanned): Multiple imputation approach – Change from baseline to W012 – Adolescents of the FAS

		Agomelatine 10 mg (N = 81)	Agomelatine 25 mg (N = 75)	Placebo (N = 81)	Fluoxetine (N = 80)
Baseline	n	81	75	81	80
	Mean ± SD	64.51 ± 8.26	66.07 ± 8.66	68.11 ± 8.78	65.30 ± 8.09
	Median	64.00	65.00	68.00	65.50
	Min ; Max	46.0 ; 87.0	52.0 ; 90.0	49.0 ; 93.0	47.0 ; 89.0
W012	n	81	75	81	80
	Mean ± SD	42.29 ± 14.08	41.35 ± 12.39	47.03 ± 15.09	42.48 ± 12.32
	Median	42.84	40.90	46.99	42.84
	Min ; Max	17.0 ; 87.0	17.0 ; 67.5	17.0 ; 90.0	18.9 ; 68.4
W012 - Baseline	n	81	75	81	80
	Mean ± SD	-22.21 ± 14.03	-24.72 ± 15.00	-21.08 ± 13.18	-22.82 ± 13.93
	Median	-22.92	-22.34	-22.00	-22.56
	Min ; Max	-53.6 ; 15.1	-66.0 ; 2.5	-50.0 ; 20.0	-53.5 ; 3.1
Statistical analysis					
	E (SE) (1)	3.26 (2.04)	5.06 (2.06)		3.55 (2.03)
	95% CI (2)	[-0.74 ; 7.25]	[1.02 ; 9.09]		[-0.44 ; 7.53]
	p-value (3)	0.110	0.028		0.081

Multiple imputation: All missing data (at each week and) at W012 are imputed by treatment group, using age subgroup, country and baseline, using MI approach based on the regression method (after a MCMC monotone-data imputation) to generate 100 complete data sets. Descriptive statistics correspond to the mean of statistical parameters of each generated data sets

Resulting complete datasets are modeled using an ANCOVA including the fixed, categorical effects of treatment (including the four treatment groups), age subgroup and country, as well as the continuous, fixed covariate of baseline.

Corresponding results are combined to produce final inference:

(1) Estimate (Standard Error) of the adjusted difference from baseline to W012 between treatment group means: Placebo minus each Agomelatine dose regimen and Fluoxetine with a multiple imputation approach

(2) 95% Confidence interval of the estimate

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

Subgroup – children

Table 39. CDRS-R raw total score – Change from baseline to last post-baseline children of the FAS

		Agomelatine 10 mg (N = 21)	Agomelatine 25 mg (N = 19)	Placebo (N = 20)	Fluoxetine (N = 19)
Baseline	n	21	19	20	19
	Mean ± SD	63.3 ± 8.7	63.1 ± 6.3	65.2 ± 7.7	63.6 ± 7.5
	Median	61.0	63.0	64.0	65.0
	Min ; Max	47 ; 87	52 ; 75	51 ; 83	49 ; 75
Last post baseline	n	21	19	20	19
	Mean ± SD	43.3 ± 11.0	46.0 ± 12.9	46.2 ± 17.2	42.9 ± 11.1
	Median	47.0	46.0	50.0	41.0
	Min ; Max	28 ; 61	21 ; 71	17 ; 78	26 ; 58
Last post baseline - Baseline	n	21	19	20	19
	Mean ± SD	-20.0 ± 13.9	-17.1 ± 13.3	-19.0 ± 18.3	-20.7 ± 14.4
	Median	-18.0	-11.0	-12.0	-22.0
	Min ; Max	-59 ; 1	-44 ; -1	-52 ; 10	-43 ; 5

Supplementary analyses

Remission at W012

In the total population of the FAS

Table 40 below presents results, in the FAS, on remission at last post-baseline value defined as a CDRS-R raw total score ≤ 28.

Table 40. CDRS-R raw total score – Comparison between groups – Supplementary analysis – Remission – Last post-baseline value – FAS

		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 101)	Fluoxetine (N = 99)
Last post baseline	n	102	94	101	99
No remission	n (%)	88 (86.3)	79 (84.0)	90 (89.1)	87 (87.9)
Remission	n (%)	14 (13.7)	15 (16.0)	11 (10.9)	12 (12.1)
Statistical analysis					
	E (SE) (1)	-2.83 (4.61)	-5.07 (4.89)		-1.23 (4.51)
	95% CI (2)	[-11.86 ; 6.19]	[-14.64 ; 4.51]		[-10.08 ; 7.62]
	p-value (3)	0.539	0.298		0.785

Remission is defined as a CDRS-R raw total score in [17;28]
Percentages are based on n
(1) Estimate (Standard Error) of the difference between the proportion of patients with remission: Placebo minus each Agomelatine dose regimen and Fluoxetine
(2) 95% Confidence interval of the estimate
(3) p-value from Chi-2 test (to be compared to 0.05)

In adolescents of the FAS

A higher proportion of adolescents with remission at last post-baseline value was also observed in both agomelatine groups (16.0% in the agomelatine 10 mg group and 17.3% in the agomelatine 25 mg group) compared to the placebo group (8.6%), without statistical significance (unplanned analysis). Similar result was observed regarding the difference between placebo and fluoxetine (i.e., 8.6% vs. 13.8%, respectively, without statistically significant difference).

Remission at each visit

Table 41 below gives the rate of patients with remission at each visit, by treatment group in the FAS.

Table 41. CDRS-R raw total score – Supplementary analysis – Remission – value at baseline, each post baseline visit and last post baseline visit – FAS

			Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 101)	Fluoxetine (N = 99)
BASELINE		n	102	94	101	99
	No remission	n (%)	102 (100.00)	94 (100.00)	101 (100.00)	99 (100.00)
	Remission	n (%)	-	-	-	-
W001		n	102	93	100	99
	No remission	n (%)	102 (100.00)	92 (98.92)	100 (100.00)	99 (100.00)
	Remission	n (%)	-	1 (1.08)	-	-
W002		n	100	94	100	98
	No remission	n (%)	100 (100.00)	93 (98.94)	100 (100.00)	97 (98.98)
	Remission	n (%)	-	1 (1.06)	-	1 (1.02)
W004		n	100	92	99	94
	No remission	n (%)	97 (97.00)	90 (97.83)	97 (97.98)	91 (96.81)
	Remission	n (%)	3 (3.00)	2 (2.17)	2 (2.02)	3 (3.19)
W008		n	98	89	93	92
	No remission	n (%)	89 (90.82)	80 (89.89)	85 (91.40)	86 (93.48)
	Remission	n (%)	9 (9.18)	9 (10.11)	8 (8.60)	6 (6.52)
W012		n	94	84	91	89
	No remission	n (%)	80 (85.11)	69 (82.14)	80 (87.91)	77 (86.52)
	Remission	n (%)	14 (14.89)	15 (17.86)	11 (12.09)	12 (13.48)
LAST POST-BASELINE VALUE		n	102	94	101	99
	No remission	n (%)	88 (86.27)	79 (84.04)	90 (89.11)	87 (87.88)
	Remission	n (%)	14 (13.73)	15 (15.96)	11 (10.89)	12 (12.12)

Remission is defined as a CDRS-R raw total score in [17;28]
Percentage are based on n

Secondary endpoints

Clinical Global Impression

Severity of illness score (CGI-S score)

In the total population of the FAS

Table 42 below presents results on CGI – severity of illness score at last post-baseline value in the W000-W012 period, in the FAS.

Table 42. CGI-S score – Comparison between groups – Last post-baseline value – FAS

		Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 101)	Fluoxetine (N = 99)
Last post baseline	n	102	94	101	99
	Mean ± SD	3.5 ± 1.1	3.5 ± 1.1	3.8 ± 1.2	3.6 ± 1.0
	Median	4.0	4.0	4.0	4.0
	Min ; Max	1 ; 6	1 ; 6	1 ; 6	1 ; 6
Statistical analysis					
	E (SE) (1)	0.27 (0.16)	0.28 (0.17)		0.18 (0.16)
	95% CI (2)	[-0.05 ; 0.59]	[-0.05 ; 0.62]		[-0.14 ; 0.49]
	p-value (3)	0.095	0.094		0.274
	p-value (4)	0.035	0.051		0.119

(1) Estimate (Standard Error) of the difference of mean between Placebo and each Agomelatine dose regimen and between Placebo and Fluoxetine
(2) 95% Confidence interval of the estimate
(3) p-value from Student t-test for independent samples (to be compared to 0.05)
(4) p-value from Mann Whitney test (to be compared to 0.05)

Adolescents of the FAS (unplanned analysis):

The means of CGI-S score of the last post-baseline value in the adolescents of the FAS were very close to those in the total population of the FAS, for all groups.

Global improvement score (CGI-I score)

In the total population of the FAS

The means of CGI-I score of the last post-baseline value were very close in each treatment group (Table 43) : 2.6 ± 1.1 in the agomelatine 10 mg group, 2.5 ± 1.0 in the agomelatine 25 mg group and 2.7 ± 1.1 in the placebo group, showing no statistically significant difference between placebo and each agomelatine dose. Similar results were observed between placebo and fluoxetine (2.6 ± 1.0).

Adolescents of the FAS

In adolescents of the FAS, as for the total population, no statistically significant difference between placebo (2.7 ± 1.1) and either of the agomelatine treatment groups (10 mg: 2.6 ± 1.1 vs. 25 mg: 2.4 ± 1.0, respectively) or between placebo and fluoxetine (2.5 ± 1.0) was shown in the adolescents of the FAS.

CGI-I score: response to treatment at W012

Response to treatment was defined as a CGI-I score = 1 ("very much improved") or 2 ("much improved").

Table 43. CGI-I score – comparison between groups – response to treatment – last post-baseline value – FAS

			Agomelatine 10 mg (N = 102)	Agomelatine 25 mg (N = 94)	Placebo (N = 101)	Fluoxetine (N = 99)
Last post baseline		n	102	94	101	99
	No response	n (%)	53 (52.0)	48 (51.1)	56 (55.4)	52 (52.5)
	Response	n (%)	49 (48.0)	46 (48.9)	45 (44.6)	47 (47.5)
Statistical analysis						
		E (SE) (1)	-3.48 (7.00)	-4.38 (7.14)		-2.92 (7.05)
		95% CI (2)	[-17.19 ; 10.23]	[-18.38 ; 9.62]		[-16.73 ; 10.89]
		p-value (3)	0.619	0.540		0.679

Response is defined as a CGI-I score = 1 (very much improved) or 2 (much improved)
(1) Estimate (Standard Error) of the difference between the proportion of patients with response: Placebo minus each Agomelatine dose regimen and Fluoxetine
(2) 95% Confidence interval of the estimate
(3) p-value from Chi-2 test (to be compared to 0.05)

In the unplanned analysis for the adolescents of the FAS, the proportion of adolescents with response to treatment at last post-baseline value was 49.4% in the agomelatine 10 mg group and 53.3% in the agomelatine 25 mg group vs. 46.9% in the placebo group without statistically significant difference. Similar result was observed for the difference between the placebo and the fluoxetine group (50.0%).

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

Table 44 below presents results on ADRS total score at last post-baseline value, in the adolescents of the FAS.

Table 44. ADRS score – Comparison between groups – Last post-baseline value – Adolescents of the FAS

		Agomelatine 10 mg (N = 81)	Agomelatine 25 mg (N = 75)	Placebo (N = 81)	Fluoxetine (N = 80)
Last post baseline	n	79	75	80	80
	Mean ± SD	18.8 ± 10.1	18.1 ± 10.6	22.2 ± 10.7	19.9 ± 10.3
	Median	20.0	18.0	22.0	22.0
	Min ; Max	0 ; 40	0 ; 38	0 ; 49	0 ; 41
Statistical analysis					
	E (SE) (1)	3.40 (1.65)	4.07 (1.72)		2.34 (1.66)
	95% CI (2)	[0.14 ; 6.67]	[0.68 ; 7.46]		[-0.95 ; 5.62]
	p-value (3)	0.041	0.019		0.162
	p-value (4)	0.064	0.032		0.276

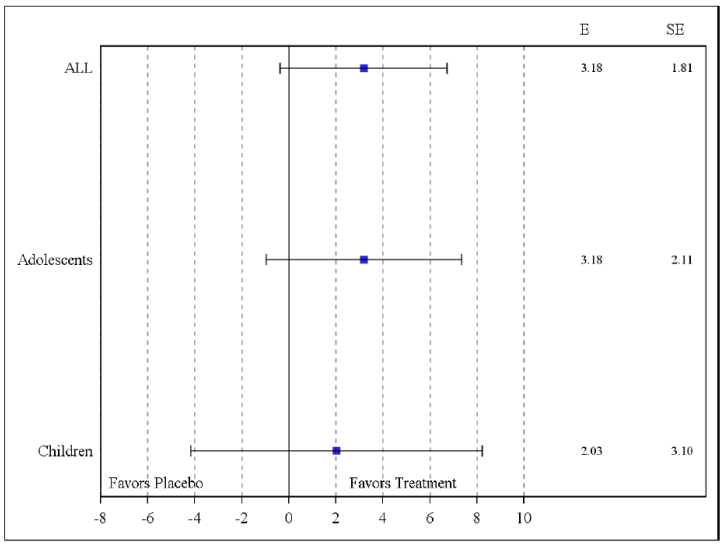
(1) Estimate (Standard Error) of the difference of mean between Placebo and each Agomelatine dose regimen and between Placebo and Fluoxetine
(2) 95% Confidence interval of the estimate
(3) p-value from Student t-test for independent samples (to be compared to 0.05)
(4) p-value from Mann Whitney test (to be compared to 0.05)

2.4.18. Treatment effect

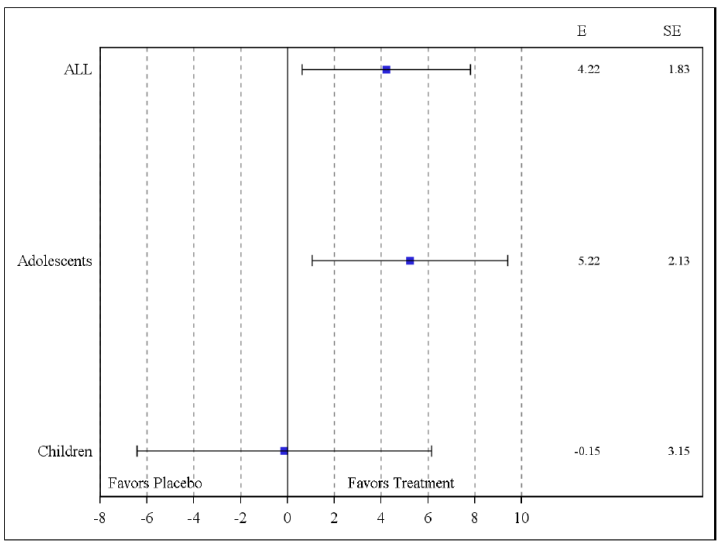
Forest plots of estimated treatment effect

Figure 15 below summarises through forest plots the estimated treatment effect in the total population, adolescents, and children of the FAS.

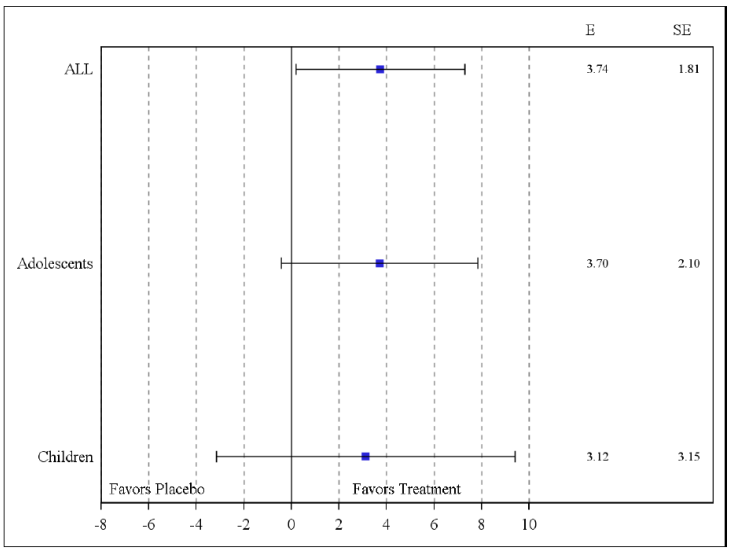
Agomelatine 10 mg group



Agomelatine 25 mg group



Fluoxetine group



Estimate (E) and Standard Error (SE) of the adjusted difference from baseline to last post baseline value between treatment group means: Placebo minus each Agomelatine dose regimen and Fluoxetine using an ANCOVA including the fixed, categorical effects of treatment (including the four treatment groups), age subgroup and country, as well as the continuous, fixed covariate of baseline*
** Age subgroup: Not used for Adolescents and Children subgroups*

Figure 15. CDRS-R raw total score – Change from baseline to last post-baseline – Forest plots of estimated treatment effect – FAS

In order to evaluate the magnitude of the effect observed in adolescents in the CL3-076 study, the MAH retrospectively conducted a meta-analysis, using meta-analytic methods, to summarise the short-term efficacy of agomelatine in positive non-elderly adult studies vs. placebo.

The MAH argued that 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 approved in the paediatric population in Europe. According to the MAH these effect sizes were lower than those previously observed or calculated for fluoxetine in ancient paediatric clinical trials (0.4–0.5) (Emslie *et al*, 2002; Emslie *et al*, 1997) but similar to those observed in clinical trials with antidepressants in adults (0.3) (Leucht *et al*, 2012).

The MAH also referred to that the magnitude of the effect observed in adolescents in the CL3-076 study (effect size on CDRS = 0.36) was the same as the one observed in positive non-elderly adult studies vs. placebo for agomelatine (mean effect size on HAM-D = 0.36 [0.19;0.53]), see Figure 16 below.

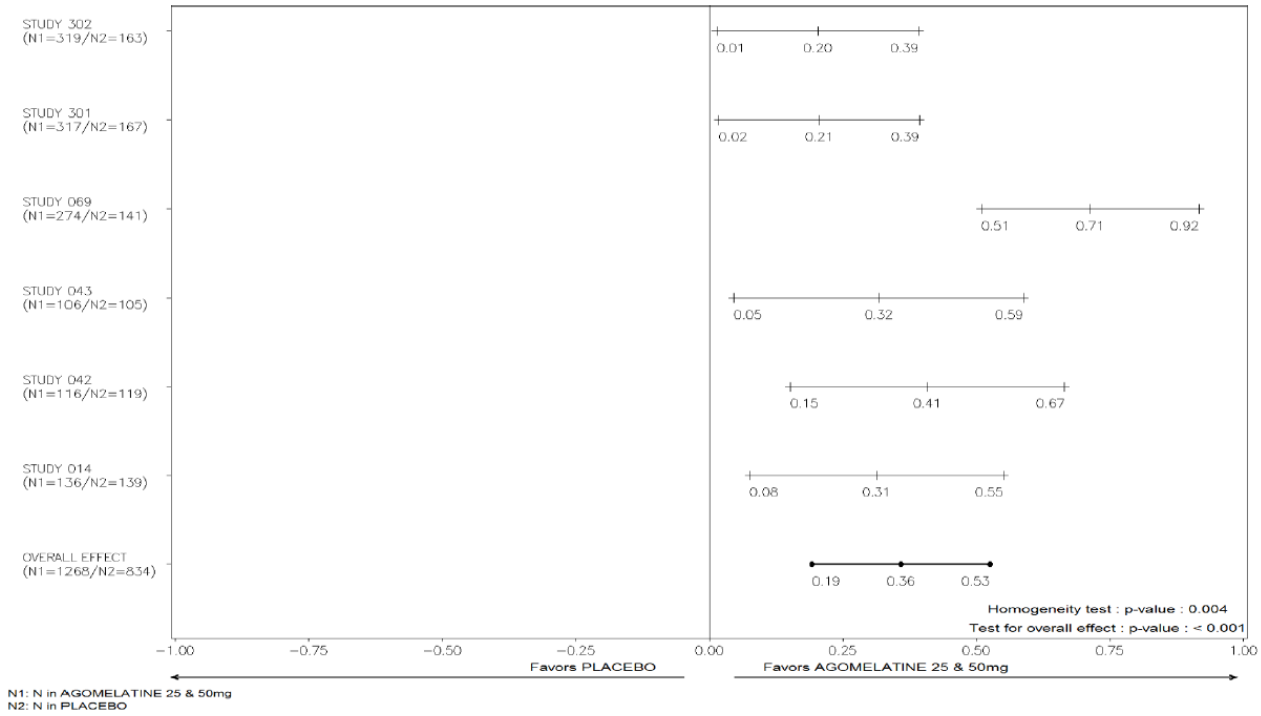


Figure 16. Positive non-elderly adult studies vs. placebo – FAS (N = 2102) – HAM-D total score
Ancillary analyses

Optional open-label 92-week extension period of Study CL3-076:

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

Treatment

From week 12 to week 14:

All patients entering the extension period took 1 tablet of agomelatine 10 mg orally per day in the evening at bedtime.

From week 14 to week 104:

The dose of agomelatine could be adjusted (flexible dose, either to increase to 25 mg or to decrease again to 10 mg) at each visit during the extension period by investigator based on the clinical picture of patient. In addition, patients in all 3 groups were given Manualized Psychosocial Counselling at W018, 024, 032, 040, 048, 052, 060, 068, 077, 086, 095 and 104.

In the W012-W104 period, the treatment groups considered were 1) agomelatine 10 or 25 mg/10-25 mg, 2) placebo/agomelatine 10-25 mg and 3) fluoxetine 10-20 mg/agomelatine 10-25 mg.

In the W000-W104 period, focusing on patients already under agomelatine (10 or 25 mg) in the W000-W012 period, the treatment group considered was agomelatine 10 or 25 mg/10-25 mg.

Primary and secondary efficacy analyses:

The primary efficacy endpoint in this part of the study was defined as the value in the CDRS-R Raw score.

Descriptive statistics at baseline and at each post-baseline visit as well as change from baseline to each post-baseline visit by treatment group were provided for all analytical approaches of CDRS-R raw total score. In the W000-W104 period this was done in patients initially randomised under agomelatine and in

the W012-W104 period it was done according to the treatment group randomised for the double-blind period.

Secondary endpoints were defined as the value in Severity of Illness (CGI-S) and Global Improvement (CGI-I).

All patients of the MRS carrying on in the optional prolongation period W012-W104 was part of the Sub-Modified Randomised Set (Sub-MRS). All efficacy analyses were performed in the Sub-MRS.

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

Response to treatment: defined as in the double-blind period; a CGI-I score of 1 or 2.

Relapse: defined as a CDRS score ≥ 40 or a withdrawal due to lack of efficacy. Stringent relapse was defined as a CDRS score ≥ 40. Time to relapse was analysed until W040 (included) in the Sub-MRS (for both relapse definitions) in patients considered as responders* in the double-blind period (based on CGI and/or CDRS criteria) in patients randomised under agomelatine 25 mg in the double-blind period and in patients randomised under agomelatine 10 mg or 25 mg in the double-blind period.

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

Disposition of patients

The overall disposition of included patients in the extension period is presented by group in Table 45 below:

Table 45. Disposition of included patients by group – open-label extension period

STATUS		Agomelatine 10 or 25 mg / 10-25 mg (N = 170)		Placebo / Agomelatine 10-25 mg (N = 85)		Fluoxetine 10-20 mg / Agomelatine 10-25 mg (N = 84)		ALL (N = 339)	
Included in W000-W104 period	**n**	**170**		**85**		**84**		**339**	
In Conformity with the Protocol	n (%)	127	(74.7)	58	(68.2)	61	(72.6)	246	(72.6)
With Protocol Deviation(s) Before or at Inclusion	n (%)	43	(25.3)	27	(31.8)	23	(27.4)	93	(27.4)
Withdrawn on W012-W104 period due to	**n (%)**	**77**	**(45.3)**	**37**	**(43.5)**	**38**	**(45.2)**	**152**	**(44.8)**
Lost to follow-up	n (%)	1	(0.6)	1	(1.2)	-	-	2	(0.6)
Adverse event	n (%)	6	(3.5)	5	(5.9)	3	(3.6)	14	(4.1)
Lack of efficacy	n (%)	4	(2.4)	2	(2.4)	2	(2.4)	8	(2.4)
Recovery	n (%)	40	(23.5)	14	(16.5)	15	(17.9)	69	(20.4)
Non-medical reason	n (%)	25	(14.7)	12	(14.1)	17	(20.2)	54	(15.9)
Protocol violation	n (%)	1	(0.6)	3	(3.5)	1	(1.2)	5	(1.5)
Completed the W012-W104 period	**n (%)**	**93**	**(54.7)**	**48**	**(56.5)**	**46**	**(54.8)**	**187**	**(55.2)**
With Protocol Deviation(s) After Inclusion	n (%)	52	(30.6)	27	(31.8)	21	(25.0)	100	(29.5)
In Conformity with the Protocol	n (%)	41	(24.1)	21	(24.7)	25	(29.8)	87	(25.7)
Performed the follow-up visit	**n(%)**	**136**	**(80.0)**	**69**	**(81.2)**	**67**	**(79.8)**	**272**	**(80.2)**

N: number of patients by group
n: number of patients
Percentages are based on n

Adolescents

Table 46. Disposition of adolescents of the Sub-MRS, by group – open-label extension period

STATUS		Agomelatine 10 or 25 mg / 10-25 mg (N = 134)		Placebo / Agomelatine 10-25 mg (N = 69)		Fluoxetine 10-20 mg / Agomelatine 10-25 mg (N = 68)		ALL (N = 271)	
Included in W000-W104 period	**n**	**134**		**69**		**68**		**271**	
In Conformity with the Protocol	n (%)	98	(73.1)	45	(65.2)	48	(70.6)	191	(70.5)
With Protocol Deviation(s) Before or at Inclusion	n (%)	36	(26.9)	24	(34.8)	20	(29.4)	80	(29.5)
Withdrawn on W012-W104 period due to	**n (%)**	**63**	**(47.0)**	**31**	**(44.9)**	**32**	**(47.1)**	**126**	**(46.5)**
Lost to follow-up	n (%)	1	(0.7)	1	(1.4)	-	-	2	(0.7)
Adverse event	n (%)	3	(2.2)	5	(7.2)	3	(4.4)	11	(4.1)
Lack of efficacy	n (%)	4	(3.0)	2	(2.9)	1	(1.5)	7	(2.6)
Recovery	n (%)	31	(23.1)	11	(15.9)	13	(19.1)	55	(20.3)
Non-medical reason	n (%)	23	(17.2)	9	(13.0)	14	(20.6)	46	(17.0)
Protocol violation	n (%)	1	(0.7)	3	(4.3)	1	(1.5)	5	(1.8)
Completed the W012-W104 period	**n (%)**	**71**	**(53.0)**	**38**	**(55.1)**	**36**	**(52.9)**	**145**	**(53.5)**
With Protocol Deviation(s) After Inclusion	n (%)	41	(30.6)	20	(29.0)	16	(23.5)	77	(28.4)
In Conformity with the Protocol	n (%)	30	(22.4)	18	(26.1)	20	(29.4)	68	(25.1)
Performed the follow-up visit	**n(%)**	**105**	**(78.4)**	**55**	**(79.7)**	**55**	**(80.9)**	**215**	**(79.3)**

N: number of patients by group
n: number of patients
Percentages are based on n

Results

Primary efficacy endpoint: value of the CDRS-R raw total score

Total population (Sub-MRS)

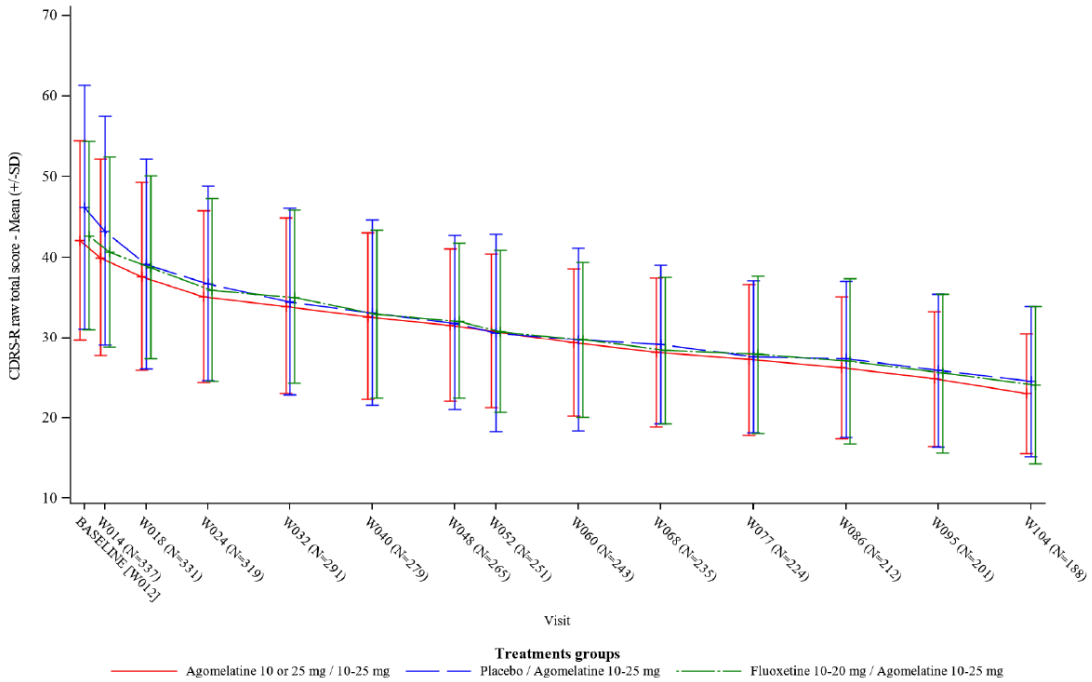


Figure 17. CDRS-R raw total score – mean value (+/-SD) at each visit during the W012-W104 period – Sub-MRS

Adolescents

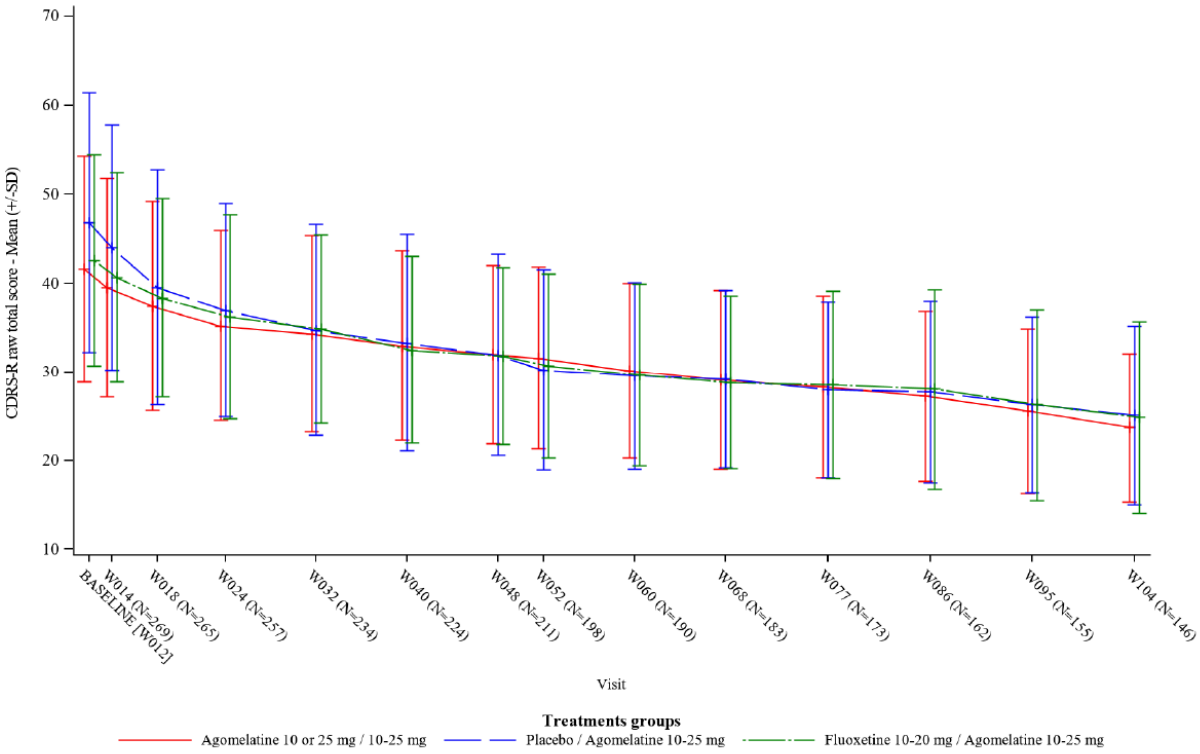


Figure 18. CDRS-R raw total score – Mean value (+/-SD) at each visit during the W012-W104 period – Adolescents of the Sub-MRS

Remission (CDRS-R raw total score ≤ 28)

Total population (Sub-MRS)

Table 47. CDRS-R raw total score – Remission – Value at baseline (W012), W024, W040, W052, W104 and last post-baseline visit – W012-W104 period – Sub-MRS

			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)
Baseline [W012-W104 period]		n	170	85	84	339
	Remission	n (%)	25 (14.7)	11 (12.9)	10 (11.9)	46 (13.6)
W024		n	160	81	78	319
	Remission	n (%)	48 (30.0)	24 (29.6)	26 (33.3)	98 (30.7)
W040		n	137	74	68	279
	Remission	n (%)	51 (37.2)	29 (39.2)	25 (36.8)	105 (37.6)
W052		n	125	63	63	251
	Remission	n (%)	54 (43.2)	32 (50.8)	30 (47.6)	116 (46.2)
W104		n	93	49	46	188
	Remission	n (%)	81 (87.1)	38 (77.6)	38 (82.6)	157 (83.5)
Last post-baseline value		n	170	85	83	338
	Remission	n (%)	129 (75.9)	60 (70.6)	63 (75.9)	252 (74.6)

Percentages are based on n
Note: Remission is defined as a CDRS-R raw total score ≤ 28
Baseline: value at W012 if analysable value

Adolescents

Table 48. CDRS-R raw total score – Remission – Value at baseline (W012), W024, W040, W052, W104 and last post-baseline visit – W012-W104 period – Adolescents of the Sub-MRS

			Agomelatine 10 or 25 mg / 10-25 mg (N = 134)	Placebo / Agomelatine 10-25 mg (N = 69)	Fluoxetine 10-20 mg / Agomelatine 10-25 mg (N = 68)	ALL (N = 271)
Baseline [W012-W104 period]		n	134	69	68	271
	Remission	n (%)	22 (16.4)	7 (10.1)	9 (13.2)	38 (14.0)
W024		n	127	67	63	257
	Remission	n (%)	36 (28.3)	19 (28.4)	20 (31.7)	75 (29.2)
W040		n	107	61	56	224
	Remission	n (%)	41 (38.3)	25 (41.0)	22 (39.3)	88 (39.3)
W052		n	96	50	52	198
	Remission	n (%)	42 (43.8)	26 (52.0)	25 (48.1)	93 (47.0)
W104		n	71	39	36	146
	Remission	n (%)	59 (83.1)	30 (76.9)	28 (77.8)	117 (80.1)
Last post-baseline value		n	134	69	67	270
	Remission	n (%)	97 (72.4)	48 (69.6)	50 (74.6)	195 (72.2)

Percentages are based on n
Note: Remission is defined as a CDRS-R raw total score ≤ 28
Baseline: value at W012 if analysable value

W000-W104 period, in patients of the Sub-MRS initially randomised in agomelatine groups

Figure 19 below illustrates the evolution of the mean CDRS-R raw total score in patients of the Sub-MRS receiving agomelatine all along the study.

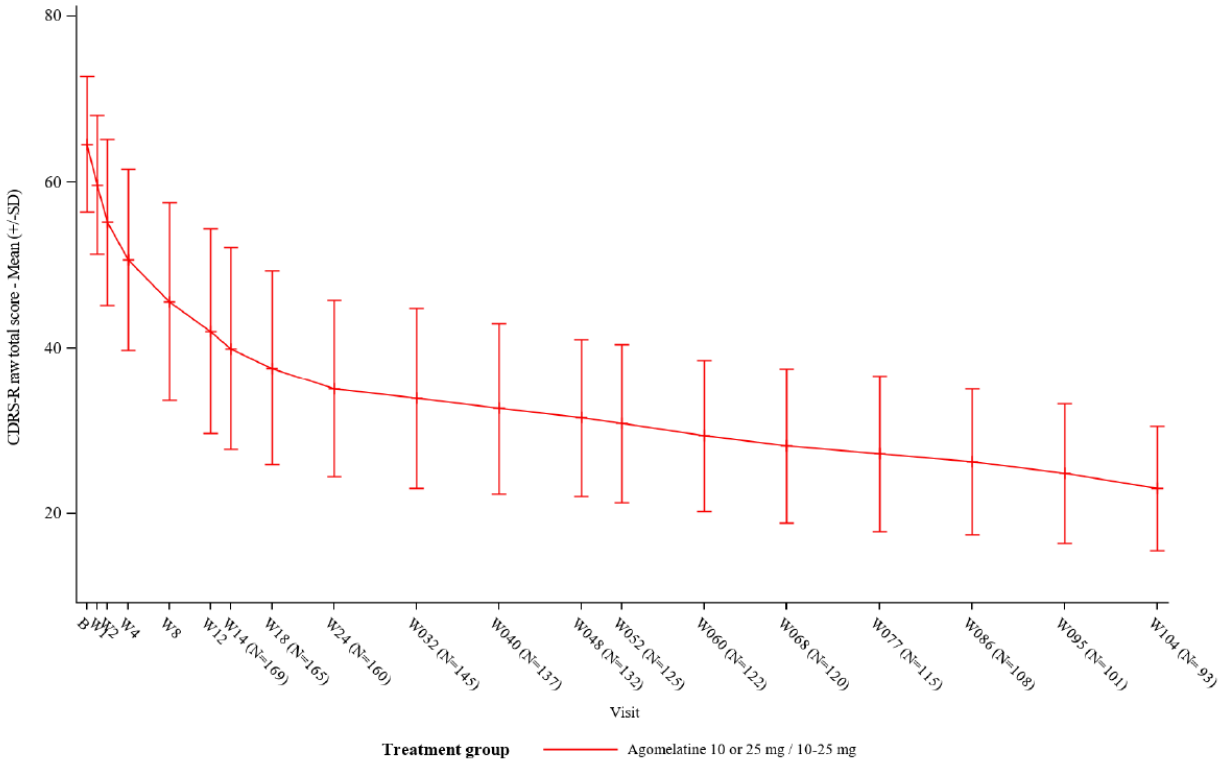


Figure 19. CDRS-R raw total score – Mean value (+/-SD) at each visit during the W000-W104 period – Sub-MRS in patients initially randomised in agomelatine groups

CGI-S and CGI-I

W012-W104 period, in the Sub-MRS

Mean scores improved from 3.5 ± 1.1 at baseline (W012, all patients) to 1.7 ± 1.0 at W104 (all patients) for the CGI-S score and from 2.5 ± 1.0 at baseline (W012, all patients) to 1.5 ± 0.8 at W104 (all patients) for the CGI-I score. Mean score 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, respectively (all patients).

The rate of responders (CGI-I score =1 or 2)

The rate increased from 49.6% at W012 (all patients) to 87.8% at W104 (all patients). The rate of responders at the last post-baseline visit was 84.9% for all patients (the largest rate was in the placebo/ago group with a rate of 88.2%).

Adolescents

The mean CGI-I score decreased from 2.5 ± 1.0 at baseline (W012) to 1.5 ± 0.9 at W104 and the mean score at the last post-baseline visit was 1.6 ± 0.9.

Considering the response to treatment, similar results were observed in the adolescents compared to the total population. The rate of responders in the adolescents increased from 51.7% at W012 to 85.6% at W104. The rate of responders in the adolescents at the last post-baseline visit was 83.3%.

W000-W104 period, in patients of the Sub-MRS initially randomised in agomelatine groups

Total population (Sub-MRS)

Among the patients receiving agomelatine all along the study, the rate of responders, defined as CGI-I score = 1 ("very much improved") or 2 ("much improved") compared to the patient's condition at the inclusion visit, increased along the W000-W104 period, from 1.8% at W001 to 86.0% at W104. When considering the last post-baseline value, 82.9% of patients were considered as responders.

Adolescents

Considering the evolution of the mean CGI-I score over the W000-W104 period, similar pattern was observed in the adolescents of the Sub-MRS initially randomised in agomelatine groups compared to the total population.

Similar results were also observed concerning the rate of responders in the adolescents of the Sub-MRS initially randomised in agomelatine groups compared to the total population. This rate increased all along the W000-W104 period, from 1.5% at W001 to 84.5% at W104. Considering the last post-baseline value, 82.1% of adolescents were considered as responders.

Relapse

W012-W040 period

Relapse (defined as CDRS score $\geq$ 40 or a withdrawal due to lack of efficacy) and stringent relapse (defined as CDRS score $\geq$ 40) were analysed on the W012-W040 period in patients initially randomised under agomelatine 10 mg or 25 mg (both groups pooled) and under agomelatine 25 mg, respectively, and presenting at least a "significant clinical response" (according to CGI and/or CDRS-R criteria) at W012.

Results when considering the "relapse" and "stringent relapse" criteria were identical.

Sub-MRS initially randomised under agomelatine 10 or 25 mg

Table 49. Relapse / Stringent relapse – Time to relapse (weeks) – W012-W40 period – Patients of the Sub-MRS initially randomised under agomelatine 10 or 25 mg and presenting at least a significant clinical response (according to CGI and/or CDRS-R criteria) at W012

			Agomelatine 10 or 25 mg / 10-25 mg (N = 170)
	N (*)	n	69
	Events (**)	n (%)	8 (11.6)
[0-6] weeks	Patients at risk	n	69
	Censored data	n	1
	Events	n	6
	Incidence (%)	E (SE) (1)	8.82 (3.44)
		95% CI (2)	[4.06 ; 18.59]
]6-28] weeks	Patients at risk	n	62
	Censored data	n	42
	Events	n	2
	Incidence (%)	E (SE)(1) (1)	12.50 (4.19)
		95% CI (2)	[6.40 ; 23.65]
> 28 weeks	Patients at risk	n	18
	Censored data	n	18
	Events	n	0

(*): Total number of patients
(**): Total number (and percentage) of events on the W012-W040 period
Kaplan-Meier's method for survival functions estimation
(1) Estimate (Standard Error) on the last week of the considered period of the percentage of patients with a relapse / stringent relapse
(2) Two-sided 95% Confidence Interval of the estimate

Sub-MRS initially randomised under agomelatine 25 mg

Table 50. Relapse / Stringent relapse – Time to relapse (weeks) – W012-W40 period – Patients of the Sub-MRS initially randomised under agomelatine 25 mg and presenting at least a significant clinical response (according to CGI and/or CDRS-R criteria) at W012

			Agomelatine 25 mg / 10-25 mg (N = 79)
	N (*)	n	31
	Events (**)	n (%)	5 (16.1)
[0-6] weeks	Patients at risk	n	31
	Censored data	n	1
	Events	n	4
	Incidence (%)	E (SE) (1)	13.33 (6.21)
		95% CI (2)	[5.22 ; 31.72]
]6-28] weeks	Patients at risk	n	26
	Censored data	n	18
	Events	n	1
	Incidence (%)	E (SE)(1) (1)	17.67 (7.25)
		95% CI (2)	[7.69 ; 37.66]
> 28 weeks	Patients at risk	n	7
	Censored data	n	7
	Events	n	0

(*): Total number of patients
(**): Total number (and percentage) of events on the W012-W040 period
Kaplan-Meier's method for survival functions estimation
(1) Estimate (Standard Error) on the last week of the considered period of the percentage of patients with a relapse / stringent relapse
(2) Two-sided 95% Confidence Interval of the estimate

Relapse in adolescents initially randomised under agomelatine 10 or 25 mg

Table 51. Relapse / Stringent relapse – Time to relapse (weeks) – W012-W40 period – Adolescents of the Sub-MRS initially randomised under agomelatine 10 or 25 mg and presenting at least a significant clinical response (according to CGI and/or CDRS-R criteria) at W012

			Agomelatine 10 or 25 mg / 10-25 mg (N = 134)
	N (*)	n	58
	Events (**)	n (%)	7 (12.1)
[0-6] weeks	Patients at risk	n	58
	Censored data	n	1
	Events	n	5
	Incidence (%)	E (SE) (1)	8.77 (3.75)
		95% CI (2)	[3.75 ; 19.80]
]6-28] weeks	Patients at risk	n	52
	Censored data	n	35
	Events	n	2
	Incidence (%)	E (SE)(1) (1)	13.08 (4.67)
		95% CI (2)	[6.40 ; 25.71]
> 28 weeks	Patients at risk	n	15
	Censored data	n	15
	Events	n	0

(*): Total number of patients
(**): Total number (and percentage) of events on the W012-W040 period
Kaplan-Meier's method for survival functions estimation
(1) Estimate (Standard Error) on the last week of the considered period of the percentage of patients with a relapse / stringent relapse
(2) Two-sided 95% Confidence Interval of the estimate

Relapse in adolescents initially randomised under agomelatine 25 mg

Table 52. Relapse / Stringent relapse – Time to relapse (weeks) – W012-W40 period – Adolescents of the Sub-MRS initially randomised under agomelatine 25 mg and presenting at least a significant clinical response (according to CGI and/or CDRS-R criteria) at W012

			Agomelatine 25 mg / 10-25 mg (N = 63)
	N (*)	n	27
	Events (**)	n (%)	4 (14.8)
[0-6] weeks	Patients at risk	n	27
	Censored data	n	1
	Events	n	3
	Incidence (%)	E (SE) (1)	11.54 (6.27)
		95% CI (2)	[3.87 ; 31.64]
]6-28] weeks	Patients at risk	n	23
	Censored data	n	15
	Events	n	1
	Incidence (%)	E (SE)(1) (1)	16.45 (7.60)
		95% CI (2)	[6.45 ; 38.43]
> 28 weeks	Patients at risk	n	7
	Censored data	n	7
	Events	n	0

(*): Total number of patients
(**): Total number (and percentage) of events on the W012-W040 period
Kaplan-Meier's method for survival functions estimation
(1) Estimate (Standard Error) on the last week of the considered period of the percentage of patients with a relapse / stringent relapse
(2) Two-sided 95% Confidence Interval of the estimate

Relapse data in adult patients and young adults as surrogate parameters for adolescents

The MAH pointed to that the short- and long-term efficacy of agomelatine has previously been demonstrated in adults. According to the MAH more than 10 years of post-marketing experience (exposure 80,060.9 patient months) associated with a large development program ensured the availability of consequent data on both short-term and long-term efficacy as well as the safety profile of the medicinal product in adult patients. MAH referred to CHMP's Guideline on depression (EMA/CHMP/185423/2010 Rev 2, 2013), concerning paediatric development, indicating that all available information including evidence available in adults, can be considered, especially to proof maintenance of efficacy. In the opinion of the MAH a relapse prevention study in paediatric population is not necessarily requested if there are other sufficient available data. In that respect, the MAH mentioned two specifically designed placebo-controlled relapse prevention studies (CL3-021, CL3-041) which evaluated the efficacy of agomelatine in preventing relapse of depression in adult patients with recurrent depression. These studies are previously assessed by the CHMP (EPAR, EMEA/655251/2008).

Agomelatine showed significant prevention of relapse compared to placebo across the whole population and in a subset of more severely depressed patients (baseline HAM-D total score ≥ 25) in the randomised withdrawal study CL3-041. The incidence of adult patients having relapse over six months was significantly lower with agomelatine compared to placebo (21.7% vs. 46.6%, log rank test p = 0.0001), the risk of relapse being reduced by 54% (Cox model HR: 0.458 [0.305; 0.690]). Despite the methodological failure of the randomised withdrawal study CL3-021 in the total population (no relapse preventing effect of agomelatine was demonstrated in the pre-specified analyses), agomelatine showed significant prevention

of relapse compared to placebo in the more sensitive severely depressed population in this study. In this *post-hoc* analysis of the more severely depressed patients (baseline HAM-D score ≥ 25 and CGI score ≥ 5; 46% of FAS), agomelatine was associated with significantly lower incidence of relapses (25.9%) than placebo (41.5%) after the one-year study period (log rank p = 0.046) only, but not during the W8-W34 period.

The MAH concluded that based on the relapse prevention studies results, more especially on the clinically relevant reduction by 54% of relapse risk observed in the CL3-041 study, the clinical benefit of a long-term treatment by agomelatine was demonstrated.

In addition to the data in the overall adult population, the MAH referred to that the expected long-term pharmacodynamic effects of the agomelatine could also be observed in young adults (18-30 years old) when the relapse rate was evaluated in this sub-set of MDD patients:

Table 53. Specific relapse prevention adult study in MDD (CL3-041) Number of relapses and crude relapse rate in the adult set and young adult sub-set of the FAS over 10 months

		Agomelatine			Placebo		
		n(2)	N(2)	Crude rate	n(2)	N(2)	Crude rate
Study in adult MDD (1)	All ages	39	165	23.6%	83	174	47.7%
	Young adults subset (18-30 y.o.)	5	23	21.7%	9	19	47.4%

(1): Number of relapses and crude relapse rate assessed over 10 months.
(2): n = number of patients who relapsed; N = total number of patients.

Comparison to Fluoxetine long-term data – TADS study

From the MAH: The TADS study evaluated the efficacy of fluoxetine both at short-term (TADS team 2004) and up to 36 weeks of treatment (TADS team 2007). Populations of the TADS study and of study CL3-076 appeared quite different, as evidenced for example by the differences in the age of the patients (the TADS study involved only adolescents) and in CDRS mean baseline scores (60.1 ± 10.4 in the TADS study [59.0 ± 10.2 in the fluoxetine group] vs. 64.3 ± 8.3 in the agomelatine 10 mg group and 65.5 ± 8.3 in the agomelatine 25 mg group [65.0 ± 8.0 in the fluoxetine group] in the present CL3-076 study). In addition, only full or partial responder patients could continue the TADS-study beyond the initial 12-week period, whereas there were no such limitations in the CL3-076 study. At last, duration of active treatment was also different: up to 36 weeks in the TADS study vs. up to 104 weeks in the present study. Of note, there was no W036 visit in the CL3-076 study but one at W040, which was the closest available to interpret the relevance of CL3-076 long term efficacy results. Despite these methodological differences, the MAH concluded that very similar results could be observed when comparing improvements in CDRS total score after 36 weeks of fluoxetine treatment in the TADS study (≈ - 32.1) and after 40 weeks of agomelatine treatment in the CL3-076 study (-31.9 ± 13.4). Similarly, using the same "CGI-I = 1 or 2" definition, the response rate at W036 for fluoxetine in the TADS study (81%) was in the same range as the ones observed at W040 in both the ago/ago group (73%, i.e., after 40 weeks of agomelatine treatment) and the placebo/ago group (82.4%, i.e., after 28 weeks of agomelatine treatment). In the MAH's opinion, these results overall indirectly suggested long-term benefits of agomelatine treatment up to 6 months of treatment.

2.4.19. Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Of note, in the Table 54 below, for the extension period; only results from the primary endpoint analysis

and remission are shown.

Table 54. Summary of efficacy for Study CL3-076

Title: Efficacy and safety of 2 doses of agomelatine (10 mg, 25 mg) given orally in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) with moderate to severe Major Depressive Episodes. A 12-week, randomised, double-blind, active (fluoxetine 10 mg/day with potential adjustment to 20 mg/day) and placebo-controlled, parallel groups, international, multicentre study followed by an optional open-labelled 21-month safety extension period.		
Study identifier	CL3-20098-076 EudraCT No.: 2015-002181-23	
Design	This study was an international, multicentre phase III study divided into a 12-week, randomised, double-blind, two-dose level, active and placebo-controlled, parallel groups period and an optional open-label 21-month extension period, conducted in children from 7 to less than 12 years of age and adolescents from 12 to less than 18 years of age suffering from MDE.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Double-blind treatment period 12 weeks 3 weeks Optional open label extension period 21 months
Hypothesis	At least 390 patients with at least 312 adolescents allowed to conclude that at least one dose of agomelatine was superior to placebo with a power of 80% in the subgroup of adolescents, assuming an effect size of 0.5 on CDRS-R raw total score change from baseline to W12 (with multiplicity correction to maintain the experiment wise type I error at 5%).	
Treatments groups	Double-blind treatment period: Agomelatine 10 mg	Agomelatine 10 mg, for 12 weeks N=102 randomised
	Double-blind treatment period: Agomelatine 25 mg	Agomelatine 25 mg, for 12 weeks N=95 randomised
	Double-blind treatment period: Placebo	Placebo, for 12 weeks N=103 randomised
	Double-blind treatment period: Fluoxetine	Fluoxetine 10/20 mg, 12 weeks N=100 randomised
	Open-label period: Agomelatine 10 or 25 mg / 10-25 mg	Agomelatine 10 or 25 mg during the double-blind treatment period and then agomelatine 10-25 mg (pooled) during the open-label period, only patients carrying on in the extension period N=170
	Open-label period: Placebo/ Agomelatine 10-25 mg	Placebo during the double-blind treatment period and then agomelatine 10-25 mg during the open-label period, only patients carrying on in the extension period N=85
	Open-label period: Fluoxetine 10-20 mg/ Agomelatine 10-25 mg	Fluoxetine during the double-blind treatment period and then agomelatine 10-25 mg during the open-label period, only patients continuing in the extension period N=84

Endpoints and definitions (double-blind period)	Primary efficacy endpoint	CDRS-R	CDRS-R raw total score, adjusted difference from baseline to last post-baseline value (by using an ANCOVA model)
	Main Secondary efficacy endpoints	CGI-S	Clinical Global Impression- Severity of Illness score
		CGI-I	Clinical Global Impression- Global Improvement score
		Response to treatment	CGI-I score of 1 or 2
		ADRS	Adolescent Depression Rating scale (only in adolescents of the FAS)
Endpoints and definitions (open-label period)	Primary efficacy endpoint	CDRS-R	CDRS-R raw total score, values at baseline, at each post-baseline visit and at last post-baseline visit as well as change from baseline to each post-baseline visit and to last post-baseline visit
		Remission	CDRS-R raw total score ≤ 28; percentage of patients
Database lock	Double-blind period date: 25 February 2020		
	Open-label period date: 29 November 2021		

Results and analysis

Analysis description	**Primary analysis**				
Analysis population and time point description	Double-blind period: Superiority of at least one dose of agomelatine as compared to placebo on antidepressant efficacy after a 12-week treatment period, from the CDRS-R raw total score expressed in terms of adjusted difference from baseline to W012 using a three-way analysis of covariance (ANCOVA) model.				
	Open-label period: Descriptive statistics by visit and in terms of last post-baseline value were provided for all analytical approaches of CDRS-R raw total score (value at the visit, change from baseline and remission) on the W000-W104 and W012-W104 periods.				
Descriptive statistics and estimate variability (double-blind period)	Treatment group	Agomelatine 10 mg	Agomelatine 25 mg	Placebo	Fluoxetine
	Number of subjects	102	94	101	99
	CDRS-R Mean change from baseline to W12	-20.9	-22.5	-19.7	-21.7
	Standard deviation	±14.0	±15.2	±14.4	±14.1
Effect estimate per comparison (double-blind period)	CDRS-R vs. placebo	Agomelatine 10 mg	Agomelatine 25 mg	-	Fluoxetine
	E	3.18	4.22	-	3.74
	SE	1.81	1.83	-	1.81
	Confidence Interval	[-0.37;6.73]	[0.63;7.82]		[0.18;7.30]

	P-value (Step Down Dunnett adjusted p-value for agomelatine dose regimen and p-value for Fluoxetine) (to be compared to 0.05)	0.079	0.040	-	0.039
Descriptive statistics and estimate variability (open-label period)	Treatment group	Agomelatine 10 or 25 mg / Agomelatine 10-25 mg		Placebo / Agomelatine 10-25 mg	Fluoxetine 10-20 mg / Agomelatine 10-25 mg
	Number of subjects	170		85	84
	CDRS-R Mean change from baseline (W012) at last post-baseline value	-16.3		-18.9	-16.1
	Standard deviation	± 12.2		± 16.1	± 15.5
	Remission Percentage of patients last post baseline value (all patients)	74.6%			
Notes	Results are reported in this document for the overall population. The adolescents represent 80% of the study population. The superiority of agomelatine 25 mg *versus* placebo was also confirmed in the adolescent subgroup for the primary endpoint.				
Analysis description	**Secondary analyses**				
Descriptive statistics and estimate variability (double-blind period)	Treatment group	Agomelatine 10 mg	Agomelatine 25 mg	Placebo	Fluoxetine
	Number of subjects	102	94	101	99
	CGI-S Mean last post baseline value	3.5	3.5	3.8	3.6
	Standard deviation	1.1	1.1	1.2	1.0
Descriptive statistics and estimate variability (double-blind period) (continued)	CGI-I Mean last post baseline value	2.6	2.5	2.7	2.6
	Standard deviation	1.1	1.0	1.1	1.0
	Response to treatment last post baseline value	48.0%	48.9%	44.6%	47.5%
	ADRS mean last post baseline value	18.8	18.1	22.2	19.9
	Standard deviation	±10.1	±10.6	±10.7	±10.3

Notes	The superiority of agomelatine 25 mg versus placebo was confirmed in the adolescent subgroup for the primary endpoint and on ADRS (the subpopulation specific endpoint). No statistically significant difference was observed between fluoxetine and placebo on any of these endpoints.

2.4.20. Discussion on clinical efficacy

In this procedure, the MAH was initially proposing to extend the indication of Valdoxan (agomelatine) to include treatment in adolescents aged 12 to 17 years with moderate to severe major depressive episodes (MDE) in combination with concurrent psychological therapy, when the depression is unresponsive to psychological therapy alone. The primary support for the efficacy of agomelatine in the target indication stems from one pivotal Phase 3 study CL3-076 including 400 patients, of which 320 were aged 12 to 17 years and 80 were 7 to < 12 years.

Design and conduct of clinical studies

Study design. Study CL3-076 was part of the paediatric investigational plan (PIP) for Valdoxan, and is a Phase 3, multicentre, randomised, double-blind, parallel groups, placebo-controlled study including an optional open-label extension period.

The primary objective was to demonstrate superiority of at least one of two doses of agomelatine (i.e., 10 mg and 25 mg) as compared to placebo in adolescents (12 – 17 years) with moderate to severe MDE and who were unresponsive to psychological therapy alone. The secondary objectives were to evaluate long-term efficacy and safety of agomelatine based on results from an open-label extension phase of the study.

The study was divided into 4 periods: 3-week run-in period, 12-week (W000 to W012) double-blind treatment period, an optional open-label extension period of 21 months (W012 to W104) and a 1-week follow-up period. In the 3-week run-in period patients did not receive any IMP but were given 2-3 sessions of Manualized Psychosocial Counselling (MPC) in order to decide their responsiveness to such therapy. Three weeks are considered too short for deciding which patients will respond or not. This was also agreed by the MAH which, in addition, admitted that not true non-responder patients possibly have been included in the study.

Patients were randomised to receive either agomelatine 10 mg, agomelatine 25 mg, placebo or fluoxetine 10-20 mg (added as active validator). In addition, MPC was given once a month in this period (i.e., W004, W008 and W012) and continued also at visits in the extension phase of the study. However, the MAH was asked to explain the reason for offering the psychosocial treatment only once a month (and even less frequently in the extension phase). At least once every other week would seem more relevant. According to the MAH the infrequent MPC-sessions were chosen mainly due to feasibility reasons. It is considered unfortunate that psychosocial therapy was not given more often. However, taking into account that Study CL3-076 is completed, this issue will not be further pursued. Nevertheless, in order to inform the prescribers, relevant information has been inserted in section 5.1 of the SmPC.

Study population. Initially both children (7 to < 12 years) and adolescents (12 to 17 years) could be included in the study. However, after encountering difficulties with recruiting patients in the lowest age group, the protocol was amended, leading to a smaller patient population consisting primarily of adolescents (80%). All enrolled patients were to have a primary diagnosis of MDD, single or recurrent episode, moderate to severe intensity, of at least 4 weeks' duration, as per the DSM-IV TR criteria. A cut-off on the raw score of Children's Depression Rating Scale – Revised (CDRS-R) of ≥ 45 (indicating moderate to severe depression) and a Clinical Global Impression-Severity (CGI-S) rating score ≥ 4 (implying at least moderate

depression) were requested for inclusion. The CDRS-R scale is originally modelled after the adult-specific Hamilton Rating Scale for Depression (HAM-D). While developed for use in children, the measure is also widely used in adolescents and has reportedly good reliability and validity within this age group as well. Overall, the use of the CDRS-R is endorsed. Generally, the inclusion and exclusion criteria for Study CL3-076 appears to largely reflect the target population of the indication sought. However, although not further pursued, as indicated above, the fact that many patients in the study might have been responders to psychosocial therapy violates the prerequisite of the applied indication which states that agomelatine should only be given to patients no longer responding to psychosocial therapy alone. For further details, see below under "Efficacy data and additional analyses" in this section 5.4.2.1.

Comparator. The study is placebo-controlled, which is considered acceptable for this type of studies. Fluoxetine was included merely for addressing the problem of assay sensitivity. No direct comparisons between the agomelatine groups and fluoxetine were planned or performed. The choice of fluoxetine is endorsed considering that it is the only antidepressant authorised in the EU for children (from ≥ 8 years) and adolescents suffering from MDE. The chosen dose regimen for fluoxetine is in accordance with the approved paediatric posology. The majority of patients (around 60%) in the fluoxetine treatment group remained on the initial dose of 10 mg/day throughout the double-blind period.

Agomelatine dose. The doses chosen in the pivotal study was 10 mg and 25 mg. This was based on results from a previous study CL2-075 evaluating the PK characteristics of 3 doses of agomelatine (5, 10 and 25 mg) in children and adolescents and indicating PK parameters in the same range as in the adult population. However, most paediatric agomelatine PK data derive from saliva concentration measurements, and it is not known whether systemic exposure following doses of 10 or 25 mg is overall comparable in children/adolescents and adults (refer to section 5.3.2).

Endpoints. The primary endpoint was adjusted difference in the CDRS-R raw total score from baseline to W012, using a 3-way ANCOVA model. Secondary efficacy endpoints included the scores on CGI-S and CGI-I, response to treatment (defined as a CGI-I score of 1 or 2; i.e., "very much improved" or "much improved", respectively), Children's Global Assessment Scale score (CGAS), and Adolescent Depression Rating Scale (ADRS) total score (the latter only in adolescents). It was noted that the MAH had not included a responder analysis examining the percentage (commonly 50%) decrease between the baseline and the concerned visit in the score of the CDRS-R. Such responder analyses are often used as primary endpoints in studies of depression. Furthermore, it is also mentioned in the CHMP's Guideline on depression, (EMA/CHMP/185423/2010 Rev. 2, 2013) that "In MDD a 50% improvement of a patient on a usual rating scale is accepted as a clinically relevant response". The lack of such a predefined cut-off value makes it difficult to conclude on clinical relevance of the primary endpoint. The MAH was asked to provide such analyses according to standard definitions of response. The requested analyses were submitted, and the results were deemed supportive of the main analyses. Supplementary analyses, examining the proportion of remitters (defined as CDRS-R raw total score ≤ 28) at W012 and at each visit, in both the total population and adolescents, were also performed.

Statistical analysis. The study was conducted in double-blind conditions**.** The treatment (agomelatine 10 mg, agomelatine 25 mg, placebo, fluoxetine) was assigned at inclusion (W000) by balanced (non-adaptative) randomisation and the patients recruited were stratified by country and children/adolescents age set (children from 7 to < 12 at selection; adolescents from 12 to < 18 at selection). It was determined that 390 patients with at least 312 adolescents (divided in each treatment group) were enough to allow to conclude that at least one dose of agomelatine was superior to placebo with a power of 89% in the overall population. A number of assumptions were made to implement the ANCOVA approach and verifications were made to ensure that the data was suitable for such an approach (linearity of the data, Normality and homoscedasticity of residuals, presence of outliers) although a number of uncertainties can be seen as affecting the robustness of the results. Furthermore, the prespecified MMRM model to be used as a sensitivity analysis which did not support the primary efficacy results was replaced by another one by the

applicant *post-hoc*. At W012, the step-down Dunnett's procedure was used to control the familywise error rate, since 2 doses of agomelatine will be compared to placebo. However, a number of secondary analyses were conducted, and p-values were presented although they can only be regarded as descriptive.

Study conduct. Two amendments were made to the original protocol after the study was initiated and patients enrolled. The first amendment pertained to strengthening of safety parameters, such as supplementary exclusion criteria for liver function. The second amendment concerned the reduction in planned sample size as mentioned above. The MAH confirmed that no EU inspectorates have performed GCP inspections of Study CL3-076. However, two sites have been inspected by inspectorates from Ukraine and Serbia. In the period between October 2019 and May 2020 no local laboratory assessments (including liver function tests) were done at the Serbian site, due to lack of central laboratory kits. As this was a serious breach, corrective and preventive actions were taken by the sponsor and the situation was later returned to normal. The MAH confirmed that the site comprised only 4 patients. It is considered very unfortunate that no laboratory assessments were performed for such a long period, however, it is reassuring that central laboratory tests later showed normal results for the 4 patients, especially concerning liver function tests.

Efficacy data and additional analyses

A total of 466 patients were screened, and 447 patients were selected for the study. The most common reason for screen failure was "non-compliance with inclusion/non-inclusion criteria" (40/66, i.e., ca. 60%). Of the selected patients, 400 were included and randomly assigned to one of the 4 following treatment groups: agomelatine 10 mg: 102 (81 adolescents); agomelatine 25 mg: 95 (75 adolescents); placebo: 103 (81 adolescents) and fluoxetine: 100 (80 adolescents). The most frequent reason for premature study withdrawals was non-medical (in total 7.8% of the patients), primarily driven by withdrawal of consent by the patient/parent. No patients were lost to follow-up. It is noted that rather few patients in each treatment group dropped out during the double-blind period (in total, 8, 11, 16 and 13 patients during W001-012 in the agomelatine 10 mg group, agomelatine 25 mg group, the placebo group and the fluoxetine 10 mg group, respectively). In total, 84.5% of the patients in the placebo group completed the study, reflecting the large placebo effect commonly observed in clinical studies of depression. The significance of frequent follow-ups of these patients in addition to concomitant psychosocial therapy is considerable. Overall, the same pattern as observed for the total population was also seen in the adolescent subset.

Baseline and disease characteristics. The mean age in the total population was 13.7 ± 2.7 years (median 14.0 years, range from 7; 17 years) with little difference between the 4 treatment groups. The study population included mainly females (in total 62.5%) with small differences between treatment groups. Considering that depression affects at least twice as many adolescent girls as adolescent boys, this imbalance is not unexpected. In total 71.5% of the patients were in their first MDE, with a higher rate in the agomelatine groups (78.4% for 10 mg vs. 74.7% in 25 mg) vs. 64.1% in the placebo group. This difference carries a risk for bias and a possible larger treatment effect for agomelatine (due to a possible higher placebo response). The episode was moderate for most of the patients (in total > 60%) and severe (without psychotic features) in a total of around 40%. The mean duration of the current episode was 143.4 ± 153.2 days with a median of 96.0 days (wide range from 29 to 1463 days). During the study, >95% of the patients participated in the MPC. All patients had CDRS-R raw total score ≥ 45 with a total mean of 65.5 ± 8.4. The differences in baseline mean score between the treatment groups were small. The total mean CGI-S score was 4.9 ± 0.6.

Overall, the baseline characteristics reported for the adolescent subset were quite similar to the characteristics observed for the total population. The specific adolescents scale, ADRS, showed a mean score at baseline of 33.1 ± 6.0.

Endpoints

Primary endpoint. In the Full Analysis Set (FAS), the numerical reduction in the CDRS-R raw score from baseline to W012 was almost similar between the placebo group (-19.7 ± 14.4) and the agomelatine 10 mg and 25 mg groups (-20.9 ± 14.0 and -22.5 ± 15.2, respectively), indicating a large placebo response. The absolute difference was 2.8 points for the agomelatine 25 mg group vs. placebo group, corresponding to only around 1/5 of the SD, which is not considered to be a robust result. The standard deviations were quite high, implying an inherent variability in the individual responses, and thus uncertainty in the overall results. It is further noted that the mean last post baseline value for the total population was around 43, not far below the cut-off value of ≥ 45 required for inclusion. This suggests that many of the patients still had moderate to severe depression. The proportion of patients reported to be remitters confirmed that very few gained a CDRS-R raw score ≤ 28 (13.7% in the agomelatine 10 mg group, 16.0% in the agomelatine 25 mg group, 10.9% in the placebo group and 12.1% in the fluoxetine group) within W012.

The adjusted difference between the placebo group and each of the two agomelatine groups, calculated as placebo minus each agomelatine dose regimen according to the ANCOVA model, showed a statistically significant difference only for agomelatine 25 mg compared to placebo (E (SE) = 4.22 (1.83); 95% CI [0.63; 7.82]; Step-Down Dunnett adjusted p-value = 0.040). However, the wide CI makes this estimate quite imprecise and the modest effect size, combined with a significant but very high p-value, raises questions on the robustness of the results. The study failed to discriminate between placebo and agomelatine 10 mg, indicating that this dose is too low and not efficacious. Assay sensitivity was demonstrated between placebo and fluoxetine.

A LOCF approach was used for handling missing data, and several sensitivity analyses were performed In order to confirm robustness of the primary endpoint. The planned MMRM model failed, though, to show any statistically significant differences between any of the groups. An ANCOVA model on complete cases at W012 demonstrated statistically significant difference between the agomelatine 25 mg group vs. placebo (but did not show assay sensitivity). However, there is an inherent risk of bias in complete case analyses. After unblinding of the data, the MAH adjusted the initial MMRM model by adding an additional covariate ("baseline-by-visit interaction"). The use of the new model led to a result in line with the one gained for the primary efficacy analysis. However, such *post-hoc* changes of the sensitivity analysis model are not acceptable for a number of reasons related to the integrity of the study, the uncertainty over whether and how the best model fit was selected, and hence the inherent risk for bias. A multiple imputation approach analysis was performed also *post-hoc*, confirming the results seen in the main analysis. However, this method assumes that data are missing at random, making the conclusions of this analysis less robust. In conclusion, none of the pre-planned sensitivity analyses gave any further reassurance of the reliability of the effect estimate achieved in the primary efficacy analysis.

In the adolescent subset agomelatine 25 mg showed a statistically significant difference vs. placebo on CDRS-R total raw score in terms of adjusted difference from baseline to last post-baseline value with an estimate of 5.22 (2.13) (95% CI [1.03; 9.40], Step-Down Dunnett adjusted p-value = 0.028). The absolute difference was 4 points for the agomelatine 25 mg (-23.8) group vs. placebo group (-19.8) corresponding to only around ¼ of the SD, which is neither considered to be a large effect size nor a robust result. Not unexpectedly, also for the subset of adolescents the 95% CI was wide, indicating low precision of the estimate. Although numerically slightly higher than in the total population, also in this subset the large placebo response led to a modest effect size and ultimately a result of clinically doubtful relevance. As for the FAS, no statistically significant difference was found between agomelatine 10 mg and placebo in the adolescent subset. In contrast to the FAS, though, assay sensitivity of fluoxetine was formally not demonstrated for the adolescent subgroup. The same sensitivity analyses performed in the FAS were all done *post-hoc* in the adolescent subgroup. As concluded for the FAS, the sensitivity analyses do not give reassurance of the primary endpoint result being reliable in the adolescent subset either.

As requested during the assessment, the MAH performed a separate analysis of each of the CDRS items 1 to 17 for the adolescent population. The results showed that overall, the mean differences between the baseline and post baseline values for all 17 items were similar or only numerically slightly higher for agomelatine 25 mg vs. placebo. For 7 of the items (i.e., difficulty having fun, social withdrawal, sleep disturbance, appetite disturbance, excessive guilt, depressed feeling, depressed facial affect) the 95% CI for agomelatine did not include 0, indicating a difference from placebo in favour of agomelatine. Due to the melatonergic agonist effect of agomelatine (MT1 and MT2 receptors) it has been postulated that agomelatine might have positive effect specifically on sleep. However, the CDRS-R subscore results did not indicate that agomelatine improved the item sleep disturbance more compared to the other items.

As requested, the MAH also performed a post-hoc subgroup-analysis on patients having moderate depression at baseline vs. patients having severe depression at baseline (both according to DSM diagnosis) in order to find out whether the CDRS-R effect estimate differed between these two subgroups. It appears that the adjusted treatment effect estimate for agomelatine was independent of whether the depression was categorised as moderate or severe at baseline (4.36, 95% CI [-0.26;8.98] vs. (4.67, 95% CI [-1.34;10.69], respectively). However, the number of patients was limited (especially in the group of patients with severe depression) and the 95% CI were quite wide and overlapped. Furthermore, considering this is an unplanned post hoc analysis no conclusions regarding statistical significance can be drawn.

Secondary endpoints. The results from the secondary endpoints did not support the primary efficacy analysis in the FAS. Corresponding (though unplanned) analyses were performed in the adolescent subset and similar results as in the FAS were observed. Concerning the specific scale in adolescents, the ADRS, this score pointed in the same direction as the results for adolescents seen on the CDRS-R. However, it is difficult to directly compare the results between the two scales.

In summary, the results from the primary efficacy analysis yielding small, non-robust effect estimates, suggest a considerable placebo response possibly amplified by the concomitantly administered psychosocial therapy. According to the sought indication, patients should be non-responsive to psychosocial treatment alone. However, this was decided during only 2-3 sessions in a 3-week period before selection.

Such a short time period is considered insufficient to fully evaluate response to psychosocial support. It is noted that the CHMP guideline on depression in regards to children and adolescents only states that all patients should receive "psychosocial interventions" throughout the trial, but that the length and frequency of such treatment is not specified. However, consulted clinical experts are also of the opinion that 3 weeks are too short to determine who would be a responder or not. The MAH agreed that this short time frame was not adequate and also admitted that misidentified non-responder patients possibly have been included. The MAH indicated that inclusion of patients being responders to psychosocial therapy would disfavor agomelatine as these patients would contribute to the placebo effect observed in the study. However, the reverse could also be true if misidentified non-responders to psychosocial therapy would respond better to agomelatine (e.g., in the short-term, or because their misidentification reflects underlying confounding factors likely to affect prognosis). This may still be clinically relevant; however, it does not reflect the patient population intended by the applied indication. The significant interaction between treatment and baseline could also reflect this potential bias, and overall, this suboptimal element of the design adds further uncertainty to the efficacy conclusions.

Another important critical aspect of including several patients who are not true non-responders is that it violates the prerequisite of the applied indication, i.e., that only patients who no longer respond to psychosocial therapy should be given agomelatine. The target population included in the study may not fully represent the patient population intended by the indication. However, it is acknowledged that it could be difficult to identify such subjects, and hence, this issue is not pursued.

The phenomenon of high placebo response is commonly seen in clinical trials of depression. Possible factors contributing to the observed large placebo response in the pivotal study might be a large proportion of

patients experiencing their first MDE and of mostly moderate severity, in addition to relatively few co-morbidities. As already mentioned, the observed larger proportion of patients (~ 10%) having their first MDE in the agomelatine 25 mg group vs. the placebo group carries a risk of bias and possibly a larger treatment effect for agomelatine.

According to the MAH, the effect size for agomelatine on CDRS-R for adolescents became 0.36 (the calculation of the sample size assumed an effect-size of 0.5). In order to contextualise the effect size in adolescents, the MAH tried making comparisons with the effect size achieved in former studies with agomelatine in adults. A form of meta-analysis, based on a selection of 6 previous positive non-elderly adult agomelatine studies vs. placebo, excluding 3 negative studies, was submitted. The overall effect size of the pooled adult studies was stated to be 0.36, but with a wide CI (95% CI 0.19; 0.53). Retrospective, and indirect comparison of data is uncertain and partly hampered due to possible important differences in e.g., methodology, study population, the use of different rating scales (HAM-D in adults vs. CDRS-R in the paediatric population), treatment duration and use of different dose regimens (e.g., in some of the studies in adults 50 mg was also allowed) and the risk of inherent selection bias in terms of which studies were used for the meta-analyses or not. Hence, this meta-analysis is not readily accepted as reliable evidence for concluding that the effect size for agomelatine is similar between adolescents and adults. The MAH reckons this meta-analysis to be an additional indirect argument in favour of relevance of the efficacy of agomelatine in adolescents but acknowledged that the adolescent vs. adult comparison is not conclusive by itself. The MAH also referred to an effect size of 0.51 stated for fluoxetine in a study comprising children and adolescents with MDD (Emslie *et al* 1997 and 2002). This was higher than what was achieved for agomelatine. However, it is difficult to interpret the significance of a given effect size and even more complex when comparing effect sizes across studies. In adults, it was previously concluded that the magnitude of effect for agomelatine was of marginal clinical relevance, even though it was acknowledged that agomelatine had documented some short-term efficacy (EPAR for Valdoxan, EMEA/655251/2008).

In their response to the 2nd Request for Supplementary Information, the MAH refers to several meta-analyses (Zhou et al, 2020, Cipriani et al, 2016 and Feeney et al, 2022, Locher et al, 2017) reporting the effect size of fluoxetine. Based on the totality of the data from these meta-analyses, standardized mean differences (SMDs) in the range of 0.21 – 0.51 could be deduced for fluoxetine (versus placebo). For agomelatine, SMD values in the range of 0.19 – 0.29 could be observed (data based on Feeney et al, 2022 and Arango et al, 2022). The true effect size of fluoxetine and agomelatine vs. placebo could probably be found within this SMD-range of 0.19-0.51. In summary, it is not considered that these articles represent any new information. The notion that the effect size of agomelatine is modest is supported by these data.

The MAH also referred to a placebo-controlled paediatric study by Findling et al (2022) reporting a SMD (Cohen's d) of 0.3 for fluoxetine vs. placebo. However, in this study fluoxetine was only added to ensure assay sensitivity and the main objective of the study was to test vortioxetine against placebo. Furthermore, the study design differed from study CL3-076, (e.g., Findling's study had a 4-week single-blind run-in period with brief psychosocial intervention followed by an 8-week double-blind, randomised period) and the sample size was considerably larger. Overall, it is not considered that these data represent any new information.

In conclusion, the short-term efficacy of agomelatine is modest, not robustly estimated and still considered to be of questionable clinical relevance. This issue was raised as Major Objection in the 3rd RSI. In their response to this RSI, the MAH informed the CHMP that they withdrew the application for extension of the indication to include adolescents. Instead, the scope of the variation was changed and the MAH proposed to reflect the data from Study CL3-076 in various sections of the SmPC. Consequently, the MO was not resolved, but no longer pursued.

Open label, optional extension period. At W012 visit, all patients who were considered to benefit (not based on any specific criteria) from a continuation of treatment with agomelatine were offered to enter the open-labelled safety 21-month extension period. As there was no control group in this period (all patients

were treated with agomelatine), this part of the study is of less relevance from an efficacy perspective. During the extension phase the agomelatine dose was 10 mg for all patients for the first 2 weeks, then the dose could be adjusted at each visit from 10 mg to 25 mg and *vice versa*. This is not in line with sought posology, where the recommended dose in adolescents is 25 mg once daily without any dose adjustment. According to the MAH flexible dosing was chosen because the efficacy results of the double-blind period were not available at the time when Study CL3-076 was initiated and also based on experience with flexible dosing in adults. It is considered unfortunate having two different dosing regimens in the double-blind vs. extension period of the study. These features make it impossible to get any impression of potential trends in the long-term efficacy development for the applied posology.

A total of 339 patients entered this period and was distributed as follows on 3 treatment groups: 170 in the agomelatine 10 mg or 25 mg/agomelatine 10-25 mg group (patients receiving either 10 mg or 25 mg in the double-blind period were pooled into one agomelatine group), 85 in the placebo/agomelatine 10-25 mg group and 84 in the fluoxetine 10-20 mg/agomelatine 10-25 mg group. It is noted that a similar proportion of patients in the agomelatine 10 mg group compared to the agomelatine 25 mg group (nearly 90% [91/102] vs. 83% [79/95], respectively) found it beneficial to continue in the study. Considering that the 12-week double-blind period of the study failed to discriminate agomelatine 10 mg from placebo and hence this dose appears to be ineffective, this further underlines the large response on placebo combined with concomitant psychosocial treatment.

The primary efficacy endpoint was defined as the value in the CDRS-R Raw score. A gradual decrease in the score was shown during the W012-W104 period in all 3 agomelatine groups. The rate of remitters gradually increased along the extension period from 13.6% at W012 to 83.5% at W104 (last post-baseline value 74.6%). Due to lack of a comparator placebo group, the true rate of remitters after long-term use with agomelatine is unknown. Relapse (CDRS score $\geq$ 40 or a withdrawal due to lack of efficacy) and stringent relapse (CDRS score $\geq$ 40) were analysed only until W040 in a very selected population of patients (i.e., only those receiving agomelatine [either of the two doses pooled or only 25 mg], in the double-blind period, and by using a rather comprehensive definition of "significant clinical response" defined as: either a CDRS-R score < 40 and a CGI-I score of 1 or 2 or a decrease of $\geq$ 50% on the CDRS-R score). Very few of the patients having a "significant clinical response" at W012, relapsed during W012-W040 (8/69 in the agomelatine 10-25 mg group vs. 5/31 in the agomelatine 25 mg, respectively). However, due to lack of a control group, no valid conclusions of the true long-term relapsing rate of agomelatine can be made on the basis of these data. Similar observations were made for all of the corresponding parameters in the adolescent subgroup. It is noted that the definition of "remitters" and "responders" differed between the double-blind period and the extension period.

No firm conclusions can be drawn with regard to the maintenance effect of agomelatine based on the data from the extension period. Overall, 30% to 70% of youth with MDE recover during the first year of illness, although 30% subsequently relapse (Birmaher *et al*, 2002). Hence, without a placebo group, it is impossible to conclude that patients would not have reached equivalent outcomes because of passage of time. In order to compensate for the lack of a double-blind relapse prevention study in the paediatric population, the MAH referred both to maintenance results achieved with agomelatine in former relapse-prevention studies in adults and long-term results reported for fluoxetine in a paediatric population (TADS study, 2007). Regarding the latter, it is acknowledged that when comparing improvements in CDRS total score after 36 weeks of fluoxetine treatment ($\approx$ - 32.1) and after 40 weeks of agomelatine treatment in the CL3-076 study (-31.9 $\pm$ 13.4), they seemed very similar. The response rate was, however, somewhat better for fluoxetine (81% vs. 73% for agomelatine). But, as previously mentioned regarding the validity of comparing the short-term efficacy results between studies of agomelatine and fluoxetine, such comparisons are hampered by several limitations and differences which makes the cross-study comparisons of effect sizes and responder rates for agomelatine and fluoxetine uncertain. Concerning the alleged similarity with long-term efficacy of agomelatine in adults, the MAH referred to that expected long-term pharmacodynamic effects

of the agomelatine can be observed in a sub-set of young adults (18-30 years old) from the previous relapse-prevention study CL3-041 in adults (crude relapse rate 21.7% on agomelatine in young adults' subset vs. 23.6% in adults of all ages). However, this small group of 23 patients examined retrospectively in a *post-hoc* analysis is not considered valid as proof for concluding that a similar relapse rate would be expected also in patients from 12 years. The MAH pointed to the CHMP's guideline on depression, where it is indicated that evidence of maintenance efficacy available from studies in adults can be taken into account for the paediatric population. However, it has to be emphasised that the acceptability of doing so, would depend on the magnitude of efficacy observed in the short-term trials, which is seriously questioned for agomelatine. Concerning the general acceptability of basing long-term efficacy in adolescents largely on the concept of extrapolation to corresponding results in adults, a reasonable degree of certainty has to be assumed in that critical elements such as disease, progression of disease and prognosis are similar for adolescents and adults. Of special importance in that respect, is the fact that adolescents are not fully developed biologically, cognitively and socially. In their response to the 1. RSI, the MAH underlined that the clinical efficacy of agomelatine, both for short- and long-term treatment, did not rely only on extrapolation of adult data to adolescents but mainly on efficacy data collected during the CL3-076 clinical study. The MAH's view is noted. The MAH argued that major depression in the paediatric population and – especially in adolescents over 12 years old – and major depression in the adult population are parts of the same disorder (Rice et al., 2019, Bylund and Reed, 2007). This is agreed to a certain extent; however, the literature is not considered to be fully consistent in this view. Rice et al. (2019) stated that evidence from twin studies suggests genetic differences between adolescent and adult depression. Furthermore, even if it from a clinical perspective is useful to consider adult and adolescent depression as the same disorder, it is nevertheless accepted that there are aetiological and treatment response differences between adolescent and adult depression. It can be agreed though that there are only minor differences in the diagnostic criteria used to define MDD in adults and in children/adolescents in the last versions of DSM (DSM-IV, DSM IVIV-TR, DSM-5). In the CHMP guideline on Depression (EMA/CHMP/185423/2010 Rev. 2, 2013) it is also indicated that "Depressive disorders in children and adolescents are phenomenologically equivalent to those in adults, but depressive disorders conforming to adult diagnostic criteria rarely present before the age of seven years." Nonetheless, the diseases are not reckoned to be so similar that extrapolation of adult efficacy and safety data is considered appropriate. Specific studies are necessary in the paediatric population. The guideline opens for taking into account results gathered from long-term studies in adults, however, as already mentioned, this depends on the magnitude of efficacy observed in the short-term trials in the paediatric population. Due to the modest and uncertain short-term efficacy, it is not considered appropriate to extrapolate from the long-term data achieved previously in adult patients. Furthermore, it is not known whether systemic exposure following doses of 10 or 25 mg is overall comparable in children/adolescents and adults.

According to the MAH it would be unethical to perform a relapse-prevention study. The MAH referred to 3 relapse prevention studies performed in patients from 13-25 years for citalopram (2 studies of very limited sample size) and fluoxetine which all showed high relapse rates in the placebo groups. However, comparing relapse rates observed in these studies with the low relapse rates achieved with agomelatine in the extension phase of study CL3-076 is not considered appropriate. When considering agomelatine's modest short-term efficacy of doubtful clinical relevance and the fact that all participants would receive psychotherapy it is not agreed that a well-designed controlled long-term study, for instance a relapse prevention study, in adolescents would be unethical. In conclusion, this type of long-term study is deemed necessary.

2.4.21. Conclusions on the clinical efficacy

In the single pivotal study CL3-076, only agomelatine 25 mg showed a statistically significant difference compared to placebo on the CDRS-R raw total score both in the FAS and the adolescent subset. However,

the considerable placebo response, possibly amplified by the concomitantly administered psychosocial therapy and the likely inclusion of responders to such therapy, translated into only a modest effect size which seriously questions the clinical relevance of the effect estimate. Furthermore, the robustness of the estimate is not confirmed by any of the sensitivity analyses.

In addition, sufficient long-term efficacy and safety data are lacking and due to the uncertain short-term efficacy, it is not considered appropriate to extrapolate in adolescents based on the long-term data achieved previously in adult patients. A well-designed controlled long-term study in adolescents is needed. These issues were raised as during the assessment process by the CHMP. In their response the MAH informed the CHMP that they withdrew the claim for extending the indication to include the adolescent population. Instead, the MAH proposed to reflect the data from Study CL3-076 in various sections of the product information.

2.5. Clinical safety

2.5.1. Introduction

Safety data for the currently approved adult indication of agomelatine (Valdoxan)

Valdoxan (agomelatine) has a favourable benefit-risk profile based on efficacy and safety data in the treatment of major depressive episodes (MDE) in adult patients.

Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were headache, nausea and dizziness. These adverse reactions were usually transient and did not generally lead to cessation of therapy.

Hepatotoxicity

The main safety concern is hepatotoxic reactions which is stated as an important identified risk in the RMP. Cases of liver injury, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors), elevations of liver enzymes exceeding 10 times upper limit of normal, hepatitis and jaundice have been reported in patients treated with agomelatine in the post-marketing setting (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with increased serum transaminases, which usually return to normal levels on cessation of agomelatine.

To avoid serious hepatotoxicity, liver transaminases should be monitored before treatment initiation, at week 3, 6, 12 and 24 and thereafter when clinically indicated.

Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)

This is another important identified risk in RMP. Concomitant use with potent CYP 1A2 inhibitors is contraindicated.

Suicide-related events

As for treatment with antidepressant agents in general, patients on agomelatine should be monitored for suicide-related events, especially in early treatment and following dose changes.

Below is a table from the current Valdoxan SmPC, where ADRs for the approved MDE indication in adults are stated.

Table 55. Adverse reactions identified primarily during clinical trials with agomelatine

System organ class	Frequency	Preferred Term
Psychiatric disorders	Common	Anxiety
		Abnormal dreams*
	Uncommon	Suicidal thoughts or behaviour (see section 4.4)
		Agitation and related symptoms* (such as irritability and restlessness)
		Aggression*
		Nightmares*
		Mania/hypomania* These symptoms may also be due to the underlying disease (see section 4.4).
		Confusional state*
	Rare	Hallucinations*
Nervous system disorders	Very common	Headache
	Common	Dizziness
		Somnolence
		Insomnia
	Uncommon	Migraine
		Paraesthesia
		Restless leg syndrome*
	Rare	Akathisia*
Eye disorders	Uncommon	Blurred vision
Ear and labyrinth disorders	Uncommon	Tinnitus*
Gastrointestinal Disorders	Common	Nausea
		Diarrhoea

		Constipation
		Abdominal pain
		Vomiting*
Hepato- biliary disorders	Common	Increased ALT and/or AST (in clinical trials, increases >3 times the upper limit of the normal range for ALT and/or AST were seen in 1.2% of patients on agomelatine 25 mg daily and 2.6 % on agomelatine 50 mg daily vs. 0.5% on placebo).
	Uncommon	Increased gamma-glutamyltransferase* (GGT)(>3 times the upper limit of the normal range
	Rare	Hepatitis
		Increased alkaline phosphatase* (>3 times the upper limit of the normal range)
		Hepatic failure*(1)
		Jaundice*
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis
		Eczema
		Pruritus*
		Urticaria*
	Rare	Erythematous rash
		Face oedema and angioedema*
Musculoskeletal and connective tissue disorders	Common	Back pain
	Uncommon	Myalgia*
Renal and urinary disorders	Rare	Urinary retention*
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Weight increased *
	Uncommon	Weight decreased*

* Frequency estimated from clinical trials for adverse reactions detected from spontaneous report
(1) Few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors.

Marketing authorisation (MA) for Valdoxan was granted in February 2009. Renewal of the MA was granted with unlimited validity in 2018; procedure no.: EMEA/H/C/0915/R/042.

The following risks are remaining for agomelatine in the current EU RMP v.25.0, see Table 56 below.

Table 56. Summary of the safety concerns from the RMP for Valdoxan

Important identified risks	- Hepatotoxic reactions - Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)
Important potential risk	- None
Missing information	- Pregnancy - Lactation

2.5.2. Patient exposure

The safety of agomelatine in adult patients was investigated in all clinical studies of the overall agomelatine clinical development programme including 55 completed phase II and phase III studies, performed by Servier (51 studies) and a co-development partner (Novartis, 4 studies in USA). Among them:

- 38 studies were in patients with MDE,
- 17 studies were in other indications.

The safety profile was also assessed in healthy volunteers and in subjects with liver failure or renal impairment, including drug interaction studies and in 3 phase IV specific safety studies (2 observational and 1 genetic susceptibility studies).

The safety of agomelatine in the paediatric population was investigated in:

- One exploratory study performed in Smith-Magenis Syndrome (CL2-044).
- One open-label PK and safety phase II study in depressive or anxiety disorders (CL2-075)
- One efficacy and safety study in the treatment of Major Depressive Disorders (MDD) in paediatric patients of moderate to severe intensity (CL2-076).

The list of studies providing safety information for agomelatine in MDD in the paediatric population is presented in the Table **57**.

Table 57. Agomelatine clinical paediatric development programme in the MDD*

Study Number	Study Design and Type of Control Number of Patients Included	Doses mg/day	Dose titration time & criteria	Duration of Treatment	Objective(s) of the Study
CL2-075 NP34026	Non-comparative, Open label, intra subject dose escalation 51 patients from 7 to 17 years old	Agomelatine: 5, 10 and 25 *o.d.*	NA	3 days	PK and safety in Depressive or Anxiety Disorder
CL3-076 NP40580	Double-blind, randomised, placebo controlled. 400 patients from 7 to 17 years old	Agomelatine: 10 mg *o.d.* or 25 mg o.d. Fluoxetine: 10-20 mg o.d.	No dose titration for agomelatine. For fluoxetine, if no improvement at week 2, the dose could be increased from 10 mg to 20 mg.	3 months (optional open extension period with agomelatine 10-25 mg o.d. up to 2 years)	Efficacy and safety in Major Depressive Disorder (of moderate to severe intensity)

**or anxiety in the CL2-075 study*

The number of exposed individual patients [MDE paediatric, MDE adolescents, all indications paediatric and MDE adults (including bipolar patients, patients with Seasonal Affective Disorder (SAD) and severely ill hospitalized depressed patients)] who received at least one dose of agomelatine, in either controlled or open studies, by oral or i.v. route, is presented below.

Table 58. Number of patients who received at least one dose of agomelatine

No. of individuals	MDE paediatric	MDE adolescent	Total paediatric in all indications*	MDE adults
Total (All studies)	416	320	425	8,532

**MDE paediatric + 9 patients in Smith Magenis Syndrome (CL2-044, NP26808)*

The strategy of the safety evaluation in the paediatric population was an analysis of the pooled safety data from phase II/III studies in adolescents and children with MDE (CL3-076) or depressive /anxiety disorders (CL3-075) and a comparison of this paediatric MDE population to the adult MDE population to assess if the safety profile in paediatric patients is similar to the safety profile already known in adult patients.

The objectives of this grouping are to assess in the MDE paediatric population:

- The overall exposure to agomelatine.

- The general safety profile of agomelatine.

The most frequently reported EAEs on agomelatine 25 mg in the Ado MDE set are studied in the Adult MDE set; those not more frequently reported on agomelatine 25 mg than on placebo in adults, are described in the Ado MDE DE PC set to confirm or not the difference between Ado and Adults.

The analysis sets are:

- The **all paediatric MDE set (paed MDE)**, including data from the CL2-075 phase II study (depressive or anxiety disorders) and the CL3-76 phase III study in the paediatric MDD, corresponding to **450 patients**

- The **adolescent MDE set (ado MDE)**, including data from the CL2-075 phase II study (depressive or anxiety disorders) and the CL3-76 phase III study in the adolescent MDD population (12 to 17 years old), corresponding to **346 patients**

- The **child MDE set**, including data from the CL2-075 phase II study (depressive or anxiety disorders) and the CL3-76 phase III study in the child MDD population (7 to 11 years old), corresponding to **104 patients**.

- The **adult MDE Set**, considering the exhaustivity of information for agomelatine exposure in the MDE adult population. Thus, it included the 35 studies performed in the indication MDE and the 2 studies in the indication Bipolar disorders, corresponding to **12826 patients** (80.1% of the Overall Safety Set). To be noted that the CL3-073 MDE study (N = 307 patients) was not included in the pooling because of its particular design (switch study, NP32125).

- The **paediatric Double-Blind Placebo-Controlled set (paed MDE DB PC)**, including data from the 12-weeks double-blind period of the CL3-076 Phase III study, corresponding to **399 patients**

- The **adolescent Double-Blind Placebo-Controlled set (ado MDE DB PC)**, including data from the 12-weeks double-blind period of the CL3-076 Phase III study, corresponding to **319 patients**.

- The **adult Double-Blind Placebo-Controlled set (adult MDE DB PC)**, including data from the double-blind placebo controlled studies, corresponding to **5615 patients**

- The **extension adolescent MDE set (ext ado MDE)**, including adolescent data from the extension period (W012-W104 period) of CL3-076 study, corresponding to **269 patients**.

- The **"One-Year" exposure Set paediatric MDE**, considering paediatric patients from the CL3-076 study exposed to agomelatine for at least 350 days corresponding to **136 patients**.

- The **"One-Year" exposure Set ado MDE**, considering adolescents from the CL3-076 study exposed to agomelatine for at least 350 days, corresponding to **115 patients**.

- The **"One-Year" exposure Set adult MDE**, considering patients from the adult MDE population exposed to agomelatine for at least 350 days corresponding to **657 patients**.

For all sets, except the extension adolescent MDE set, patients were allocated to the treatment group corresponding to the dose defined in the study, and in case of dose increase (10 to 25 mg) under agomelatine, the considered dose was the one received during the longest period of time.

Patients having received placebo during the double-blind period and continuing in the extension period, were analysed according to the treatment received during the longest period of time, explaining both the low number and the short duration of treatment in the "Paediatric placebo" group as only prematurely withdrawn or patients non-continuing in the extension period remain in this group.

For the extension adolescent MDE set, patients were allocated to the agomelatine 10/25 mg treatment group.

This document mainly presents safety information of the CL2-075 study in depressive/anxiety disorders and the CL3-076 study in MDE paediatric population compared to safety in 37 studies phase II/III performed in the MDE adult population, focussing on adolescents treated with agomelatine 25 mg in comparison to patients on placebo. The most frequently reported EAEs on agomelatine 25 mg in the Ado MDE set are studied in the Adult MDE set; those not more frequently reported on agomelatine 25 mg than on placebo in adults, are described in the Ado MDE DB PC set to confirm or not the difference between ado and adults.

The main analysis sets used in this document for adverse events description are given in the table below which displays the distribution of patients per treatment and dose group in each set.

Table 59. MDE Sets of analysis and number of patients by treatment group

Dosage	1-5 mg	10 mg	25 mg	50 mg	100 mg	All Ago	Placebo	All comp*
Paed MDE set		174	242	-	-	416	18	16
Ado MDE set		128	192	-	-	320	13	13
Ado MDE DB PC set		81	75	-	-	156	82	81
Adult MDE set	302	132	5662	2422	14	8532	1393	2901

**Comp: comparators*

Overall, 5662 adults were treated with agomelatine 25 mg. Out of the 416 paediatric patients treated with agomelatine, 192 were adolescents treated with agomelatine 25 mg.

Table 60. Number of exposed patients and treatment duration (months) in the MDE

	Paediatric MDE		Ado MDE		Adult MDE	
	Ago 25 mg (N = 242)	Placebo (N = 18)	Ago 25 mg (N = 192)	Placebo (N = 13)	Ago 25 mg (N = 5662)	Placebo (N = 1393)
Treatment duration	2 studies		2 studies		37 studies	
Mean ± SD	13.2 ± 9.8	1.6 ± 0.8	14.1 ± 9.3	1.7 ± 0.9	4.5 ± 3.7	3.3 ± 2.9
Median	16.7	1.6	17.9	1.8	3.7	1.9
At least 1-month n (%)	188 (77.69)	13 (72.22)	161 (83.85)	10 (76.92)	4927 (87.02)	1135 (81.48)
At least 3 months n (%)	169 (69.83)	-	145 (75.52)	-	3058 (54.01)	555 (39.84)
At least 6 months n (%)	157 (64.88)	-	134 (69.79)	-	992 (17.52)	107 (7.68)
At least 9 months n (%)	150 (61.98)	-	128 (66.67)	-	773 (13.65)	79 (5.67)
At least 12 months n (%)	135 (55.79)	-	114 (59.38)	-	312 (5.51)	12 (0.86)

N: number of patients

Regarding the 242 children and adolescents (paediatric population) who received the 25 mg dose, mean treatment duration was 13.2 ± 9.8 months, 157 had at least a 6-month exposure and 135 had at least a 1-year exposure. The mean treatment duration on agomelatine 25 mg is much lower in the adult MDE population set (4.5 ± 3.7 months).

It is important to note that the large difference of treatment duration between the paediatric and the adult populations is due to the fact that the Adult MDE set includes a large number of short-term studies without or with brief extension periods whereas most paediatric patients continued and many finished the long open-label extension period of study CL3-076.

The second important point to note is that the treatment duration was much higher in the agomelatine than in the placebo groups especially in the paediatric and adolescent populations.

The unbalanced treatment duration between groups is explained by the design of the studies (all continuing patients received only agomelatine during the open-label extension periods of several studies). Furthermore, the choice to provide the opportunity for all patients to receive an agomelatine treatment during the study maximized the agomelatine exposure period in these sets: indeed only the agomelatine exposure period is considered for patients who were treated by both placebo and agomelatine (agomelatine treatment in extension periods).

Both above mentioned points have an impact on many analyses presented in this document, comparing adolescent and adult patients data.

When regarding MDE DB PC sets, mean treatment durations were similar in agomelatine 25 mg and placebo groups for both paediatric population (2.6 ± 0.5 versus 2.6 ± 0.6 months) and adolescents (2.7 ± 0.5 versus 2.6 ± 0.5 months).

Demographic and Other Characteristics of Study Population

Demographic and other characteristics of the study population are presented for the paediatric and adolescent MDE sets in comparison to the adult MDE set below. Further relevant demographic and baseline data, medical history and previous and concomitant treatments for the pivotal paediatric study CL3-076 may be found in section 5.4. Clinical efficacy (in subsection 5.4.15 Baseline data).

The main baseline characteristics (demography, vital signs and risk factors) in the paediatric MDE, adolescent MDE and adult MDE sets are shown in Table 61 below.

Table 61. Demographic and main baseline characteristics – Paediatric, Ado and adult MDE sets

	Paediatric MDE		Ado MDE		Adult MDE	
	Ago 25 mg (N = 242)	Placebo (N = 18)	Ago 25 mg (N = 192)	Placebo (N = 13)	Ago 25 mg (N = 5662)	Placebo (N = 1393)
Age (years)						
Mean ± SD	13.6 ± 2.7	13.7 ± 3.1	14.7 ± 1.6	15.4 ± 1.1	44.4 ± 13.1	46.1 ± 14.0
Median	14.0	14.5	15.0	16.0	45.0	46.0
< 12, n (%)	50 (20.7)	5 (27.8)	-	-	-	-
[12; 18[, n (%)	192 (79.3)	13 (72.2)	192 (100)	13 (100)	-	-
[18; 65[, n (%)	-	-	-	-	5294 (93.5)	1232 (88.4)
[65; 75[, n (%)	-	-	-	-	293 (5.2)	123 (8.8)
≥ 75 years, n (%)	-	-	-	-	75 (1.3)	38 (2.7)
Gender						
Female, n (%)	163 (67.4)	10 (55.6)	140 (72.9)	8 (61.5)	3976 (70.2)	977 (70.1)
Male, n (%)	79 (32.6)	8 (44.4)	52 (27.1)	5 (38.5)	1686 (29.8)	416 (29.9)
BMI (Kg/m²)						
Obese*, n (%)	12 (4.96%)	3 (16.67%)	9 (4.69%)	3 (23.08%)	1119 (19.76%)	291 (20.89%)

N: number of patients, median (months)
**≥ 30 for adults; > +2SD for paediatric population*

In the paediatric MDE set, patients on agomelatine 25 mg were on average 13.6 +/- 2.7 years old, most of them were girls (67.4%) and 5% of patients were obese. In the Ado MDE set, patients on agomelatine 25 mg were on average 14.7 +/- 1.6 years old, and 72.9% were females.

The overall safety assessment described in the application focussed on the paediatric MDE set including 242 patients treated with agomelatine 25 mg for a mean duration of around 13 months and 192 adolescents treated around 14 months. In the placebo group, the mean duration was around 2 months in both paediatric (18 patients) and adolescent (13 patients) MDE sets. Median treatment duration was 16.7, 17.9 and 3.7 months in the paediatric, Ado and Adult MDE sets, respectively.

As agomelatine and placebo groups were very unbalanced in terms of size (242 versus 18 patients, respectively) and treatment duration, data should be interpreted with caution and conclusions on possible safety issues in the paediatric MDE set compared to the adult MDE set should be considered as regard to paediatric MDE DB PC set.

2.5.3. Adverse events

Adverse events during the double-blind phase

Table 62. Overall summary for adverse events in the Safety Set in CL3-076

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

EAE leading to treatment withdrawal					
Total population	n (%)	3 (2.9)	4 (4.3)	2 (1.9)	3 (3.0)
Adolescents	n (%)	2 (2.5)	3 (4.0)	1 (1.2)	3 (3.7)
Children	n (%)	1 (4.8)	1 (5.3)	1 (4.8)	-
Serious EAE leading to treatment withdrawal					
Total population	n (%)	3 (2.9)	2 (2.1)	-	2 (2.0)
Adolescents	n (%)	2 (2.5)	2 (2.7)	-	2 (2.5)
Children	n (%)	1 (4.8)	-	-	-
Treatment-related EAE leading to treatment withdrawal					
Total population	n (%)	-	3 (3.2)	1 (1.0)	3 (3.0)
Adolescents	n (%)	-	2 (2.7)	1 (1.2)	3 (3.7)
Children	n (%)	-	1 (5.3)	-	-
Treatment-related serious EAE leading to treatment withdrawal					
Total population	n (%)	-	1 (1.1)	-	2 (2.0)
Adolescents	n (%)	-	1 (1.3)	-	2 (2.5)
Children	n (%)	-	-	-	-

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

Table 63. Most frequently reported treatment emergent adverse events in the adolescent of the safety set (in at least 2% of the adolescents in any of the compared groups)

Preferred Term	Agomelatine 10 mg (N = 81)			Agomelatine 25 mg (N = 75)			Placebo (N = 82)			Fluoxetine (N = 81)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%	NEAE	n	%
ALL	**170**	**51**	**63.0**	**167**	**47**	**62.7**	**157**	**49**	**59.8**	**145**	**47**	**58.0**
Thirst	15	15	18.5	13	11	14.7	9	9	11.0	13	13	16.0
Dry mouth	18	18	22.2	11	10	13.3	11	10	12.2	11	11	13.6
Nausea	10	9	11.1	12	10	13.3	15	12	14.6	8	8	9.9
Headache	17	13	16.0	9	7	9.3	12	12	14.6	9	9	11.1
Increased appetite	5	5	6.2	6	6	8.0	-	-	-	3	3	3.7
Fatigue	4	4	4.9	6	6	8.0	6	4	4.9	2	2	2.5
Abdominal pain	6	5	6.2	5	5	6.7	8	6	7.3	3	3	3.7
Dizziness postural	2	2	2.5	5	5	6.7	1	1	1.2	2	2	2.5
Weight increased	4	4	4.9	4	4	5.3	-	-	-	1	1	1.2
Acne	3	2	2.5	4	4	5.3	2	2	2.4	2	2	2.5
Decreased appetite	1	1	1.2	4	4	5.3	4	4	4.9	4	4	4.9
Nasopharyngitis	1	1	1.2	4	4	5.3	3	3	3.7	1	1	1.2
Diarrhoea	5	5	6.2	4	3	4.0	6	5	6.1	9	8	9.9
Dizziness	5	4	4.9	3	3	4.0	3	3	3.7	3	3	3.7

Muscular weakness	1	1	1.2	3	3	4.0	5	5	6.1	1	1	1.2
Tachycardia	1	1	1.2	3	3	4.0	3	2	2.4	-	-	-
Somnolence	1	1	1.2	3	3	4.0	1	1	1.2	1	1	1.2
Blood bilirubin increased	3	3	3.7	2	2	2.7	1	1	1.2	-	-	-
Tremor	2	2	2.5	2	2	2.7	1	1	1.2	1	1	1.2
Insomnia	1	1	1.2	2	2	2.7	1	1	1.2	-	-	-
Rhinorrhoea	1	1	1.2	2	2	2.7	1	1	1.2	-	-	-
Enterocolitis	1	1	1.2	2	2	2.7	-	-	-	-	-	-
Blood thyroid stimulating hormone increased	-	-	-	2	2	2.7	2	2	2.4	1	1	1.2
Sinusitis	-	-	-	2	2	2.7	1	1	1.2	-	-	-
Blood prolactin increased	3	3	3.7	1	1	1.3	1	1	1.2	-	-	-
Vomiting	2	2	2.5	1	1	1.3	1	1	1.2	2	2	2.5
Rhinitis	2	2	2.5	1	1	1.3	-	-	-	-	-	-
Hypersomnia	1	1	1.2	1	1	1.3	2	2	2.4	-	-	-
Dysmenorrhoea	-	-	-	1	1	1.3	6	4	4.9	2	1	1.2
Anxiety	-	-	-	1	1	1.3	2	2	2.4	1	1	1.2
Aggression	-	-	-	1	1	1.3	-	-	-	3	3	3.7
Aspartate aminotransferase increased	-	-	-	1	1	1.3	-	-	-	2	2	2.5
Oestradiol increased	-	-	-	1	1	1.3	-	-	-	2	2	2.5
Weight decreased	2	2	2.5	-	-	-	4	4	4.9	2	2	2.5
Dyspepsia	2	2	2.5	-	-	-	-	-	-	2	1	1.2
Conjunctivitis	2	2	2.5	-	-	-	-	-	-	-	-	-
Respiratory tract infection viral	2	1	1.2	-	-	-	2	2	2.4	1	1	1.2
Bilirubin conjugated increased	1	1	1.2	-	-	-	2	2	2.4	-	-	-
Blood bilirubin unconjugated increased	1	1	1.2	-	-	-	2	2	2.4	-	-	-
Viral upper respiratory tract infection	1	1	1.2	-	-	-	2	2	2.4	-	-	-
Syncope	1	1	1.2	-	-	-	-	-	-	2	2	2.5
Suicidal ideation	-	-	-	-	-	-	2	2	2.4	2	2	2.5
Medical device pain	-	-	-	-	-	-	2	2	2.4	-	-	-
Urticaria	-	-	-	-	-	-	1	1	1.2	2	2	2.5
Accidental overdose	-	-	-	-	-	-	-	-	-	2	2	2.5
Tension headache	-	-	-	-	-	-	-	-	-	2	2	2.5

N: Number of patients by group.
NEAE: Number of events.
n: Number of patients with at least one emergent adverse event.
Percentages are based on N.

The most frequent EAEs (in more than 5 adolescents) reported in the agomelatine 10 mg and/or 25 mg groups were: thirst (18.5% and 14.7% of adolescents, respectively), dry mouth (22.2% and 13.3%), nausea (11.1% and 13.3%), headache (16.0% and 9.3%), increased appetite (6.2% and 8.0%) and fatigue (4.9% and 8.0%).

Among the most frequent EAEs on agomelatine, increased appetite was more frequently reported (i.e. a difference of at least 3 patients) in the agomelatine 10 and 25 mg groups than in the placebo group (6.2% and 8.0% versus none, respectively) (3.7% in the fluoxetine group).

In addition, the following EAEs were more frequently reported in the agomelatine 10 mg group than in the placebo group:

Thirst: 18.5% versus 11.0%, respectively (14.7% in the agomelatine 25 mg group and 16.0% in the fluoxetine group).

Dry mouth: 22.2% versus 12.2%, respectively (13.3% in the agomelatine 25 mg group and 13.6% in the fluoxetine group).

Among the other EAEs (reported in ≤ 5 adolescents in both agomelatine groups), weight increased was reported with a higher frequency in the agomelatine 10 mg and 25 mg groups (4.9% and 5.3%, respectively) than in the placebo group (none) (1.2% in the fluoxetine group).

In addition, dizziness postural was more frequently reported in the agomelatine 25 mg group (6.7%) than the placebo group (1.2%) (2.5% in the agomelatine 10 mg and fluoxetine groups).

Except thirst, the EAEs more frequently reported in at least one of the agomelatine groups than in the placebo group were also more frequently reported than in the fluoxetine group.

No increase of frequency of adverse events with the dose was observed.

Table 64. Analysis of treatment-related emergent adverse events (in at least 2 patients in any group) by system organ class and preferred term in the adolescents of the Safety Set

System Organ Class Preferred Term	Agomelatine 10 mg (N = 81)			Agomelatine 25 mg (N = 75)			Placebo (N = 82)			Fluoxetine (N = 81)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%	NEAE	n	%
ALL	64	27	33.3	69	28	37.3	50	24	29.3	51	24	29.6
Gastrointestinal disorders	27	20	24.7	22	14	18.7	19	15	18.3	17	16	19.8
Dry mouth	16	16	19.8	10	9	12.0	9	8	9.8	9	9	11.1
Nausea	6	6	7.4	8	7	9.3	8	7	8.5	4	4	4.9
Abdominal pain	2	2	2.5	2	2	2.7	1	1	1.2	-	-	-
Diarrhoea	1	1	1.2	-	-	-	1	1	1.2	3	3	3.7
Nervous system disorders	12	9	11.1	13	12	16.0	8	6	7.3	9	6	7.4
Headache	4	4	4.9	2	2	2.7	3	3	3.7	4	4	4.9
Dizziness	3	3	3.7	2	2	2.7	2	2	2.4	2	2	2.5
Tremor	2	2	2.5	2	2	2.7	1	1	1.2	1	1	1.2
Dizziness postural	2	2	2.5	2	2	2.7	-	-	-	1	1	1.2
Somnolence	1	1	1.2	2	2	2.7	1	1	1.2	1	1	1.2
General disorders and administration site conditions	11	11	13.6	10	9	12.0	8	8	9.8	9	9	11.1
Thirst	11	11	13.6	7	7	9.3	7	7	8.5	9	9	11.1
Investigations	4	4	4.9	6	4	5.3	7	6	7.3	4	3	3.7
Blood bilirubin increased	2	2	2.5	-	-	-	1	1	1.2	-	-	-
Bilirubin conjugated increased	-	-	-	-	-	-	2	2	2.4	-	-	-
Psychiatric disorders	3	3	3.7	7	4	5.3	2	2	2.4	3	2	2.5
Metabolism and nutrition disorders	1	1	1.2	3	3	4.0	1	1	1.2	2	2	2.5
Increased appetite	1	1	1.2	2	2	2.7	-	-	-	1	1	1.2
Skin and subcutaneous tissue disorders	2	1	1.2	2	2	2.7	-	-	-	3	2	2.5
Acne	2	1	1.2	-	-	-	-	-	-	-	-	-
Cardiac disorders	1	1	1.2	2	2	2.7	-	-	-	-	-	-
Tachycardia	-	-	-	2	2	2.7	-	-	-	-	-	-
Musculoskeletal and connective tissue disorders	-	-	-	2	2	2.7	2	2	2.4	-	-	-
Muscular weakness	-	-	-	2	2	2.7	2	2	2.4	-	-	-
Eye disorders	1	1	1.2	-	-	-	-	-	-	2	2	2.5

N: number of patients by group.
NEAE: Number of events.
n: number of patients affected.
Percentages are based on N.
Treatment emergent AE related to IMP include sponsor upgrade.

The most frequent treatment-related EAEs (in more than 2 patients) reported in the agomelatine 10 mg and/or 25 mg groups were: dry mouth (16.7% and 12.8%, respectively), thirst (11.8% and 9.6%), nausea (5.9% and 9.6%), abdominal pain (2.0% and 3.2%), headache (3.9% and 2.1%), and dizziness (2.9% and 2.1%).

Among the most frequent treatment-related EAEs on agomelatine, dry mouth was more frequently reported (i.e. a difference of at least 2 patients) in the agomelatine 10 and 25 mg groups (16.7% and 12.8% of the patients, respectively) than in the placebo group (8.7%) (10.0% in the fluoxetine group).

In addition, thirst was more frequently reported in the agomelatine 10 group (11.8%) than in the placebo group (7.8%) (9.6% in the agomelatine 25 mg group and 10.0% in the fluoxetine group) and abdominal pain was more frequently reported in the agomelatine 25 mg group (3.2%) than in the placebo group (1.0%) (2.0% in the agomelatine 10 mg group and 1.0% in the fluoxetine group).

Among the other treatment-related EAEs (reported in $\leq$ 2 patients in both agomelatine groups), dizziness postural was more frequently reported in the agomelatine 10 and 25 mg groups (2.0% and 2.1%) than in the placebo group (none) (1.0% in the fluoxetine group).

In addition, increased appetite and tachycardia were more frequently reported in the agomelatine 25 mg group (2.1%, each) than in the placebo group (none, each) (1.0% in the agomelatine 10 mg and fluoxetine groups for increased appetite and none in the 2 groups for tachycardia). Except dizziness postural and increased appetite, the EAEs more frequently reported in at least one of the agomelatine groups than in the placebo group were also more frequently reported than in the fluoxetine group.

To note, dermatitis allergic and urticaria papular reported in one patient each in the agomelatine 25 mg group were considered related to IMP.

Concerning the 2 doses of agomelatine, no increase of frequency of treatment-related EAEs with the dose was observed.

Adverse events in the adolescent (ado) MDE

The CL3-076 study included an optional extension phase where all patients in the study were offered treatment with agomelatine 25 mg. In the ado MDE patients were assigned to the agomelatine 25 mg group if they received agomelatine 25 mg for a longer time period than agomelatine 10 mg, placebo or fluoxetine.

The results presented hereafter in the Ado MDE sets, therefore consider patients who received the agomelatine 25 mg dose during the longest period of time in the study CL3-076, and which are pooled with patients from CL2-75. The results presented focus on the adolescent MDE set and are compared to the adult MDE set (Table 65).

Table 65. Overall summary of emergent adverse events – Paed MDE, Ado and adult MDE sets

	Paed MDE						Ado MDE						Adult MDE					
	Ago 25 mg (N = 242)			Placebo (N = 18)			Ago 25 mg (N = 192)			Placebo (N = 13)			Agot 25 mg (N = 5662)			Placebo (N = 1393)		
Median treatment duration (months)	**16.7**			**1.6**			**17.9**			**1.8**			**3.7**			**1.9**		
	NEAE	n	%	NEAE	n	%	NEAE	n	%	NEAE	n	%	NEAE	n	%	NEAE	n	%
EAEs	528	155	64.0	19	8	44.4	449	129	67.2	12	6	46.2	9668	3420	60.4	1983	776	55.7
Severe EAE	29	19	7.9	-	-	-	25	16	8.3	-	-	-	683	484	8.5	192	135	9.7
SEAE*	35	23	9.5	-	-	-	32	20	10.4	-	-	-	241	199	3.5	69	55	3.9
WEAE	18	11	4.5	4	2	11.1	14	9	4.7	3	1	7.7	598	462	8.2	216	143	10.3
Related EAEs**	133	66	27.3	4	1	5.6	126	61	31.8	4	1	7.7	3702	1831	32.3	851	434	31.2
WEAE related	7	4	1.7	3	1	5.6	4	3	1.6	3	1	7.7	350	263	4.6	89	56	4.0
EAE leading to death	-	-	-	-	-	-	-	-	-	-	-	-	5	4	0.1	2	2	0.1

**SEAE = Serious EAE with sponsor upgrade serious and **related EAE with sponsor upgrade WEAE: EAE leading to treatment withdrawal*
Number of patients (N) in the analysis set n number of patients presenting at least one event; NEAE: Number of events

On agomelatine 25 mg in the paediatric and adolescent MDE sets, in which the median treatment duration was much longer than in the adults (16.7 months and 17.9 months versus 3.7 months), EAEs, particularly the serious EAEs, were more frequently reported than in adults (64.0% and 67.2% versus 60.4% of patients for EAEs and 9.5% and 10.4% versus 3.5% of the patients for serious EAE, respectively).

No relevant difference between paediatric/adolescent population and adults was observed for severe, related EAEs or EAE leading to drug withdrawal.

Table 66. Emergent adverse events reported by at least 1% of patients in agomelatine 25 mg group in the Ado MDE set – Ado and adult MDE sets

	Ado MDE				Adult MDE			
	Ago 25 mg (N = 192)		Placebo (N = 13)		Ago 25 mg (N = 5662)		Placebo (N = 1393)	
Median treatment duration (months)	**16.7**		**1.6**		**17.9**		**1.8**	
	n	%	n	%	n	%	n	%
ALL	**129**	**67.19**	**6**	**46.15**	**3420**	**60.40**	**776**	**55.71**
Headache	31	16.15	3	23.08	766	13.53	198	14.21
Dry mouth	18	9.38	-	-	185	3.27	49	3.52
Thirst	16	8.33	-	-	7	0.12	6	0.43
Fatigue	14	7.29	-	-	156	2.76	28	2.01
Nasopharyngitis	14	7.29	-	-	311	5.49	46	3.30
Nausea	12	6.25	1	7.69	358	6.32	95	6.82
Decreased appetite	11	5.73	-	-	41	0.72	10	0.72
Dizziness	10	5.21	2	15.38	295	5.21	49	3.52
Dizziness postural	9	4.69	-	-	8	0.14	0	0.00
Somnolence	9	4.69	-	-	246	4.34	40	2.87
Blood prolactin increased	8	4.17	-	-	-	-	-	-
Depression	6	3.13	-	-	66	1.17	45	3.23
Diarrhoea	6	3.13	1	7.69	189	3.34	43	3.09
Hypersomnia	6	3.13	-	-	9	0.16	1	0.07
Influenza	6	3.13	-	-	177	3.13	42	3.02
Weight increased	6	3.13	-	-	67	1.18	19	1.36
Abdominal pain	5	2.60	-	-	40	0.71	11	0.79
Dysmenorrhoea	5	2.60	-	-	35	0.62	7	0.50
Respiratory tract infection viral	5	2.60	1	7.69	22	0.39	3	0.22
Alanine aminotransferase increased	4	2.08	-	-	32	0.57	4	0.29
Aspartate aminotransferase increased	4	2.08	-	-	18	0.32	2	0.14
Blood thyroid stimulating hormone increased	4	2.08	-	-	-	-	1	0.07
Gamma-glutamyltransferase increased	4	2.08	-	-	23	0.41	4	0.29
Gastritis	4	2.08	-	-	35	0.62	5	0.36
Increased appetite	4	2.08	-	-	42	0.74	7	0.50
Upper respiratory tract infection	4	2.08	-	-	129	2.28	17	1.22
Abdominal pain upper	3	1.56	-	-	120	2.12	19	1.36
Acne	3	1.56	-	-	22	0.39	2	0.14
Anxiety	3	1.56	-	-	137	2.42	26	1.87
Blood bilirubin increased	3	1.56	-	-	5	0.09	3	0.22
Haemoglobin decreased	3	1.56	-	-	1	0.02	1	0.07
Intentional self-injury	3	1.56	-	-	2	0.04	1	0.07
Iron deficiency anaemia	3	1.56	-	-	2	0.04	1	0.07
Sinusitis	3	1.56	1	7.69	63	1.11	5	0.36
Stress	3	1.56	-	-	3	0.05		
Syncope	3	1.56	-	-	4	0.07	3	0.22
Tachycardia	3	1.56	1	7.69	18	0.32	5	0.36

Vomiting	3	1.56	-	-	85	1.50	24	1.72
Akathisia	2	1.04	-	-	-	-	-	-
Contusion	2	1.04	-	-	13	0.23	-	-
Depressed mood	2	1.04	-	-	5	0.09	-	
Disturbance in attention	2	1.04	1	7.69	14	0.25	3	0.22
Enterocolitis	2	1.04	-	-	-	-	-	-
Hyperprolactinaemia	2	1.04	-	-	-	-	-	-
Insomnia	2	1.04	-	-	170	3.00	47	3.37
Intentional overdose	2	1.04	-	-	7	0.12	-	-
Irritability	2	1.04	-	-	58	1.02	7	0.50
Muscular weakness	2	1.04	-	-	6	0.11	1	0.07
Musculoskeletal chest pain	2	1.04	-	-	10	0.18	2	0.14
Platelet count decreased	2	1.04	-	-	1	0.02	-	-
Respiratory tract infection	2	1.04	-	-	13	0.23	1	0.07
Rhinitis	2	1.04	-	-	31	0.55	5	0.36
Rhinorrhoea	2	1.04	-	-	4	0.07	1	0.07
Suicide attempt	2	1.04	-	-	33	0.58	10	0.72
Tension headache	2	1.04	-	-	26	0.46	7	0.50
Tonsillitis	2	1.04	-	-	24	0.42	3	0.22
Tremor	2	1.04	-	-	30	0.53	14	1.01
Viral pharyngitis	2	1.04	-	-	2	0.04	-	-
Viral upper respiratory tract infection	2	1.04	-	-	15	0.26	1	0.07

*n number of patients presenting at least one event;%: (n/N)*100 (N : number of patients by group)*

The most frequent EAEs reported in adolescents in the agomelatine 25 mg group (i.e. reported by more than 5% of the adolescents) were headache, dry mouth, thirst, fatigue, nasopharyngitis, nausea, decreased appetite and dizziness.

Among them, headache, dry mouth, thirst, nausea and decreased appetite, were less frequently or similarly reported in the agomelatine 25 mg than in the placebo group in the adult MDE set. When regarding these EAEs in the ado MDE DB set, no relevant difference was observed between agomelatine 25 mg and placebo groups.

Regarding the other EAEs reported by the adolescents, that were less or similarly reported in the agomelatine 25 mg group than/and in the placebo group in the adult MDE set, none of them were more frequently reported in the agomelatine 25 mg than in the placebo group in the ado MDE DB set except increased appetite (8.0% *versus* none) and weight increased (5.3% *versus* none) (Table 67).

	Ado MDE				Adult MDE			
	Ago 25 mg (N = 192)		Placebo (N = 13)		Ago 25 mg (N = 5662)		Placebo (N = 1393)	
Median treatment duration (months)	**16.7**		**1.6**		**17.9**		**1.8**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
ALL	**61**	**31.77**	**1**	**7.69**	**1831**	**32.34**	**434**	**31.16**
Dry mouth	17	8.85	-	-	157	2.77	44	3.16
Thirst	12	6.25	-	-	6	0.11	5	0.36
Dizziness	8	4.17	1	7.69	223	3.94	38	2.73
Nausea	8	4.17	1	7.69	270	4.77	71	5.10
Somnolence	8	4.17	-	-	230	4.06	32	2.30
Headache	6	3.13	1	7.69	391	6.91	121	8.69
Hypersomnia	4	2.08	-	-	9	0.16	1	0.07
Alanine aminotransferase increased	3	1.56	-	-	19	0.34	2	0.14
Aspartate aminotransferase increased	3	1.56	-	-	10	0.18	-	-
Blood prolactin increased	3	1.56	-	-	-	-	-	-
Dizziness postural	3	1.56	-	-	7	0.12	-	-
Fatigue	3	1.56	-	-	122	2.15	18	1.29
Abdominal pain	2	1.04	-	-	13	0.23	5	0.36
Akathisia	2	1.04	-	-	-	-	-	-
Decreased appetite	2	1.04	-	-	28	0.49	5	0.36
Increased appetite	2	1.04	-	-	27	0.48	7	0.50
Irritability	2	1.04	-	-	42	0.74	6	0.43
Muscular weakness	2	1.04	-	-	5	0.09	1	0.07
Tremor	2	1.04	-	-	22	0.39	7	0.50

Table 67 .

In the Ado MDE set, 61 patients (31.8%) on agomelatine 25 mg reported at least one EAE considered as treatment-related. No relevant difference between groups was observed in the MDE adults (32.3% versus 31.2%)

The most frequent (more than 3%) related EAEs in the adolescent MDE set on agomelatine 25 mg were dry mouth (8.9%), thirst (6.3%), dizziness (4.2%), somnolence (4.2%), nausea (4.2%) and headache (3.1%). In the adult MDE group, those EAEs were less frequently reported in the agomelatine 25 mg group than in the placebo group, except dizziness and somnolence (3.9% *versus* 2.7% and 4.1% *versus* 2.3%), respectively.

When regarding MDE DB set, the rate of adolescents who reported at least one EAE considered as related to the investigational medicial product (IMP) was higher on agomelatine 25 mg than on placebo (37.3% versus 28.1%). No relevant difference between groups (less than 2 patients' difference) was observed for dry mouth (12.0% *versus* 9.8%), thirst (9.3% *versus* 8.5%), nausea (9.3% *versus* 8.5%) and headache (2.7% *versus* 2.4%).

"One-year" Agomelatine Exposure Set

This section presents for the ado and adult MDE sets, the EAEs reported by at least 2% of patients on agomelatine 25 mg in the Ado MDE set, exposed to agomelatine for at least one year (reported at any moment under treatment) (see Table 68).

Table 68. EAEs reported by at least 2% of patients on agomelatine 25 mg in the Ado MDE set – Ado and adult MDE one-year exposure sets

PT	Ado MDE one-year exp		Adult MDE one-year exp			
	Ago 25mg (N = 115)		Ago 25mg (N = 593)		Placebo (N = 64)	
Median treatment duration (months)	**21.2**		**12.0**		**12.0**	
	n	**%**	**n**	**%**	**n**	**%**
ALL	**87**	**75.65**	**424**	**71.50**	**46**	**71.88**
Headache	21	18.26	103	17.37	13	20.31
Decreased appetite	10	8.70	6	1.01	1	1.56
Nausea	9	7.83	35	5.90	5	7.81
Dizziness postural	8	6.96	1	0.17	-	-
Dry mouth	8	6.96	28	4.72	1	1.56
Fatigue	8	6.96	25	4.22	-	-
Nasopharyngitis	8	6.96	71	11.97	2	3.13
Thirst	8	6.96	1	0.17	1	1.56
Blood prolactin increased	7	6.09	-	-	-	-
Dizziness	7	6.09	37	6.24	6	9.38
Diarrhoea	6	5.22	27	4.55	6	9.38
Influenza	5	4.35	40	6.75	3	4.69
Dysmenorrhoea	4	3.48	6	1.01	-	-
Respiratory tract infection viral	4	3.48	7	1.18	-	-
Weight increased	4	3.48	13	2.19	2	3.13
Alanine aminotransferase increased	3	2.61	2	0.34	-	-
Aspartate aminotransferase increased	3	2.61	1	0.17	-	-
Depression	3	2.61	5	0.84	1	1.56
Gamma-glutamyltransferase increased	3	2.61	3	0.51	-	-
Haemoglobin decreased	3	2.61	-	-	-	-
Iron deficiency anaemia	3	2.61	1	0.17	-	-
Somnolence	3	2.61	26	4.38	3	4.69
Syncope	3	2.61	1	0.17	1	1.56
Tachycardia	3	2.61	4	0.67	-	-
Upper respiratory tract infection	3	2.61	27	4.55	1	1.56
Vomiting	3	2.61	11	1.85	2	3.13

*n: Number of patients with at least one event in a given preferred term; % (n/N)*100 (N : number of patients by group)*

In the one-year exposure MDE sets, no relevant difference was observed between the adolescents and the adults regarding the rates of patients with at least one EAE except for decreased appetite (8.7% *versus* 1.0%), dizziness postural (7.0% *versus* 0.2%) and thirst (7.0% *versus* 0.2%). In addition, blood prolactine increased was only reported in adolescents, knowing that blood prolactin testing was not planned in most adults' studies.

Table 69 summarises the reported adverse events, in the total population and adolescents of the Sub-SS, **over the W012-W104 period,** for the CL3-076 study alone.

Table 69. Overall summary for adverse events in the Sub-Safety Set – W012-W104 period in study CL3-076

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

Intensity of Emergent Adverse Events

Most of EAES were reported as mild or moderate. Number and frequencies of patients with at least one severe EAE by treatment group are displayed in Table 70 for both adolescent and adult MDE sets.

Table 70. Severe emergent adverse events by treatment group – Ado and adult MDE sets

	Ado MDE set		Adult MDE set	
	Ago 25 mg (N = 192)	Placebo (N = 13)	Ago 25 mg (N = 5662)	Placebo (N = 1393)
Median treatment duration (months)	**16.7**	**1.6**	**17.9**	**1.8**
Severe NEAE/NEAE	25/449	-/12	683/9668	192/1983
n (%)	16 (8.33)	-	484 (8.55)	135 (9.69)

N: number of patients in the considered set; severe NEAE: number of severe event;NEAE: number of events; n: number of patients with at least one severe event ; %: (n/N) x 100

In the Ado MDE set, severe EAEs were reported in the agomelatine 25 mg group with a similar rate as in the adult MDE set (8.3% and 8.6%, respectively) where no relevant difference was observed between groups (8.6% versus 9.7%).

The severe EAEs reported in more than one patient on agomelatine 25 mg in the Ado MDE set were depression and fatigue (3 patients, 1.6% for each) and headache and irritability (2 patients, 1.0% for each).

Time to onset of Emergent Adverse Events

Time-effect of the most frequent EAEs (reported by at least 5% of patients on agomelatine 25 mg in the ado MDE set) according to 9 classes: [0-15 days[, [15 days-1 month (mths)[, [1-2[mths, [2-3[mths, [3-4[mths, [4-6[mths, [6-9[mths, [9-12[mths and more than 12 months, is presented in Table 71 and Table 72 for ado and adult MDE sets in agomelatine 25 mg groups.

In the ado MDE set, except nasopharyngitis and decreased appetite reported all along the study, the most frequent EAEs reported on agomelatine 25 mg occurred at the beginning of the treatment, mainly within the first two weeks of treatment for dry mouth, thirst, fatigue, nausea and dizziness. The trend was roughly the same as in the adults.

Table 71. Time to onset of the most frequent EAEs (reported by at least 10 patients on agomelatine 25 mg in the Ado MDE set) – Agomelatine 25 mg group in the Ado MDE set (N = 192)

PREFERRED TERM	ALL	TIME TO ONSET																	
		[0-15 days[		[15 days-1 mth[		[1-2[mths		[2-3[mths		[3-4[mths		[4-6[mths		[6-9[mths		[9-12[mths		>= 12 mths	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Headache	31	9	29.0	6	19.4	1	3.2	1	3.2	1	3.2	1	3.2	4	12.9	5	16.1	3	9.7
Dry mouth	18	16	88.9	1	5.6	1	5.6	-	-	-	-	-	-	-	-	-	-	-	-
Thirst	16	14	87.5	-	-	1	6.3	1	6.3	-	-	-	-	-	-	-	-	-	-
Fatigue	14	7	50.0	2	14.3	1	7.1	-	-	-	-	-	-	1	7.1	2	14.3	1	7.1
Nasopharyngitis	14	2	14.3	2	14.3	1	7.1	2	14.3	1	7.1	1	7.1	-	-	1	7.1	4	28.6
Nausea	12	8	66.7	1	8.3	1	8.3	1	8.3	-	-	-	-	-	-	1	8.3	-	-
Decreased appetite	11	2	18.2	2	18.2	-	-	-	-	-	-	2	18.2	2	18.2	1	9.1	2	18.2
Dizziness	10	5	50.0	-	-	-	-	-	-	-	-	-	-	3	30.0	1	10.0	1	10.0

*TIME TO ONSET: duration between the first intake of treatment and the onset of the first event; n: Number of patients having their first event per given level in the class of time to onset; %: (n/total number of patients with at least one event in a given level)*100*

Table 72. Time to onset of the most frequent EAEs (reported by at least 10 patients on agomelatine 25 mg in the Ado MDE set) – Agomelatine 25 mg group in the adult MDE set (N = 5662)

PREFERRED TERM	ALL	TIME TO ONSET																	
		[0-15 days[		[15 days-1 mth[		[1-2[mths		[2-3[mths		[3-4[mths		[4-6[mths		[6-9[mths		[9-12[mths		>= 12 mths	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Headache	766	411	53.7	128	16.7	110	14.4	48	6.3	25	3.3	27	3.5	7	0.9	7	0.9	3	0.4
Dry mouth	185	112	60.5	35	18.9	24	13.0	5	2.7	3	1.6	4	2.2	2	1.1	-	-	-	-
Thirst	7	6	85.7	1	14.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatigue	156	99	63.5	23	14.7	17	10.9	5	3.2	1	0.6	7	4.5	2	1.3	1	0.6	1	0.6
Nasopharyngitis	311	62	19.9	61	19.6	58	18.6	35	11.3	27	8.7	38	12.2	9	2.9	18	5.8	3	1.0
Nausea	358	242	67.6	55	15.4	29	8.1	9	2.5	7	2.0	8	2.2	5	1.4	2	0.6	1	0.3
Decreased appetite	41	19	46.3	7	17.1	6	14.6	2	4.9	-	-	3	7.3	3	7.3	-	-	1	2.4
Dizziness	295	215	72.9	31	10.5	15	5.1	14	4.7	3	1.0	8	2.7	3	1.0	5	1.7	1	0.3

*TIME TO ONSET: duration between the first intake of treatment and the onset of the first event; n: Number of patients having their first event per given level in the class of time to onset; %: (n/total number of patients with at least one event in a given level)*100*

2.5.4. Analysis of Adverse Events by Organ System or Syndrome

Hepatic adverse events

Hepatotoxicity is the main safety concern with agomelatine and is stated as an important identified risk in the RMP. Cases of liver injury, including hepatic failure, transaminases exceeding 10 times the upper limit of normal, hepatitis and jaundice have been reported. Most of them occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with increased serum transaminases, which usually return to normal levels on cessation of agomelatine. Warnings and precautions to avoid serious hepatic events, including an extensive transaminases monitoring programme, must be followed as described in the SmPC.

The following exclusion criteria applied:

1. Transaminases values (AST and/or ALT) ≥ 2 times the upper limit of normal range (ULN).
2. Total bilirubin ≥ 1.5 times ULN and/or free bilirubin ≥ 2 times ULN.
3. Transaminases (AST and/or ALT) and total bilirubin values > upper reference value.
4. Alkaline phosphatase (ALP) ≥ 3 times ULN and both ALP and gamma-glutamyl transferase (GGT) > 1 time ULN.

In the Ado MDE set, the hepatic adverse events from the TME Hepatic Disorders were reported by 12 (6.3%) adolescents on agomelatine 25 mg group which was higher than in the adult MDE set (1.7%).

Table 73 summarizes, for both ado and adult MDE sets, the number of emergent hepatic adverse events reported by at least 1 patient on agomelatine 25 mg in the Ado MDE set.

In the ado MDE set, the most frequently reported emergent hepatic adverse events in the agomelatine 25 mg group were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased and gamma-glutamyl transferase (GGT) increased, each reported by 4 patients and blood bilirubin increased reported by 3 patients.

In the Adult MDE set, AST and ALT increased were more frequently reported in the agomelatine 25 mg than in the placebo groups (0.6% versus 0.3% and 0.3% versus 0.1%, respectively) whereas no relevant difference was observed for GGT and blood bilirubin increased.

Table 73. TME Hepatic disorders (reported by at least 1 patient on agomelatine 25 mg in the Ado MDE set) – Ado and adult MDE sets

PT	Ado MDE				Adult MDE			
	Ago 25 mg (N = 192)		Placebo (N = 13)		Ago 25 mg (N = 5662)		Placebo (N = 1393)	
Median treatment duration (months)	17.9		1.8		3.7		1.9	
	n	%	n	%	n	%	n	%
ALL	**12**	**6.25**	**1**	**7.69**	**97**	**1.71**	**13**	**0.93**
Alanine aminotransferase increased	4	2.08	-	-	32	0.57	4	0.29
Aspartate aminotransferase increased	4	2.08	-	-	18	0.32	2	0.14
Gamma-glutamyltransferase increased	4	2.08	-	-	23	0.41	4	0.29
Blood bilirubin increased	3	1.56	-	-	5	0.09	3	0.22
Bilirubin conjugated increased	1	0.52	-	-	-	-	-	-
Blood bilirubin unconjugated increased	1	0.52	1	7.69	-	-	-	-
Hyperbilirubinaemia	1	0.52	-	-	1	0.02	-	-

n:Number of patients with at least one emergent AE in a given preferred term
*%:(n/N)*100 (N : number of patients by group)*

Liver parameters

Double-blind period (12 weeks)

In the adolescents from the CL3-076 study, (ado MDE DB PC set), neither clinically relevant changes nor differences between groups in mean values over time were detected except a slight increase of transaminases in the agomelatine 25 mg group compared to the placebo. For ALT, the mean change from baseline to last post-baseline value was 2.9 ± 12.5 IU/L on agomelatine 25 mg versus -0.9 ± 6.8 IU/L on placebo. For AST, the mean change was 4.9 ± 38.0 IU/L on agomelatine 25 mg versus -0.7 ± 5.5 IU/L on placebo.

Table 74. Liver parameters. Counts of patients with emergent abnormal values (> 1 ULN) and/or PCSA values (>3ULN) – Ado and adult MDE DB sets

			Ado MDE DB*		Adult MDE DB*	
			Ago 25 mg	Placebo	Ago 25 mg	Placebo
AST	> 1 ULN	n (%)	2 (2.7)	-	93 (5.79)	62 (3.71)
	> 3 ULN	n (%)	1 (1.4)	-	6 (0.37)	3 (0.18)
ALT	> 1 ULN	n (%)	2 (2.7)	1 (1.3)	122 (7.60)	93 (5.56)
	> 3 ULN		-	-	9 (0.56)	7 (0.42)
ALP	> 1 ULN	n (%)	4 (5.4)	-	15 (0.93)	18 (1.08)
	>3 ULN		-	-	-	1 (0.06)
GGT	> 1 ULN	n (%)	1 (1.4)	2 (2.5)	71 (4.42)	56 (3.34)
	> 3 ULN		-	1 (1.3)	8 (0.05)	12 (0.72)
Total bilirubin	> 1 ULN	n (%)	4 (5.4)	6 (7.5)	47 (2.93)	29 (1.73)
	> 2 ULN		-	-	1 (0.06)	5 (0.30)

n :Number of patients with at least one emergent event
*%:(n/Number of patients (N) with at least one available value on treatment)*100*
Upper emergent abnormal value is defined as a baseline value <= to the threshold (or missing) and at least one value on treatment above this threshold
**See Module 5.3.5.3 (NP42056, section 3.3)*

In the adolescents, no relevant difference between agomelatine 25 mg and placebo groups was observed for liver abnormal values.

One adolescent in the agomelatine 25 mg ado MDE DB group reported at least one emergent potentially clinically significant abnormal (PCSA) value (AST value > 3ULN) versus none in the placebo group. In addition, one child in the agomelatine group 10 mg reported one emergent PCSA value of ALT (data not shown). Narratives are provided below.

Extension period (W012-W104)

Regarding the liver acceptability on the W012-W104 period, no clinically relevant mean/median change over time was observed in the adolescents (Table 75).

Table 75. Liver parameters – Counts of patients with at least one emergent abnormal value (> 1 ULN) and/or PCSA value (> 3 ULN) on treatment in the ext Ado MDE set – W012-W104 period

Parameter	(unit)			Agomelatine
AST	(IU/L)	> 1 ULN	n (%)	23 (8.6)
	(IU/L)	> 3 ULN	n (%)	1 (0.4)
ALT	(IU/L)	> 1 ULN	n (%)	30 (11.2)
	(IU/L)	> 3 ULN	n (%)	2 (0.7)
GGT	(IU/L)	> 1 ULN	n (%)	22 (8.2)
		> 3 ULN	n (%)	4 (1.5)
ALP	(IU/L)	> 1 ULN	n (%)	9 (3.4)
		> 3 ULN		-
Total bilirubin	(µmol/L)	> 1 ULN	n (%)	19 (7.1)
		> 2 ULN	n (%)	-

n :Number of patients with at least one emergent event
*%:(n/Number of patients (N) with at least one available value on treatment)*100*
Upper emergent abnormal value is defined as a baseline value <= to the threshold (or missing) and at least one value on treatment above this threshold
**See Module 5.3.5.3 (NP42056, section 3.3)*

In the adolescents, the most common emergent PCSA liver values on treatment were high direct bilirubin (6.0%) and high indirect bilirubin (3.0%). No emergent PCSA value was reported for high total bilirubin. A total of 2 adolescents reported high emergent PCSA values (> 3 ULN) of ALT and/or AST on treatment and 4 adolescents high emergent PCSA values (> 3 ULN) of GGT on treatment including one worsening.

Narratives

A clinical review of narratives of all patients with potentially clinically significant transaminases elevations (PCSA values: aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3 ULN) was made by a Liver Safety Committee (LSC) composed of four independent academic clinical hepatologists and one academic specialist in internal medicine in order to assess causality of the reported abnormalities.

Patients with at least one emergent PCSA value on treatment in the DB-phase

A total of 2 patients on agomelatine and 2 patients on fluoxetine reported high emergent PCSA values (> 3 ULN) of **ALT and/or AST**. Only cases related to agomelatine are presented:

- One child (8 years old) in the agomelatine group 10 mg reported one emergent PCSA value of ALT (119 IU/L) on treatment at W012. This PCSA value was associated with a high value of AST not above PCSA limit

(113 IU/L) and with a PCSA value of GGT (119 IU/L). A diagnostic of infectious mononucleosis had been made few days before the laboratory test. This EAE was considered serious and led to drug withdrawn. The event was not related to study drug intake according to LSC and resolved.

- One adolescent (15 years old) in the agomelatine 25 mg group presented one emergent PCSA value of AST (341 IU/L) on treatment at W012. This PCSA value was associated with a high value of ALT not above PCSA limit (92 IU/L). Two non-serious EAEs (ALT increased and AST increased) considered as related to IMP were reported by the investigator. Four days after one retest was performed, the values of transaminases decreased but remained above the upper limit of reference without reaching the PCSA limit (85 and 83 IU/L for AST and 69 IU/L for ALT) and the study drug was withdrawn. As creatine phosphokinases were also increased, the LSC considered that these abnormalities were due to muscle injury possibly related to study drug.

Two patients on agomelatine 10 mg versus one on placebo presented emergent PCSA values of **GGT**. The first on agomelatine 10 mg was the child with the diagnostic of infectious mononucleosis described above. The second patient (adolescent) had a transient increase of GGT at W004. A non-serious EAE, GGT increased, was reported by the investigator and considered as not related to IMP.

Patients with at least one emergent PCSA value on treatment in the extension (W012-W104) phase:

A total of 3 patients (one child) reported high emergent PCSA values [> 3 Upper Limit of Normal laboratory reference range (ULN)] of **ALT and/or AST on treatment**, during the W012-W104 period, as follows:

- One adolescent (17 years old at randomisation) (placebo/ago group) reported at W018 (i.e. 43 days after switching from placebo to agomelatine) one emergent PCSA value of ALT (129 IU/L, 3.9 ULN) and AST (117 IU/L, 3.5 ULN) on treatment. There was no concomitant treatment. The study drug was maintained. Two AEs "ALT increased" and "AST increased" were reported as serious and considered as not related to IMP by the investigator. Two weeks later, the values returned to normal. No etiological investigations were performed. It was reported that there was intense physical exertion the month before (no CPK value). The event could be related with adaptation, exercise (normal ALT/AST ratio) or intercurrent viral illness (no symptoms reported). **The LSC considered that these abnormalities were possibly related to study drug.** Then, ALT and AST high abnormal values (no PCSA) were reported at W024 and returned to normal three weeks later.

- One adolescent (15 years old at randomisation) (placebo/ago group) had developed overweight during the study (weight gain of 10 kg). The patient reported from W048 (i.e. 251 days after switching from placebo to agomelatine) high emergent out-of-reference range values of ALT (no PCSA) on treatment. A serious AE "ALT increased" due to obesity was reported at W068, considered as not related to IMP by the investigator. An emergent PCSA value was reported during a retest at W068 (126 IU/L, 3.4 ULN) (i.e. 405 days after initiation of agomelatine). Six days later, the value of ALT decreased to 2.8 ULN (no PCSA). The value remained high (no PCSA) until W104. Fatty liver disease was suspected, but the abdominal ultrasound did not confirm this diagnosis. The study drug was maintained. **The LSC considered that the event was unlikely related to the study drug** but rather possibly due to hepatic metabolic disorder secondary to weight gain.

- One child (8 years old at randomisation) (fluox/ago group) reported at W077 [i.e. 456 days (~15 months) after switching from fluoxetine to agomelatine] one emergent PCSA value of AST (296 IU/L, i.e. 7.6 ULN) on treatment. One AE "AST increased" was reported as serious, considered as not related to IMP by the investigator and led to temporary interruption treatment of 7 days. One AE "ALT" increased was also reported the same day for a high out-of-reference-range value (2.4 ULN, no PCSA) of ALT. Three days after, the value of AST decreased but remained above the upper limit of reference without reaching the PCSA limit then 4 days after, the value returned to normal. Agomelatine was reintroduced and the value of AST remained normal until the last value on treatment of W077. At W104, the value (not under treatment)

was still normal. **According to the LSC, the event was not related to the study drug because** of late occurrence, strong predominance on AST which is not suggestive of drug induced liver injury but rather muscular injury (unknown cause, apparent intense muscle exercise) with very quick recovery.

A total of 4 patients (all adolescents) reported high emergent PCSA values (> 3 ULN) of **GGT** on treatment including one worsening, during the W012-W104 period. All patients had reported AEs "GGT increased", all non-serious. Only the case of worsening was considered as related to IMP.

For 2 patients (ago/ago group and placebo/ago group), the values of GGT returned to normal [2.5 months (value not on treatment) and 3 weeks later (value on treatment), respectively]. For the patient with one worsening (placebo/ago group), the GGT values remained PCSA values at the following 2 visits, then decreased to high abnormal values (not PCSA) until 2 days after the last intake. For the last patient (placebo/ago group), the emergent PCSA GGT value occurred one day after the last intake. Several out-of-reference range high abnormal values (PCSA or not) were reported until 114 days after the last intake.

Psychiatric effects

- Suicidality

In the ado MDE set, 6 (3.1%) patients reported suicidality (targeted medical event [TME] suicidal events) on agomelatine 25 mg, with a higher rate than in the adult MDE set (1.2%).

In the adult MDE set, the rate of patients was lower on agomelatine 25 mg than on placebo (1.2% versus 1.6%).

Table 76. TME suicidal events – Emergent events reported by at least 1 patient in the agomelatine 25 mg group in the Ado MDE set – Ado and adult MDE sets

PT	Ado MDE				Adult MDE			
	Ago 25 mg (N = 192)		Placebo (N = 13)		Ago 25 mg (N = 5662)		Placebo (N = 1393)	
Median treatment duration (months)	17.9		1.8		3.7		1.9	
	n	%	n	%	n	%	n	%
ALL	**6**	**3.13**	-	-	**65**	**1.15**	**22**	**1.58**
Intentional self-injury	3	1.56	-	-	2	0.04	1	0.07
Intentional overdose	2	1.04	-	-	7	0.12	-	-
Suicide attempt	2	1.04	-	-	33	0.58	10	0.72
Self-injurious ideation	1	0.52	-	-	-	-	-	-
Suicidal behaviour	1	0.52	-	-	1	0.02	-	-
Suicidal ideation	1	0.52	-	-	14	0.25	7	0.50

*N : number of patients by group, n: Number of patients with at least one emergent AE leading to IMP withdrawal in a given preferred term ; %: (n/N)*100*

The following exclusion criteria applied:

- Patients who had a current suicide risk according to the investigator (based on the information obtained during the evaluation of the Columbia-Suicide Severity Rating Scale Children version (C-SSRS-C) Baseline/Screening "suicidal ideation" part, item 4 or 5 is "yes" in "6 months" part).

- Patients having a high suicidal risk according to the investigator based on the MINI-Kid or having suicide attempt in the previous 3 months based on information obtained during the investigator interview.

In addition, there were several criteria leading to mandatory withdrawal from the study, which included:

Worsening of depression based on the investigator's clinical judgment or a CGI-S = 7; any suicide attempt (whatever its severity); high suicidal risk, according to investigator's judgment and or with a suicidal ideation of 4 or 5 on Columbia-Suicide Severity Rating Scale (C-SSRS).

Baseline status:

Over 20% in each treatment group (highest in the agomelatine 10 mg group with > 25%) of the patients had suicidal behaviour or suicidal ideation according to CSSRS-C. Actual suicide attempts were reported in a total of 3.3% (13/400) of the patients (highest in the agomelatine 25 mg group with 5/95, 5.3%).

Double-blind phase:

In the Safety Set, the analysis of suicide risk using the Columbia- Suicide Severity Rating Scale Children's version (C-SSRS-C) showed that a total of 4 patients presented **emergent suicidal ideations** on treatment distributed as one patient in each group.

The case in the agomelatine 10 mg group concerned a child (severity = 1). No emergent suicidal ideation was rated as serious (defined as score of 4 or 5).

A total of 7 patients had a **worsening of their suicidal ideation** on treatment without relevant difference between groups: 2 patients (2.0%) and 1 patient (1.1%) in the agomelatine 10 mg and 25 mg, respectively, versus 3 patients (3.0%) in the placebo group, and 1 patient (1.0%) in the fluoxetine group. No child was affected by these aggravations.

One patient in the agomelatine 25 mg group and one in the placebo group reported **emergent self-injurious behaviour without suicidal intent** on treatment.

Based on this scale, no patient in any group presented **emergent suicidal behaviour**. Nevertheless, in the agomelatine 25 mg group, an intentional IMP overdose associated with scarification was reported as a serious adverse event. The patient reported overdose of IMP mainly for attracting attention and no suicidal ideation or behaviour was reported on the C-SSRS-C scale. As some suicide intention cannot be ruled out by clinician, the reported event was coded as suicide attempt.

Extension phase:

In the ext ado MDE set on agomelatine the analysis of suicide risk showed that 12 patients (3.6%) [including 11 adolescents (4.1%)] presented emergent suicidal ideations on treatment during the W012-W104 period distributed as 3 patients (1.8%) in the ago/ago group, 4 patients (4.7%) in the placebo/ago group and 5 patients (6.0%) in the fluox/ago group). Emergent suicidal ideation was rated as serious (defined as score of 4 or 5) in one patient (in the fluox/ago group, adolescent patient).

One adolescent (in the placebo/ago group) had a worsening of his/her suicidal ideation on treatment during the W012-W104 period.

A total of 6 patients (1.8%, all adolescents) reported emergent self-injurious behaviour without suicidal intent on treatment, distributed as 3 patients (1.8%) in the ago/ago group, 1 patient (1.2%) in the placebo/ago group and 2 patients (2.4%) in the fluox/ago group.

Based on this scale, two adolescents (1 in each of the placebo/ago and fluox/ago groups,) presented 3 emergent suicidal behaviours: both made emergent actual suicide attempt on treatment; in addition, the patient in the placebo/ago group also undertook emergent preparatory actions toward imminent suicidal behaviour.

Post-marketing experience:

- Eight adolescents (≥ 12 years old) used agomelatine in a suicide attempt by overdose (50 to 1000 mg). Five of these presented associated adverse events such as fatigue, abdominal pain, somnolence, nausea, dizziness and hallucination.

- Manic/hypomanic Episodes

There are concerns that antidepressants may induce manic/hypomanic episodes during treatment or at treatment discontinuation. No case was observed in paediatric MDE set.

- Sedative/stimulating effects

Antidepressants may present sedative or stimulating properties.

The number and the percentage of patients, for both adolescent and adult MDE sets, having reported at least one EAE suggestive of a possible sedative or stimulating effects on agomelatine 25 mg group in the adolescent MDE set are presented in Table 84.

In the adolescents, the rate of patients with at least one sedative-type event was slightly higher than in the adults (10.4% and 7.9%) whereas stimulating-type events were less reported than in the adults (3.1% and 6.5%).

When regarding the ado MDE DB PC set, sedative-type events were more frequently reported on agomelatine 25 mg than on placebo (9 patients, 12.0% *versus* 5 patients, 6.1%) whereas no relevant difference between both groups were observed for stimulating-type events (3 patients, 4.0% *versus* 3 patients, 3.7%).

Table 77. Treatment EAE suggestive of possible "sedative" or "stimulating" effects* reported in at least 1 patient on agomelatine 25 mg in the Ado MDE set – Ado and adult MDE sets

	Ado MDE				Adult MDE			
	Ago 25 mg (N = 192)		Placebo (N = 13)		Ago 25 mg (N = 5662)		Placebo (N = 1393)	
	n	%	n	%	n	%	n	%
"Sedative effect"	20	10.42	-	-	446	7.88	83	5.96
Fatigue	14	7.29	-	-	156	2.76	28	2.01
Somnolence	9	4.69	-	-	246	4.34	40	2.87
"Stimulating effect"	6	3.13	-	-	370	6.53	88	6.32
Anxiety	3	1.56	-	-	137	2.42	26	1.87
Insomnia	2	1.04	-	-	170	3.00	47	3.37
Irritability	2	1.04	-	-	58	1.02	7	0.50

**List of selected PT; n: Number of patients with at least one emergent AE in a given preferred term*
*%:(n/N)*100 (N : number of patients by group)*

Emergent symptoms after treatment discontinuation

The possibility of a discontinuation syndrome following abrupt discontinuation of agomelatine treatment has been examined in a specific safety study in adult MDE patients (CL3-030, NP15915). The study showed the absence of significant discontinuation symptoms after agomelatine discontinuation in adult population.

No data are available in the paediatric population but based on data in adult population there is no evidence that the abrupt discontinuation of agomelatine could be associated with discontinuation symptoms.

Effects on sexual function

In the ado MDE set, only one boy (1.92%) reported sexual dysfunction events (libido decreased and premature ejaculations) on agomelatine. The absence of drug-induced sexual dysfunction with agomelatine has been previously demonstrated in both healthy adult volunteers (males and females) and MDE patients; these data were previously provided in the frame of adult MDE indication file. No safety concern has been identified in adolescents.

Long-term safety and pubertal development (Tanner stage, weight and BMI, hormonal safety)

As regards preclinical safety data, the following is stated in section 5.3 of the SmPC:

No effect of agomelatine on juvenile animals' behavioural performances, visual and reproductive function were observed. There were mild non-dose dependent decreases in body weight related to the pharmacological properties and some minor effects on male reproductive tract without any impairment on reproductive performances.

The EMA guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev 2, 2013), states that long-term effects on learning, development, growth and sexual function may be studies post-marketing, but appropriate protocols should be available when use in children are applied for.

- **Cognitive functioning**

Tanner Stage – (Pubertal development)

Assessment of pubertal status by Tanner stage in the ado MDE DB PC set in the CL3-076 study for pubic hair development in boys and in girls, genitalia development in boys and breast development in girls showed that the mean age in each stage at baseline and at W012 was consistent with stage according to normal development without relevant change between baseline and W012. Most of the patients remained in the same stage between baseline and W012, in each treatment group.

In the extension adolescents MDE set on agomelatine, age description by Tanner stage on the W012-W104 period i.e. at W012, W052 and W104 showed a mean age consistent with stage, in female as in male adolescents. This mean age per stage was globally stable all over the extension period.

Table 78. Tanner stage in female patients. Adolescents of the safety set (N=319). Values at baseline and week 12.

				Agomelatine 10 mg (N = 63)	Agomelatine 25 mg (N = 50)	Placebo (N = 56)	Fluoxetine (N = 49)
Pubic hair development	BASELINE		n	63	50	56	49
		STAGE II	n (%)	1 (1.6)	2 (4.0)	1 (1.8)	-
		STAGE III	n (%)	14 (22.2)	6 (12.0)	6 (10.7)	11 (22.4)
		STAGE IV	n (%)	28 (44.4)	25 (50.0)	26 (46.4)	24 (49.0)
		STAGE V	n (%)	20 (31.7)	17 (34.0)	23 (41.1)	14 (28.6)
	W012		n	56	45	53	44
		STAGE II	n (%)	1 (1.8)	1 (2.2)	1 (1.9)	-
		STAGE III	n (%)	12 (21.4)	5 (11.1)	4 (7.5)	8 (18.2)
		STAGE IV	n (%)	21 (37.5)	22 (48.9)	24 (45.3)	20 (45.5)
		STAGE V	n (%)	22 (39.3)	17 (37.8)	24 (45.3)	16 (36.4)
Breast (for female) / Genitalia (for male) development	BASELINE		n	63	50	56	49
		STAGE II	n (%)	2 (3.2)	2 (4.0)	1 (1.8)	-
		STAGE III	n (%)	13 (20.6)	6 (12.0)	5 (8.9)	12 (24.5)
		STAGE IV	n (%)	26 (41.3)	25 (50.0)	28 (50.0)	21 (42.9)
		STAGE V	n (%)	22 (34.9)	17 (34.0)	22 (39.3)	16 (32.7)
	W012		n	56	45	53	44
		STAGE II	n (%)	2 (3.6)	1 (2.2)	1 (1.9)	-
		STAGE III	n (%)	9 (16.1)	5 (11.1)	3 (5.7)	7 (15.9)
		STAGE IV	n (%)	21 (37.5)	23 (51.1)	27 (50.9)	22 (50.0)
		STAGE V	n (%)	24 (42.9)	16 (35.6)	22 (41.5)	15 (34.1)

The number of female patients with changes in Tanner stage showed no relevant difference between the agomelatine 10 and 25 mg groups versus placebo:

- Increase of Tanner stage for pubic hair development: 5 patients (8.2%) and 5 patients (9.3%) versus 3 patients (5.1%) respectively (3 patients (6.0%) in the fluoxetine group).

- Increase of Tanner stage for breast development: 5 patients (8.2%, including one patient with a change of 2 stages) and 5 patients (9.3%) versus 2 patients (3.4%) respectively (4 patients (8.0%) in the fluoxetine group).

Table 79. Tanner stage in male patients. Adolescents of the safety set (N=319). Values at baseline and week 12.

				Agomelatine 10 mg (N = 18)	Agomelatine 25 mg (N = 25)	Placebo (N = 26)	Fluoxetine (N = 32)
Pubic hair development	BASELINE		n	18	25	26	32
		STAGE I	n (%)	-	-	-	2 (6.3)
		STAGE II	n (%)	4 (22.2)	3 (12.0)	6 (23.1)	2 (6.3)
		STAGE III	n (%)	4 (22.2)	9 (36.0)	2 (7.7)	8 (25.0)
		STAGE IV	n (%)	7 (38.9)	5 (20.0)	14 (53.8)	11 (34.4)
		STAGE V	n (%)	3 (16.7)	8 (32.0)	4 (15.4)	9 (28.1)
	W012		n	17	23	22	30
		STAGE I	n (%)	-	-	-	2 (6.7)
		STAGE II	n (%)	4 (23.5)	2 (8.7)	4 (18.2)	2 (6.7)
		STAGE III	n (%)	3 (17.6)	5 (21.7)	3 (13.6)	7 (23.3)
		STAGE IV	n (%)	7 (41.2)	8 (34.8)	12 (54.5)	11 (36.7)
		STAGE V	n (%)	3 (17.6)	8 (34.8)	3 (13.6)	8 (26.7)
Breast (for female) / Genitalia (for male) development	BASELINE		n	18	25	26	32
		STAGE I	n (%)	-	-	-	2 (6.3)
		STAGE II	n (%)	2 (11.1)	2 (8.0)	4 (15.4)	1 (3.1)
		STAGE III	n (%)	7 (38.9)	9 (36.0)	3 (11.5)	7 (21.9)
		STAGE IV	n (%)	5 (27.8)	8 (32.0)	15 (57.7)	13 (40.6)
		STAGE V	n (%)	4 (22.2)	6 (24.0)	4 (15.4)	9 (28.1)
	W012		n	17	23	22	30
		STAGE I	n (%)	-	-	-	2 (6.7)
		STAGE II	n (%)	2 (11.8)	1 (4.3)	3 (13.6)	1 (3.3)
		STAGE III	n (%)	6 (35.3)	7 (30.4)	3 (13.6)	7 (23.3)
		STAGE IV	n (%)	6 (35.3)	8 (34.8)	13 (59.1)	12 (40.0)
		STAGE V	n (%)	3 (17.6)	7 (30.4)	3 (13.6)	8 (26.7)

The number of male patients with changes in Tanner stage showed no relevant difference between the agomelatine 10 and 25 mg groups versus placebo:

- Tanner stage increases for pubic hair development: 3 patients (9.1%) and 4 patients (13.3%) versus 3 patients (9.4%) respectively (1 patient (2.5%) in the fluoxetine group).

- Tanner stage increases for genitalia development: 3 patients (9.1%, including one patient with a change of 2 stages) and 4 patients (13.3%) versus 2 patients (6.3%) respectively (none in the fluoxetine group).

Hormonal safety

In the adolescent DB PC set emergent abnormal values on treatment (no PCSA limit was defined for hormonology parameters) were more frequently reported (i.e. a difference of at least 3 patients) on agomelatine 25 mg for low FSH (28.8% *versus* 22.5% of patients) and for low and high cortisol (15.1% *versus* 10.0% and 20.5% *versus* 15.0%, respectively) compared to placebo.

Of note, data regarding gonadotrophic hormonal safety were previously evaluated in adults: Two double-blind, randomised, placebo-controlled Phase I studies were specifically designed to assess the influence of agomelatine on gonadotrophic function, one in males (CL1-032) and one in females (CL1-034)/

They showed that chronic administration (4 months in males and 3 months in females) of agomelatine 50 mg did not modify the hypothalamo-hypophyseal axis in male and female healthy volunteers. No clinically relevant change over time was observed on hormone parameters in males (prolactin, free and total testosterone, Luteinizing hormone (LH), Follicle stimulating hormone (FSH), inhibin B) and females (prolactine, LH, FSH, estradiol, inhibin B, free and total testosterone and progesterone) and on spermogram in males or menstrual cycle duration in females.

Not mentioned in the "Summary of Clinical Safety", but stated in the study report of the DB phase:

In the pubertal girls, neither clinically relevant changes nor differences between agomelatine and placebo groups over time were detected except for TSH with an absolute mean change showing an increase in the agomelatine 25 mg group (0.613 ± 4.778 µUI/mL) versus no relevant change in the placebo group (-0.010 ± 1.232 µUI/mL), probably due to a high maximum last post-baseline value of 32.64 µIU/mL (hypothyroidism reported as SEAE upgraded by the Sponsor). The mean relative change was also higher in the agomelatine 25 mg group (610.2 ± 4224.0%) than in the placebo group (12.4 ± 54.4%). The values of absolute and relative mean changes were -0.050 ± 0.859 µIU/mL and 6.3 ± 52.5% in the agomelatine 10 mg group and 0.316 ± 1.838 µIU/mL and 23.9 ± 96.2 in the fluoxetine group.

In the male adolescents, neither clinically relevant changes nor differences between agomelatine and placebo groups over time were detected except for TSH with a mean decrease between baseline and last post-baseline value of -0.731 ± 1.356 μIU/mL in the agomelatine 10 mg group versus a slight increase in the placebo group (0.236 ± 1.169 μIU/L). The relative change associated to the decrease in the agomelatine 10 mg group was slight at -17.9 ± 38.6% versus an increase of 25.2 ± 55.1% in the placebo group. The values of absolute and relative mean changes were 0.338 ± 1.345 μIU/L and 18.6 ± 50.5% in the agomelatine 25 mg group and 0.154 ± 1.019 μIU/L and 15.4 ± 42.6% in the fluoxetine group. Moreover, fluctuations were observed on relative change for testosterone without clinical significance.

Extension phase: (thyrotropin and cortisol)

In the adolescents of the Sub-SS treated all along with agomelatine, no clinically relevant mean change over time was detected in cortisol and thyrotropin.

Weight and BMI

In the adolescent MDE DB PC set, adolescents gained on average almost 1 kg between baseline and the last post-baseline value over the 12-week double-blind treatment period without relevant difference between groups (Mean ± SD = 1.0 ± 2.0 kg on agomelatine 25 mg and 0.7 ± 2.8 kg on placebo). No clinically relevant mean changes, nor relevant difference between groups was observed regarding BMI.

In the "ext adolescent MDE" set, on agomelatine, weight gain was on average 3.5 ± 5.5 kg over the W012-W104 period, with a slight gradual increase of mean BMI (0.50 ± 1.60 kg/m^2), which could be expected, due to muscle mass gain, in a peri pubertal population (Cole *et al*, 2000).

2.5.5. Serious events and deaths

Deaths

In the clinical paediatric studies with agomelatine, no death was reported.

Serious Adverse Events

In the ado MDE set, SEAEs were reported by 20 patients (10.4%) in the agomelatine 25 mg group. This rate was higher than in the adult MDE set where no relevant difference between agomelatine and placebo groups (3.5% *versus* 4.0%) was observed.

Table 80. – Serious EAEs (reported by at least 1 patient on agomelatine 25 mg in the Ado MDE Set – Ado and adult MDE sets

PT	Ado MDE						Adult MDE					
	Ago 25 mg (N = 192)			Placebo (N = 13)			Ago 25 mg (N = 5662)			Placebo (N = 1393)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%	NEAE	n	%
ALL	**32**	**20**	**10.42**	**-**	**-**	**-**	**241**	**199**	**3.51**	**69**	**55**	**3.95**
Depression	4	4	2.08	-	-	-	19	19	0.34	12	12	0.86
Syncope	3	3	1.56	-	-	-	2	2	0.04	-	-	-
Intentional self-injury	2	2	1.04	-	-	-	-	-	-	-	-	-
Platelet count decreased	2	2	1.04	-	-	-	-	-	-	-	-	-
Suicide attempt	2	2	1.04	-	-	-	31	30	0.53	10	10	0.72
Adjustment disorder	1	1	0.52	-	-	-	-	-	-	-	-	-
Appendicitis	1	1	0.52	-	-	-	1	1	0.02	-	-	-
Dehydration	1	1	0.52	-	-	-	-	-	-	-	-	-
Emotional disorder of childhood	1	1	0.52	-	-	-	-	-	-	-	-	-
Gastritis	1	1	0.52	-	-	-	2	2	0.04	-	-	-
Goitre	1	1	0.52	-	-	-	1	1	0.02	-	-	-
Hypothyroidism	1	1	0.52	-	-	-	-	-	-	-	-	-
Intentional overdose	1	1	0.52	-	-	-	1	1	0.02	-	-	-
Latent tetany	1	1	0.52	-	-	-	-	-	-	-	-	-
Meniscus injury	1	1	0.52	-	-	-	-	-	-	-	-	-
Pancreatitis	1	1	0.52	-	-	-	-	-	-	-	-	-
Pneumonia	1	1	0.52	-	-	-	1	1	0.02	-	-	-
Respiratory tract infection	1	1	0.52	-	-	-	-	-	-	-	-	-
Self-injurious ideation	1	1	0.52	-	-	-	-	-	-	-	-	-
Somnolence	1	1	0.52	-	-	-	1	1	0.02	-	-	-

Suicidal behaviour	1	1	0.52	-	-	-	1	1	0.02	-	-	-
Suicidal ideation	1	1	0.52	-	-	-	5	5	0.09	-	-	-
Thrombocytopenia	1	1	0.52	-	-	-	-	-	-	-	-	-
Tracheitis	1	1	0.52	-	-	-	-	-	-	-	-	-

*n: Number of patients with at least one serious emergent AE in a given preferred term ;%: (n/N)*100*

In the ado MDE set, the most frequent SEAEs reported on agomelatine 25 mg were depression and syncope both reported by 4 (2.1%) and 3 (1.6%) patients, respectively. In the adult MDE set, depression was less frequent on agomelatine 25 mg than on placebo and syncope was reported by 2 patients (0.04%) versus none in the placebo group.

Regarding the MDE DB PC set, no relevant difference was observed between agomelatine 25 mg and placebo as regards frequency of SEAEs (2 patients in both groups: 2.7% *versus* 2.4%, respectively).

Among the serious EAEs, only one, hypothyroidism, was considered as related to the study drug.

Table 81. Emergent serious adverse events during the treatment period – paed MDE DB PC – analysis by SOC and PT (Safety set)

System Organ Class Preferred Term	Agomelatine 10 mg (N = 102)			Agomelatine 25 mg (N = 94)			Placebo (N = 103)			Fluoxetine (N = 100)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%	NEAE	n	%
ALL	7	6	5.9	7	3	3.2	-	-	-	9	7	7.0
Psychiatric disorders	2	2	2.0	2	1	1.1	-	-	-	2	2	2.0
Intentional self-injury	1	1	1.0	1	1	1.1	-	-	-	1	1	1.0
Suicide attempt	-	-	-	1	1	1.1	-	-	-	-	-	-
Anorexia nervosa	1	1	1.0	-	-	-	-	-	-	-	-	-
Suicidal ideation	-	-	-	-	-	-	-	-	-	1	1	1.0
Nervous system disorders	1	1	1.0	1	1	1.1	-	-	-	2	2	2.0
Somnolence	-	-	-	1	1	1.1	-	-	-	-	-	-
Syncope	1	1	1.0	-	-	-	-	-	-	2	2	2.0
Injury, poisoning and procedural complications	1	1	1.0	1	1	1.1	-	-	-	2	1	1.0
Intentional overdose	-	-	-	1	1	1.1	-	-	-	-	-	-
Alcohol poisoning	1	1	1.0	-	-	-	-	-	-	-	-	-
Concussion	-	-	-	-	-	-	-	-	-	1	1	1.0
Fall	-	-	-	-	-	-	-	-	-	1	1	1.0
Investigations	-	-	-	1	1	1.1	-	-	-	2	1	1.0
Neutrophil count decreased	-	-	-	1	1	1.1	-	-	-	-	-	-
Alanine aminotransferase increased	-	-	-	-	-	-	-	-	-	1	1	1.0
Aspartate aminotransferase increased	-	-	-	-	-	-	-	-	-	1	1	1.0
Endocrine disorders	-	-	-	2	1	1.1	-	-	-	-	-	-
Goitre	-	-	-	1	1	1.1	-	-	-	-	-	-
Hypothyroidism	-	-	-	1	1	1.1	-	-	-	-	-	-
Infections and infestations	2	2	2.0	-	-	-	-	-	-	1	1	1.0
Infectious mononucleosis	1	1	1.0	-	-	-	-	-	-	-	-	-
Measles	1	1	1.0	-	-	-	-	-	-	-	-	-
Appendicitis	-	-	-	-	-	-	-	-	-	1	1	1.0
Vascular disorders	1	1	1.0	-	-	-	-	-	-	-	-	-
Haemorrhagic vasculitis	1	1	1.0	-	-	-	-	-	-	-	-	-

N: Number of patients by group; NEAE: Number of events; n: Number of patients affected; Percentages are based on N; Treatment emergent serious AE include sponsor upgrade.

In the paediatric subset 16 patients (4.0%), all in the agomelatine and fluoxetine groups, experienced at least one SEAE during the treatment period versus none in the placebo group, as follows:

- 6 patients in the agomelatine 10 mg group (5.9%) with a total of 7 SEAEs.
- 3 patients in the agomelatine 25 mg group (3.2%) with a total of 7 SEAEs.
- No patient in the placebo group.
- 7 patients in the fluoxetine group (7.0%) with a total of 9 SEAEs.

All SEAEs associated with agomelatine were reported only once.

SEAEs considered as treatment-related were:

-Hypothyroidism in the agomelatine 25 mg group.

-ALT and AST increased (one patient) and suicidal ideation in the fluoxetine group.

SEAEs led to IMP withdrawal in:

- 3 patients (2.9%) in the agomelatine 10 mg group for anorexia nervosa, alcohol poisoning and infectious mononucleosis.

-2 patients (2.1%) in the agomelatine 25 mg group for intentional self-injury, suicide attempt, somnolence, intentional overdose (all events in one patient) and hypothyroidism.

-2 patients (2.0%) in the fluoxetine group for suicidal ideation (one patient), ALT increased and AST increased (one patient).

Almost all SEAEs described in the total population occurred in the adolescents. In adolescents of the Safety Set:

-5 patients (6.2%) in the agomelatine 10 mg group with a total of 5 SEAEs.

-2 patients (2.7%) in the agomelatine 25 mg group with a total of 6 SEAEs;

-No patient in the placebo group.

-7 patients (8.6%) in the fluoxetine group with a total of 9 SEAEs.

Table 82. Serious treatment emergent adverse events by SOC and PT during the W012-W104 period – Adolescents of the sub-safety set

System Organ Class Preferred Term	Agomelatine 10 or 25 mg / 10-25 mg (N = 134)			Placebo / Agomelatine 10-25 mg (N = 69)			Fluoxetine 10-20 mg / Agomelatine 10-25 mg (N = 68)			ALL (N = 271)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%	NEAE	n	%
ALL	**8**	**7**	**5.2**	**21**	**11**	**15.9**	**9**	**8**	**11.8**	**38**	**26**	**9.6**
Infections and infestations	**2**	**2**	**1.5**	**1**	**1**	**1.4**	**3**	**3**	**4.4**	**6**	**6**	**2.2**
Pneumonia	1	1	0.7	-	-	-	1	1	1.5	2	2	0.7
Respiratory tract infection	1	1	0.7	-	-	-	-	-	-	1	1	0.4
Appendicitis	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Tonsillitis bacterial	-	-	-	-	-	-	1	1	1.5	1	1	0.4
Tracheitis	-	-	-	-	-	-	1	1	1.5	1	1	0.4
Investigations	**1**	**1**	**0.7**	**3**	**2**	**2.9**	**1**	**1**	**1.5**	**5**	**4**	**1.5**
Platelet count decreased	1	1	0.7	-	-	-	1	1	1.5	2	2	0.7
Alanine aminotransferase increased	-	-	-	2	2	2.9	-	-	-	2	2	0.7
Aspartate aminotransferase increased	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Gastrointestinal disorders	**1**	**1**	**0.7**	**2**	**2**	**2.9**	-	-	-	**3**	**3**	**1.1**
Pancreatitis	1	1	0.7	-	-	-	-	-	-	1	1	0.4
Abdominal pain	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Gastritis	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Injury, poisoning and procedural complications	**1**	**1**	**0.7**	**1**	**1**	**1.4**	**1**	**1**	**1.5**	**3**	**3**	**1.1**
Ankle fracture	1	1	0.7	-	-	-	-	-	-	1	1	0.4
Meniscus injury	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Intentional overdose	-	-	-	-	-	-	1	1	1.5	1	1	0.4
Metabolism and nutrition disorders	**1**	**1**	**0.7**	**1**	**1**	**1.4**	-	-	-	**2**	**2**	**0.7**
Latent tetany	1	1	0.7	-	-	-	-	-	-	1	1	0.4
Dehydration	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Nervous system disorders	**1**	**1**	**0.7**	-	-	-	**1**	**1**	**1.5**	**2**	**2**	**0.7**
Syncope	1	1	0.7	-	-	-	1	1	1.5	2	2	0.7
Blood and lymphatic system disorders	**1**	**1**	**0.7**	-	-	-	-	-	-	**1**	**1**	**0.4**
Thrombocytopenia	1	1	0.7	-	-	-	-	-	-	1	1	0.4
Psychiatric disorders	-	-	-	**13**	**6**	**8.7**	**3**	**3**	**4.4**	**16**	**9**	**3.3**
Depression	-	-	-	3	3	4.3	1	1	1.5	4	4	1.5
Suicidal ideation	-	-	-	1	1	1.4	1	1	1.5	2	2	0.7
Adjustment disorder	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Anger	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Drug abuse	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Emotional disorder of childhood	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Intentional self-injury	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Irritability	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Mood swings	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Self-injurious ideation	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Suicidal behaviour	-	-	-	1	1	1.4	-	-	-	1	1	0.4
Suicide attempt	-	-	-	-	-	-	1	1	1.5	1	1	0.4

NEAE: Number of events
Percentages are based on N
Treatment emergent serious AE include sponsor upgrade
Adverse events were coded using MedDRA 24.0

In the adolescents, 26 (9.6%) had 38 serious TEAEs during the W012-W104 period. The percentage of adolescents having experienced at least one serious TEAE was 5.2% in the ago/ago group, 15.9% in the placebo/ago group and 11.8% in the fluox/ago group.

The most common serious TEAE was depression reported in 4 patients. Platelet count decreased, pneumonia, syncope, ALT increased and suicidal ideation were reported by 2 patients each. All other serious TEAEs were reported once. No serious TEAE was considered as related to IMP. Ten serious TEAEs led to IMP withdrawal in 6 patients, mainly Psychiatric disorders [9 serious TEAEs in 5 patients: depression (3 cases), anger, drug abuse, irritability, mood swings, suicidal behaviour and suicide attempt (one case each)] and one case of intentional overdose in one patient.

2.5.6. Laboratory findings

Liver parameters, hormonal status, weight and BMI are described in the section on "Analysis of Adverse Events by Organ System"

Description of laboratory evaluations was based on the CL3-076 study in the following sets:

- ado MDE DB PC set compared to the adult MDE DB PC set for the acute phase (12 weeks),

- ext ado MDE set for the extension period (W012-W104) in which all patients on agomelatine (10 mg or 25 mg) were considered.

Haematology

Double-blind period (12 weeks)

In the adolescents from the ado MDE DB PC set, neither clinically relevant changes nor differences between agomelatine and placebo groups in mean values over time were detected. Nevertheless, fluctuations were observed on relative change for basophils and neutrophils without clinical significance.

Table 90 presents for both ado and adult MDE sets, the counts of patients with emergent potentially clinically significant abnormal (PCSA) haematological values in the ado MDE DB set.

Emergent PCSA values were sparse without relevant difference between agomelatine 25 mg and placebo groups in the adolescent MDE DB set. Of note, high leucocytes values were reported by 2 patients on agomelatine 25 mg *versus* none on placebo.

Table 83. Haematological parameters – Counts of patients with at least one emergent PCSA value in the Ado MDE DB PC set on agomelatine 25 mg – Ado and adult MDE DB PC sets

			Ado MDE DB PC*		Adult MDE DB PC **	
			Ago 25 mg (N = 94)	Placebo (N = 103)	Ago 25 (N = 1796)	Placebo (N = 1909)
Haemoglobin (g/L)	Low	n (%)	1 (1.4)	1 (1.3)	2 (0.1)	1 (0.1)
Haematocrit (RATIO)	Low	n (%)	1 (1.4)	-	4 (0.3)	8 (0.5)
WBC (G/L)	High	n (%)	2 (2.7)	-	6 (0.4)	7 (0.4)
Neutrophils (G/L)	High	n (%)	1 (1.4)	-	3 (0.2)	5 (0.3)
Eosinophils (G/L)	High	n (%)	1 (1.4)	-	-	1 (0.1)

Low emergent abnormal value: baseline value above or equal to the lower limit (or missing) and at least one value on treatment below this limit
High emergent abnormal value:baseline value below or equal to the upper limit (or missing) and at least one value on treatment above this limit
n: number of patients;%:n/nb of patients with at least one post-baseline value under treatment
**see appendix 15.3.3.2 of the report CL3-076 (NP40580); **see Module 5.3.5.3 (NP42056, section 3.1)*

Extension period (W012-W104)

In the extension adolescent MDE set, no clinically relevant mean change over time was detected in the haematological parameters.

Emergent PCSA haematological values on treatment were rather few (the most frequent were low haemoglobin and low platelets and high eosinophils, all reported in 5 patients).

Counts of patients with emergent PCSA haematological values on treatment over the W012- W104 period are summarised in Table 91. Upper and lower limits used to define PCSA values were not defined for erythrocyte mean corpuscular volume.

Table 84. Haematological parameters – Counts of patients* with at least one emergent PCSA value on treatment in the ext ado MDE Set – W012-W104 period

Parameter	(unit)			Agomelatine
Haemoglobin	(g/L)	Low	n (%)	5 (2.0)
Eosinophils	(10^9/L)	High	n (%)	5 (2.0)
Platelets	(10^9/L)	Low	n (%)	5 (2.0)
		High	n (%)	1 (0.4)
Leucocytes	(10^9/L)	Low	n (%)	4 (1.6)
		High	n (%)	1 (0.4)
Haematocrit	(RATIO)	Low	n (%)	3 (1.2)
		High	n (%)	1 (0.4)
Neutrophils	(10^9/L)	Low	n (%)	1 (0.4)

Low emergent abnormal value: baseline value above or equal to the lower limit (or missing) and at least one value on treatment below this limit
High emergent abnormal value:baseline value below or equal to the upper limit (or missing) and at least one value on treatment above this limit
n : number of patients;%:n/nb of patients with at least one post-baseline value under treatment
**see appendix 15.3.3.2 of the report CL3-076 final (NP40580)*

Biochemistry other than liver parameters

Double-blind period (12 weeks)

In the adolescents from the CL3-076 study (ado MDE DB PC set), neither clinically relevant changes nor differences between agomelatine and placebo groups in mean values over time were detected.

No emergent PCSA biochemical values were observed on agomelatine 25 mg group in the adolescents MDE DB set.

Extension period (W012-W104)

In the extension adolescent MDE set, no clinically relevant mean change over time was detected in the biochemical parameters other than liver parameters.

Emergent PCSA biochemical (other than liver parameters) values on treatment were few, except low HDL cholesterol (3.1%, 8 patients) and high triglycerides (1.6%, 4 patients).

Count of patients with emergent PCSA biochemical values on treatment over the W012-W104 period are summarised in Table 85.

Table 85. Biochemical parameters other than liver- Count of patients* with at least one emergent PCSA value on treatment in the ext Ado MDE Set – W012-W104 period

Parameter	(unit)			Agomelatine
Potassium	(mmol/L)	High	n (%)	1 (0.4)
HDL Cholesterol	(mmol/L)	Low	n (%)	8 (3.1)
Triglycerides	(mmol/L)	High	n (%)	4 (1.6)

Low emergent abnormal value: baseline value above or equal to the lower limit (or missing) and at least one value on treatment below this limit
High emergent abnormal value:baseline value below or equal to the upper limit (or missing) and at least one value on treatment above this limit
n : number of patients;%:n/nb of patients with at least one post-baseline value under treatment
**see appendix 15.3.3.1 of the report CL3-076 final (NP40580)*

Vital Signs, Physical Findings, And Other Observations Related To Safety

Description of vital signs, physical findings and other safety evaluations was based only on CL3-076 study in ado MDE DB PC set compared to the adult MDE DB PC set for the acute phase (12 weeks), as well as the ext ado MDE set for the extension period (W012-W104) in which all patients on agomelatine (10 mg or 25 mg) were considered. No new safety concern has been identified for adolescents.

Blood pressure and heart rate

In the adolescent MDE DB PC set, there were no clinically relevant mean changes in sitting SBP, sitting DBP and sitting heart rate between baseline and the last post-baseline value over the 12-week double-blind treatment period in any group, nor relevant difference between the agomelatine 25 mg and placebo groups.

On the same way, there were no clinically relevant mean changes in sitting SBP, sitting DBP and sitting heart rate, in the long-term ado MDE set on agomelatine over the W012-W104 period.

ECG

In the adolescent MDE DB PC set, one adolescent in the agomelatine 25 mg group presented at least one clinically significant ECG abnormality (sinus bradycardia) at the last post-baseline value over the 12-week treatment period, versus none in the placebo group. The patient did not withdraw for adverse event.

In the extension ado MDE set on agomelatine, no adolescent had clinically significant ECG abnormality at W104 or considering the last post-baseline value.

2.5.7. Safety in special populations

Intrinsic Factors

Liver impairment

Data are available for the adult population. No data on adolescents are available. Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 ULN are contra-indications in the SmPC.

Renal impairment

Data are available for the adult population. No data on adolescents are available. As limited clinical data are available in patients with moderate or severe renal impairment, caution should be exercised when prescribing agomelatine to these patients.

Sex

The bioavailability is increased in women compared with men (SmPC section 5.2).

Extrinsic Factors

Due to the low number of concerned subjects in the adolescents population, no analysis of extrinsic factors, such as smoking and alcohol consumption were performed. The SmPC states that smoking induces CYP1A2 and has been shown to decrease the bioavailability of agomelatine, especially in heavy smokers (> 15 cigarettes/day). The combination of agomelatine and alcohol is not recommended.

2.5.8. Discontinuation due to adverse events

This section presents for both ado and adult MDE sets, the most frequent EAEs leading to discontinuation of study drug (WEAE) reported in agomelatine 25 mg group in the MDE sets (see table below).

Table 86. WEAE reported by at least one patient on agomelatine 25 mg in the Ado MDE set – Ado and adult MDE sets

	Ado MDE				Adult MDE			
	Ago 25 mg (N = 192)		Placebo (N = 13)		Ago 25 mg (N = 5662)		Placebo (N = 1393)	
	n	%	n	%	n	%	n	%
ALL	**9**	**4.69**	**1**	**7.69**	**462**	**8.16**	**143**	**10.27**
Depression	4	2.08	-	-	39	0.69	33	2.37
Suicide attempt	2	1.04	-	-	28	0.49	9	0.65
Alanine aminotransferase increased	1	0.52			9	0.16	-	-
Aspartate aminotransferase increased	1	0.52			6	0.11	-	-
Headache	1	0.52	-	-	29	0.51	15	1.08
Hypothyroidism	1	0.52	-	-	-	-	1	0.07
Intentional overdose	1	0.52	-	-	3	0.05	-	-
Intentional self-injury	1	0.52	-	-	-	-	1	0.07
Somnolence	1	0.52	-	-	9	0.16	2	0.14
Suicidal behaviour	1	0.52	-	-	1	0.02	-	-

*n: Number of patients with at least one emergent AE leading to IMP withdrawal in a given preferred term ;%: (n/N)*100 (N : number of patients by group)*

In the adolescent MDE set, 9 patients (4.7%) reported at least one WEAE on agomelatine 25 mg with a lower rate than in the adult MDE set (8.2%). Except depression and suicide attempt reported by 4 (2.1%) and 2 (1.0%) adolescents, respectively, WEAEs were reported only once. Both depression and suicide attempt were less frequently reported on agomelatine 25 mg than on placebo in the adult MDE set (0.7% versus 2.4% and 0.5% versus 0.7%, respectively).

When regarding MDE DB set, depression was not reported and one suicide attempt in the agomelatine 25 mg group led to IMP withdrawal versus none in the placebo group.

Serious EAEs (SEAEs) led to IMP withdrawal in:

- 3 patients (2.9%) in the agomelatine 10 mg group for anorexia nervosa, alcohol poisoning and infectious mononucleosis.

-2 patients (2.1%) in the agomelatine 25 mg group for intentional self-injury, suicide attempt, somnolence, intentional overdose (all events in one patient) and hypothyroidism.

-2 patients (2.0%) in the fluoxetine group for suicidal ideation (one patient), ALT increased and AST increased (one patient).

Table 87 . Treatment emergent adverse events leading to IMP withdrawal – Analysis by system organ class and preferred term – Safety Set in CL3-076 (DB phase)

System Organ Class Preferred Term	Agomelatine 10 mg (N = 102)			Agomelatine 25 mg (N = 94)			Placebo (N = 103)			Fluoxetine (N = 100)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%	NEAE	n	%
ALL	3	3	2.9	10	4	4.3	4	2	1.9	6	3	3.0
Psychiatric disorders	1	1	1.0	2	1	1.1	1	1	1.0	1	1	1.0
Intentional self-injury	-	-	-	1	1	1.1	-	-	-	-	-	-
Suicide attempt	-	-	-	1	1	1.1	-	-	-	-	-	-
Anorexia nervosa	1	1	1.0	-	-	-	-	-	-	-	-	-
Major depression	-	-	-	-	-	-	1	1	1.0	-	-	-
Suicidal ideation	-	-	-	-	-	-	-	-	-	1	1	1.0
Injury, poisoning and procedural complications	1	1	1.0	1	1	1.1	-	-	-	-	-	-
Intentional overdose	-	-	-	1	1	1.1	-	-	-	-	-	-
Alcohol poisoning	1	1	1.0	-	-	-	-	-	-	-	-	-
Nervous system disorders	-	-	-	1	1	1.1	1	1	1.0	-	-	-
Somnolence	-	-	-	1	1	1.1	-	-	-	-	-	-
Dizziness	-	-	-	-	-	-	1	1	1.0	-	-	-
Immune system disorders	-	-	-	1	1	1.1	-	-	-	1	1	1.0
Drug hypersensitivity	-	-	-	1	1	1.1	-	-	-	1	1	1.0
Investigations	-	-	-	2	1	1.1	-	-	-	2	1	1.0
Alanine aminotransferase increased	-	-	-	1	1	1.1	-	-	-	1	1	1.0
Aspartate aminotransferase increased	-	-	-	1	1	1.1	-	-	-	1	1	1.0
Skin and subcutaneous tissue disorders	-	-	-	1	1	1.1	-	-	-	1	1	1.0
Dermatitis allergic	-	-	-	1	1	1.1	-	-	-	1	1	1.0
Endocrine disorders	-	-	-	1	1	1.1	-	-	-	-	-	-
Hypothyroidism	-	-	-	1	1	1.1	-	-	-	-	-	-
General disorders and administration site conditions	-	-	-	1	1	1.1	-	-	-	-	-	-
Drug interaction	-	-	-	1	1	1.1	-	-	-	-	-	-
Infections and infestations	1	1	1.0	-	-	-	-	-	-	-	-	-
Infectious mononucleosis	1	1	1.0	-	-	-	-	-	-	-	-	-
Gastrointestinal disorders	-	-	-	-	-	-	2	1	1.0	-	-	-
Diarrhoea	-	-	-	-	-	-	1	1	1.0	-	-	-
Nausea	-	-	-	-	-	-	1	1	1.0	-	-	-
Eye disorders	-	-	-	-	-	-	-	-	-	1	1	1.0
Swelling of eyelid	-	-	-	-	-	-	-	-	-	1	1	1.0

N: Number of patients by group.
NEAE: Number of events.
n: Number of patients affected.
Percentages are based on N.

2.5.9. Post marketing experience

Since the first marketing authorisation and up to 19 February 2022, the estimated number of patients exposed to Agomelatine is 3,942,237 patient-years (calculated from the sales volumes) for all countries.

Since MA, regular European Periodic Benefit Risk Evaluation Reports (PBRERs) have been submitted to European Competent Authorities. The last European PBRER covered the period from 20 February 2018 to 19 February 2021 (PBRER 12, 2021).

Drug use in unapproved age group: paediatric population

Since MA up to 19 February 2022, a total of 161 cases of Agomelatine use were reported in the paediatric population (< 18 years old), most of them (78.9%) in adolescents.

In 48.4% of cases, no adverse event was reported. Among the cases that reported adverse events, the 5 most frequently reported were: ALT increased (9), fatigue (7), abdominal pain (7), AST increased (6) and nausea (6), all of them listed in the section 4.8 of the European SmPC.

In addition to its use in the treatment of depressive disorders, Agomelatine was mainly prescribed in the paediatric population for the following conditions (off label use): sleep disorders, anxiety, attention deficit hyperactivity disorder and autism.

Out of the 161 reported cases:

– One hundred twenty-seven (127) cases were reported in adolescents (≥ 12 years old). Among them:

- 121/127 were regularly treated with Agomelatine (dose ranging from 12.5 to 75 mg). Among them, 51.2% reported adverse events;
- 8/127 used Agomelatine in suicide attempt by overdose (50 to 1000 mg), 5 out of 8 patients presented associated adverse events such as fatigue, abdominal pain, somnolence, nausea, dizziness and hallucination;
- 2/127 had an accidental intake (only one of them reported somnolence as associated adverse event).

- Thirty (30) cases were reported in children (< 12 years old). Among them:

- 15/30 were exposed during mother's pregnancy (13) or breastfeeding (2), and among them, 14 reported associated adverse events (different congenital anomalies, respiratory disorders, developmental delay, neonatal drug withdrawal syndrome, irritability);
- 6/30 were regularly treated with Agomelatine (dose ranging from 12.5 to 25 mg). Among them, only one patient reported adverse event (abdominal pain);
- 9/24 had an accidental intake (6 of them reported associated adverse events such as abdominal pain, agitation, somnolence, fatigue, vomiting, feeling cold).
- No case of suicide attempt was reported in this age group.

- In the remaining four (4) cases, the age group was not reported. All of them received regular treatment with Agomelatine without adverse events.

From this analysis, no new safety concern has been identified.

2.5.10. Discussion on clinical safety

During the assessment, it was considered that the Summary of Clinical Safety is in general not of sufficient quality for assessing the safety data. Data were summarised too briefly, and critical discussions were lacking, for instance regarding hepatotoxic reactions, suicidality, and possible long-term effects when treating depression in the paediatric population, as well as differences in frequencies of adverse events between adolescents and adults. Several aspects regarding the documentation needed to be revised and re-analysed and submitted in the response to the safety concerns raised. The MAH addressed these issues during the assessment.

Exposure and strategy

The strategy of the safety evaluation was an analysis of pooled safety data from phase II/III studies in the adolescent population, and a comparison of this adolescent (ado) MDE set with the corresponding adult MDE set to assess if the safety profile in adolescents is similar to the safety profile known in adults. The MAH has pooled data from **study CL-2-075** which is an open, non-comparative phase II study including 51 paediatric patients (of which 27 adolescents), with **study CL3-076**, a phase III, 12-week, multicentre, randomised, double-blind and placebo-controlled trial comparing two doses (10 mg and 25 mg) of agomelatine in children (from 7 to < 12 years) and adolescent patients (from 12 years to < 18 years) suffering from moderate to severe MDD. This latter, pivotal study enrolled in total 400 paediatric patients, including 320 adolescents. Due to the design of study CL2-075, with three different single doses on three following days only, the study was not deemed suitable for pooling with the pivotal study CL3-076. It was therefore considered that all safety data based on the adolescent MDE set presented, needed to be re-analysed; i.e. based on data from study CL3-076 only. The new analyses were expected to include presentations of relevant tables and corresponding discussions, including causality assessments. In addition, differences in EAE frequencies between adolescents and adults and possible consequences thereof, should be thoroughly discussed. The MAH has not followed up this request. Instead, the MAH based their comparison on short-term data from the double-blind placebo-controlled phase of the CL3-076 study (25 mg agomelatine, 12 weeks duration) in adolescents with pooled double-blind placebo-controlled studies (25-50 mg agomelatine, duration 6-8 weeks) from adults and based their discussion on this. The MAH also prepared a safety set on adolescents from weeks 0-18 (ado MDE W0-W18 set) in order to have a comparable treatment duration to adult data (3.7 months in average).

Study CL3-076 had an optional open, follow-up extension period of 21 months from W012, where all patients continuing, received agomelatine. From W014 to W104, the dose could be adjusted at each visit from 10 mg to 25 mg and vice versa. Accordingly, the mean dose during the extension study is lower than 25 mg. Regarding the dose level received most of the time, the MAH states that 56.5% (153 patients) of the adolescents received agomelatine 25 mg most of the time, while 43,5% (118 patients) received agomelatine 10 mg. Accordingly, the number of adolescents exposed long-term to agomelatine 25 mg is low (n=153). It should also be mentioned that this group, was not analysed separately, but together with all patients receiving agomelatine in lower (10 mg) or adjusted doses (10 mg, 25 mg) during treatment. Long-term safety data for agomelatine 25 mg in adolescents is therefore limited. However, the MAH informed that they withdrew the claim for extension of the indication to include adolescents. Instead, the inclusion of data from Study CL3-076 in various sections of the SmPC was requested by the MAH.

The pooled ado MDE set, based on pooled data from the CL2-075 and CL3-076 study, consisted of 192 adolescents treated for a median duration of 17.9 months, while the adult MDE set consisted of 5662 adults treated for a median duration of 3.7 months. The placebo group in the adult MDE set consisted of 1393 adults with a median treatment duration of 1.9 months. It should be noted that the placebo group in the ado MDE set is very small (n=13). The reason is that most of the 85 adolescents on placebo in the double-blind (DB) phase who entered the optional extension phase, continued long enough on active treatment to

be assigned to the ago 25 mg group. Hence, only prematurely withdrawn or patients non-continuing in the extension period, remained in the corresponding placebo group.

Adverse events

CL3-076 DB phase: In the Ado MDE DB set no relevant differences in frequencies of EAEs were seen between the groups agomelatine 10 mg and agomelatine 25 mg (63.0% and 62.7%, respectively)–and placebo (59.8%). However, EAEs considered related to treatment was higher in the agomelatine 10 mg and 25 mg group (33.3% and 37.3%, respectively) than in the placebo group (29.3). The frequency of SEAEs was higher in the agomelatine 10 mg group (6.2%) than in the agomelatine 25 mg g (2.7%) and placebo group (2.4%). However, only one SEAE (1.3%) in the agomelatine 25 mg group was considered by the investigator to be treatment-related.

The most frequent EAEs reported in the agomelatine 10 mg and 25 mg groups in the DB-phase were: thirst (18.5% and 14.7% of adolescents, respectively), dry mouth (22.2% and 13.3%), nausea (11.1% and 13.3%), headache (16.0% and 9.3%), increased appetite (6.2% and 8.0%) and fatigue (4.9% and 8.0%). The most frequent EAEs considered to be *treatment-related* in the agomelatine 10 mg and 25 mg groups were dry mouth (16.7% and 12.8%, respectively), thirst (11.8% and 9.6%), nausea (5.9% and 9.6%), abdominal pain (2.0% and 3.2%), headache (3.9% and 2.1%), and dizziness (2.9% and 2.1%). Most EAEs are mild or moderate and occurs within the first two weeks of treatment. Based on differences in reporting between agomelatine 10 and 25 mg and placebo, the MAH was requested to discuss whether increased appetite, dry mouth and thirst should be included as ADRs in section 4.8 of the SmPC. The MAH considers that none of these events should be included as ADRs in section 4.8. Increased appetite is regarded to be a therapeutic effect rather than an ADR. Further, the MAH argues that children and adolescents have inadequate hydration which can explain the high frequencies of dry mouth and thirst reported. Many of the most frequently reported EAEs, are already listed as ADRs in the current SmPC for Valdoxan. On request, the MAH has included frequencies of ADRs in the adolescent population if they are different from frequencies in the adult population.

Pooled data set (MDE ado and adult): EAEs, including serious EAEs (SEAEs), were reported with higher frequencies in the adolescent MDE set than in the adult MDE set (67.2% and 10.5% vs. 60.4% and 3.5%, respectively). The frequency of EAEs considered treatment-related by the investigator was similar between the ado and adult MDE sets (31.2% and 32.3%, respectively). The MAH does not discuss the fact that most EAEs, including serious EAEs (SEAEs), are reported with higher frequencies in the adolescent MDE set than in the adult MDE set. A critical discussion was therefore requested from the MAH. In their response the MAH has compared short-term data from the DB PC phase of the CL3-076 study (agomelatine 25 mg, 12 weeks duration) in adolescents with pooled DB PC studies (agomelatine 25-50 mg, duration 6-8 weeks) in adults. The observed percentage of patients having at least one EAE in the adolescent group versus the adult group can be considered as similar (62.7% and 62.2%, respectively). As the number of adolescents is low, frequency estimates of most EAEs are uncertain. Accordingly, for most of the reported EAEs, frequencies are too low in adolescents to allow any meaningful comparison with adult data. All serious EAEs are reported only once, except from two cases of syncope. Therefore, data do not allow any comparison of frequencies of serious EAEs between adolescents and adults.

In the ado MDE set eight cases of blood prolactin increased, two of hyperprolactinemia, nine cases of dizziness postural and six of hypersomnia have been reported. The MAH was requested to make a review of these events and consider whether (any of) these events should be included as ADRs in the SmPC. As regards blood prolactin increased/hyperprolactinemia the information provided is too scarce to make any meaningful evaluation. A new OC was raised and response given, see under Long-term effects in adolescents below. Cases of dizziness postural were regarded to be of little clinical significance. All patients continued treatment with agomelatine without recurrence of the event. Dizziness is already listed as an ADR in the SmPC. For cases of hypersomnia, all events recovered spontaneously under treatment. It is

concluded that evidence is not sufficient to include hypersomnia as an ADR in section 4.8 of the SmPC. Somnolence is listed for agomelatine.

Hepatotoxic reactions

Hepatotoxicity is the main safety concern with agomelatine and is stated as an important identified risk in the RMP. Cases of liver injury, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors), transaminases exceeding 10 times the upper limit of normal, hepatitis and jaundice have been reported in the adult population. Most of them occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with increased serum transaminases, which usually return to normal levels on cessation of therapy. The hepatotoxicity is probably idiosyncratic in nature. Warnings and precautions to avoid serious hepatic events, including an extensive transaminase monitoring programme, must be followed as described in the SmPC. Non-compliance with this monitoring programme has been a concern in the adult population. In addition, as the pharmacokinetic variability of agomelatine is large, the risk of adverse events may also be unpredictable.

In study CL3-076, the following exclusion criteria were applied: transaminases values (AST and/or ALT) ≥ 2 times the upper limit of normal range (ULN), total bilirubin ≥ 1.5 ULN and/or free bilirubin ≥ 2 ULN, transaminases (AST and/or ALT) and total bilirubin values > 1 ULN and Alkaline phosphatase (ALP) ≥ 3 ULN and both ALP and gamma-glutamyl transferase (GGT) > 1 ULN. In addition, the safety was further strengthened by a protocol amendment with significance for the safety evaluation. This pertained to supplementary non-inclusion criteria for liver function, measures concerning liver function tests and the addition of PAERS (Paediatric Adverse Event Rating Scale) as individual safety assessment in addition to AEs. The MAH was requested to declare how many patients were enrolled into the study before the safety measures were strengthened and how this might have influenced the collection of safety data. According to the MAH 28 patients were enrolled into the study before the safety measures were strengthened. This amounts to around 7% of the total number of patients (28/400). Overall, it is considered that these 28 patients would not have had a large impact on the overall collection of safety data.

For the pooled data set, in the ado MDE set, the hepatic adverse events from the TME Hepatic Disorders were reported by 12 (6.3%) adolescents in the agomelatine 25 mg group which was remarkably higher than in the adult MDE set (1.7%). The MAH was asked to thoroughly discuss this fact considering that hepatotoxicity is the major safety concern with agomelatine. The MAH has compared data from the DB PC phase of the CL3-076 study in adolescents (dose 25 mg, 12 weeks duration) with pooled DB PC studies in adults (dose 25 mg, 6-8 weeks duration). The frequency of hepatic EAE* (i.e. hepatic EAEs based on Targeted Medical Events (TME) Hepatic events) in adolescents was 4.0% in comparison to 1.8% in the adult population. The frequency in adolescents was lower than reported in the adolescent placebo group (7.3%). As previously discussed, it should be noted that frequency estimates in the adolescents are uncertain due to the few events reported. In addition, the duration of the double-blind placebo-controlled studies in adults was shorter (between 6-8 weeks) than the study in adolescents (12 weeks). It is considered that it has not been adequately shown that the frequency of liver EAEs in adolescents is not higher than in adults. Given the well-established liver toxicity of agomelatine in adults, the data presented for adolescents is of concern. Accordingly, hepatotoxicity in adolescents should be further characterized, however no new proposals for characterization of this risk have been given (see further below in this subsection).

Available data could suggest that the systemic exposure of agomelatine in children and adolescents is in the higher end of range of the observed adult data following a 25 mg dose of agomelatine. Data are hampered by uncertainty considering that most paediatric PK data derive from saliva (and not plasma). Therefore, it is not known whether the higher frequency of adverse events observed in adolescents compared to adults could be related to increased agomelatine exposure.

According to the SmPC most hepatic EAEs have occurred during the first months of treatment. Nevertheless, events have also been reported following longer-term use. This has not been addressed by the MAH.

Overall, based on adolescent data from the double-blind phase of the CL3-076 study, compared to corresponding values in adults, the following frequencies of abnormal liver function tests were observed on agomelatine 25 mg: AST >1 ULN and > 3ULN: 2.7% and 1.47% (one patient) in adolescents, respectively, vs 5.79%, and 0.37% in adults, and ALT > 1 ULN and > 3 ULN: 2.7% and 0 vs. 7.6% and 0.56% in adults.

In the extension phase, changes for the patients who switched from blinded placebo to the active drug (i.e. agomelatine 10-25 mg) were similar to the observed values (in patients on agomelatine) in the blinded phase, and no further elevations in liver tests were observed.

Overall, based on the available data there seem to be no clinically relevant differences in liver toxicity between adolescents and what has been observed in adults for the same indication and dose. It has to be kept in mind that the risk of hepatotoxicity in adults is identified as an important safety concern, and risk minimization measures have been introduced, as mentioned above. It appears reasonable to apply the same liver function surveillance assessment for adolescents as in place for adults; i.e. liver function tests should be performed before starting treatment with agomelatine, then after around 3 weeks, 6 weeks (end of acute phase), after 12 weeks and 24 weeks (end of maintenance phase), and thereafter when clinically indicated.

However, available data for children and adolescents are scarce. The pivotal trial included in total only 400 patients which is small given the absolute incidence of liver toxicity associated with the drug. Confidence intervals around the point estimates for liver toxicity for adolescents are likely wide, indicating low precision of the estimate. Due to this uncertainty, it is again considered that the risk of hepatotoxic reactions is not sufficiently characterized in the adolescent population. In the response, the MAH has offered little new information to assess, however, it is again concluded that regular monitoring of liver transaminases is mandatory to identify patients with agomelatine-related hepatotoxicity. It is important that the same extensive monitoring regimen as approved for adults is implemented in adolescents. Overall, the risk of hepatotoxicity seems to be manageable when serum transaminases are measured. However, as previously mentioned, non-compliance with this monitoring programme has been a concern in the adult population. Characterisation of hepatotoxic reactions is further discussed in the RMP (section 6.3 Pharmacovigilance plan).

According to the SmPC, in clinical trials in adults, increases > 3 times the upper limit of the normal (ULN) range for ALT and/or AST were seen for 1.2% of patients on agomelatine 25 mg daily and 2.6% on agomelatine 50 mg daily vs. 0.5% on placebo. The frequencies of ALT and AST increased above 3 ULN presented in the adult MDE in this application, is much lower for both the agomelatine 25 mg (0.56% and 0.37%), and the placebo group (0.29% and 0.14%, respectively). The MAH was requested to provide an explanation for the differences. The MAH has adequately addressed this in the response to the 1. RSI.

Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)

This is an important identified risk in the RMP, however no new information is available from the adolescent dataset. In adults, fluvoxamine increased agomelatine exposure by 60-fold (range 12-412) and concomitant use of strong CYP1A2 inhibitors is therefore contraindicated.

Suicide-related events

Suicide-related events was initially an important potential risk in the RMP, but has later been removed as it was considered that this risk is well known among clinicians treating adults, and that necessary precautions to take were implemented in major treatment guidelines on depression. In the pivotal study CL3-076, the suicidal risk was assessed using the Columbia-Suicide Severity Rating Scale Children version (C-SSRS-C). The MAH states, but does not discuss, that suicidal EAEs were reported with an almost 3 times

higher frequency in the ado MDE set (3.1%) than in the adult MDE set (1.2%) based on the TME Suicidal events. The MAH has failed to provide an acceptable explanation for this. In addition, it was uncertain whether all relevant events had been included in the frequency estimate for the ado MDE set. The MAH was therefore requested to clarify and present rates of suicidal-related events in a better way. The MAH showed that all events had been included. It is worrying that two adolescents on agomelatine presented with three emergent suicidal behaviours in the extension phase (both made suicide attempts). In addition, a case of overdose was registered as a suicide attempt in the double-blind phase. The MAH was requested to provide short narratives of all suicidal events associated with agomelatine in the pediatric population and discuss these regardless of relatedness to therapy. Seriousness and time to onset of the event was also addressed. The MAH submitted these narratives. In general, causality to agomelatine is difficult to evaluate for these cases. Suicidal thoughts or behaviour are listed for agomelatine, but some of the suicidal events can represent repetition of previous behaviour. For some others, lack of efficacy of agomelatine may be the most plausible explanation. Various stressors may also have triggered or contributed to the events. Monitoring for suicidal events is well-known and considered adequately handled by psychiatrists treating adolescents with depression. Treatment should therefore be initiated and monitored under specialist supervision in line with fluoxetine MDD treatment in adolescents.

In section 4.4 in the SmPC it is stated that suicide-related behaviour (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed compared to those treated with placebo in clinical trials among children and adolescents treated with other antidepressants. The MAH wanted to add that "such higher frequencies were not reported in the clinical trials with agomelatine". As this statement was not sufficiently justified by the MAH, or documented it is therefore deleted from the SmPC. Since suicidal events were reported with a numerically higher frequency in the ado MDE set than in the adult MDE set, the MAH proposed relevant wording to reflect this in the SmPC which the CHMP accepted

The MAH was also requested to state the reason for using targeted medical events (TME) instead of SMQs, when grouping similar adverse events. The MAH has confirmed that the TME suicidal events comprises exactly the same preferred terms (PT) as the SMQn suicide self-injury.

Sedation/stimulation

In the double-blind phase sedative-type events were more frequently reported on agomelatine 25 mg than on placebo (12.0% *versus* 6.1%) whereas no relevant difference between the groups was observed for stimulating-type events (4.0% *versus* 3.7%).

Long-term effects in adolescents

Cognitive functioning, including possible influences on memory, learning and school performances, is not discussed at all by the MAH in the Summary of the Clinical Safety. It seems from the study reports that "Continuous Performance Task" has been performed. This is a test measuring parameters like selective attention and vigilance. The MAH was requested to describe and discuss the results of this test. As discussed by the MAH in their response, no clinically relevant discrepancies were identified. Nevertheless, data on possible long-term influences on cognitive functions is limited.

According to the MAH, assessment of pubertal status by Tanner stage in the CL3-076 study, for pubic hair development in boys and in girls, genitalia development in boys and breast development in girls, showed that the mean age was consistent with stage according to normal development at baseline and at weeks 12, 52 and 104 for male as well as for female adolescents. The MAH was requested to discuss these results more thoroughly. The MAH has provided an adequate discussion. The CHMP considers that as the variability within puberty development in the target group (12-18 years) is large, this makes it difficult to measure any impact on Tanner stage development in the small population. Nevertheless, although data are limited, they do not suggest an impact on Tanner stage development.

As regards hormonal analyses in the double-blind phase for the adolescent population, emergent abnormal values on treatment (no PCSA limit was defined) were more frequently reported on agomelatine 25 mg compared to placebo for low FSH (28.8% *versus* 22.5% of patients) and for low and high cortisol (15.1% *versus* 10.0% and 20.5% *versus* 15.0%, respectively). For all hormonal parameters investigated, a clear statement was expected from the MAH, whether the changes seen were of clinical significance. The MAH has responded that none of the deviations observed on hormonal parameters were assessed to be of clinical significance. The MAH was also asked to review reported cases of "prolactin increased" during the study and consider whether this is an ADR of agomelatine. Based on additional data presented by MAH, it is agreed that fluctuations in prolactin levels cannot be conclusively associated with the use of agomelatine.

In the 12-week double-blind period, there was a slight weight gain in both the agomelatine 25 mg and placebo groups. In the extension period (week 12 – 104) weight gain on agomelatine was on average 3.5 ± 5.5 kg, which could be expected, due to muscle mass gain, in a peri pubertal population.

Serious events and deaths

No deaths were reported in the pediatric studies CL2-075 and CL3-076.

In the Ado MDE set, serious EAEs (SEAEs) were reported by 20 patients (10.4%) on agomelatine 25 mg which is three times higher than in the adult MDE set (3.5%) and the corresponding adult placebo group (4.0%). Regarding the double-blind phase (W000-W012), the MAH states that no relevant difference was observed between agomelatine 25 mg and placebo as regards frequency of SEAE (2 patients in both groups: 2.7% *versus* 2.4%, respectively). This does not seem to be correct. When looking at relevant tables from the CSR, five adolescents (6.2%) on agomelatine 10 mg reported a total of 5 SEAEs and 2 adolescents (2.7%) on agomelatine 25 mg reported a total of 6 SEAEs *versus* no patients in the placebo group. The MAH was asked to clarify the discrepancy. The MAH has clarified that in the placebo group 2 patients (2.4%) reported SAEs. During the W012-W104 period 26 adolescents (9.6%) had 38 serious TEAEs.

Depression and syncope were the most frequently reported SEAEs on agomelatine 25 mg in the Ado MDE set. They were reported by 4 (2.1%) and 3 (1.6%) patients, respectively. Corresponding frequencies in the adult MDE set were 0.34% and 0.04%. The MAH was asked to provide short narratives for all cases of depression and syncope, including an assessment on whether the event is possibly or plausibly related to treatment with agomelatine. Based on the MAH`s response it is considered that for most of the events of serious worsening of depression, lack of efficacy of agomelatine- and/or various stressors may be the most plausible explanation. Further, a causal relationship between cases of syncope and agomelatine seems unlikely. Suicide attempt, intentional self-injury and platelet count decreased were all reported by 1.04% in the ado MDE set *vs.* 0.53%, 0% and 0% in the adult MDE set. Suicidal events are discussed above. Based on the CHMP assessment a causal relationship between cases of thrombocytopenia and agomelatine is not likely.

Discontinuation due to adverse events

In the adolescent MDE set, 9 patients (4.7%) reported at least one EAE leading to withdrawal on agomelatine 25 mg which is a lower rate than in the adult MDE set (8.2%). The adverse events most frequently leading to discontinuation in the adolescent MDE set, were depression and suicide attempt (2.1% and 1.0%, respectively), which were higher than reported in the adult MDE set (0.7% and 0.5%), respectively. One adolescent on agomelatine 25 mg was withdrawn after having experienced increased transaminases (ALT and AST).

The lack of sufficient long-term safety data for agomelatine 25 mg in adolescents was raised by the CHMP during the assessment. The MAH decided to not further pursue the extension of the indication to include adolescents. Instead, the inclusion of data from Study CL3-076 in various sections of the product information.

2.5.11. Conclusions on clinical safety

Most adverse events, including serious events (all-causality), are reported with higher frequencies in adolescents than in adults. This applies also to TME Hepatic disorders, TME suicidal events and PT (worsening) of depression.

Hepatotoxicity is a main safety concern with agomelatine. For the pooled data set, (the grouping of hepatic adverse events) TME Hepatic Disorders were reported by 6.3% of the adolescents on agomelatine 25 mg which was considerably higher than in the adults (1.7%), which is concerning. Even if the level of liver toxicity in adolescents seems to be in line with what has been observed in the adult population based on double-blind, placebo-controlled data, this observation, in addition to very limited data in adolescents, causes uncertainty related to the risk of hepatotoxicity in adolescents. Hepatotoxicity, which is probably idiosyncratic in nature, is also an important safety concern in adults, and regular monitoring of liver transaminases is mandatory to identify patients with agomelatine-related hepatotoxicity. It is important that the same extensive monitoring regimen as approved for adults is implemented in adolescents. Overall, the risk of hepatotoxicity seems to be manageable when serum transaminases are measured.

2.5.12. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

Initially the MAH proposed an updated RMP version 25.1 with the extension of indication application.

However, following the assessment and the change of scope of the procedure, no update of the RMP is required and it is agreed to maintain the current RMP version (version 25.0).

Notwithstanding the above, at the next regulatory opportunity, the RMP Part II Module III and IV should be updated to reflect that studies in adolescents have been performed.

2.7. Update of the Product information

As a consequence of this variation, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly. In addition, section 6.6 of the SmPC was updated to reflect the Safety Working Party position.

Please refer to the appended SmPC and PL (attachment 1)

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Agomelatine Anpharm 25 mg film coated tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed extension of indication for Valdoxan (agomelatine) was for "*the treatment of moderate to severe major depressive episodes in adolescents aged 12 to 17 years, if depression is unresponsive to psychological therapy alone. Antidepressant medication should be offered to an adolescent with moderate to severe depression only in combination with concurrent psychological therapy*."

The proposed dose for adolescent patients (12 to 17 years of age) is 25 mg once daily at bedtime, without any dose adjustments. This is in accordance with the recommended daily dose for adults, although, in adults a dose increase to 50 mg is possible. Liver function tests are to be performed in adolescents in line with what is recommended for adults.

The prevalence of Major Depressive Disorder (MDD) in Europe is approximately 0.5% to 2.5% in children and increases with puberty, with a rate rising to approximately 8% in adolescents (INSERM, 2002; Calles, 2007; Shorey *et al*, 2021), but sometimes much higher in some countries or under special circumstances such as during the coronavirus disease (Covid 19) pandemic (Balazs *et al*, 2012; Racine *et al*, 2021). Depression in childhood affects as many boys as girls, but twice as many girls during adolescence (Birmaher and Brent, 2007). Globally, depression is the fourth leading cause of illness and disability among adolescents aged 15-19 years, and fifteenth for those aged 10-14 years (WHO 2020). Suicide is the second leading cause of death among adolescents in the European region (WHO 2018) and depression is a leading risk factor for suicidal behaviour (Joint Action on Mental Health and Well-being 2015 by the European Commission).

The primary objective of the treatment with agomelatine would be, in combination with psychosocial counselling, to contribute to a reduction in the symptoms of depression making the patient functioning better in everyday life.

3.1.2. Available therapies and unmet medical need

Treatment guidelines recommend starting with a psychotherapy first-line in the paediatric population, then to use antidepressants as second-line treatment in addition to psychotherapy (NICE, 2019; HAS, 2014). Only fluoxetine is, at present, approved in the EU for treatment of depression in children/adolescents (from 8 years). Thus, the psychopharmaceutical repertoire for management of major depressive disorder in this age group is very limited. Data have shown that the efficacy of such treatments is modest, with less consistent results in children compared to adolescents. Depression in adolescents leads to serious disability and impact negatively on the ability to function and live a rewarding life. It is also a leading risk factor for suicidal behaviour. Thus, further studies on efficacy and safety of antidepressants in the paediatric population are needed. Taking this into account, a novel antidepressant treatment in paediatric Major Depressive Episodes (MDE) would fulfil a medical need.

3.1.3. Main clinical studies

The main support of efficacy is a single Phase III, 12-week, multicentre, randomised, double-blind, parallel groups, and placebo-controlled study comparing two doses (10 mg and 25 mg) of agomelatine in children (from 7 to 11 years) and adolescent patients (from 12 years to 17 years) suffering from moderate to severe

MDE (as diagnosed by the DSM-IV R criteria). Fluoxetine was included for assay sensitivity. Patients were to be unresponsive to psychosocial therapy. The primary endpoint was to demonstrate superiority of at least one dose of agomelatine as compared to placebo on the Children's Depression Rating Scale – Revised (CDRS-R) total score expressed in terms of an adjusted difference (by using an ANCOVA model) from baseline to W012. Remission was defined as a CDRS-R Raw total score ≤ 28 at each visit.

A total of 400 patients were included in the double-blind 12-week period. After a protocol amendment the main proportion of patients (i.e., 320 [80%]) belonged to the adolescent subgroup and was distributed as follows in four treatment groups; agomelatine 10 mg: 81/102; agomelatine 25 mg: 76/95; placebo: 82/103 and fluoxetine 10-20 mg: 81/100. All efficacy analyses were carried out in the Full Analysis Set (FAS) which comprised all patients having taken at least one dose of the investigational medicinal product and having a value at baseline and at least one post-baseline value for the primary efficacy endpoint. Pre-planned subgroup analyses were performed in the adolescent subset.

The double-blind period was succeeded by an optional open-labelled 21-month extension period where all patients received agomelatine. This data set was called the sub-MRS. No specific criteria were set for which patients that could continue into this phase. Patients were distributed in the following 3 groups: a pooled agomelatine group (consisting of those using agomelatine 10 or 25 mg in the double-blind period); agomelatine 10 or 25 mg/agomelatine 10-25 mg group (n=170, whereof 91 had used 10 mg agomelatine); a group consisting of those who received placebo in the double blind phase; placebo/agomelatine 10-25 mg group (n=85) and those who had received fluoxetine; fluoxetine 10-20 mg/agomelatine 10-25 mg group (n=84). The number of adolescents in the three groups were 134, 69 and 68, respectively. A dose of 10 mg agomelatine for 2 weeks was given, followed by a flexible dosing regimen of agomelatine where the dose could be adjusted up to 25 mg or decreased to 10 mg depending on the patient's response.

3.2. Favourable effects

12-week double blind period

- The primary analysis on CDRS-R total score expressed in terms of an adjusted difference from baseline to last post-baseline value (W012) in the FAS, using an ANCOVA model, demonstrated a statistically significant difference in favour of agomelatine 25 mg vs. placebo (E (SE) = 4.22 (1.83); 95% CI [0.63; 7.82]; Step-Down Dunnett adjusted p-value = 0.040).
- In the subgroup analysis of adolescents in the FAS, using an ANCOVA model, a statistically significant between-group difference in favour of agomelatine 25 mg vs. placebo of 5.22 (2.13) (95% CI [1.03; 9.40], Step-Down Dunnett adjusted p-value =0.028) was shown on the CDRS-R total score.

Extension (W012-W104) period

- A gradual decrease in the CDRS-R Raw score was shown during the W012-W104 period in all 3 agomelatine groups in the sub-MRS: considering the change from baseline (W012) to last post-baseline value, the means ± SD were -16.3 ± 12.2 in the agomelatine 10 or 25 mg/ago 10-25 mg group vs. -18.9 ± 16.1 in the placebo/agomelatine 10-25 mg group.
- In the adolescent subset of the sub-MRS, the change from baseline (W012) to last post-baseline value was -15.2 ± 12.1 in the agomelatine 10 or 25 mg/agomelatine 10-25 mg group vs. -18.4 ± 16.1 in the placebo/agomelatine 10-25 mg group.
- The rate of remitters in the sub-MRS data set gradually increased along the extension period, both in the agomelatine 10 or 25 mg/agomelatine 10-25 mg group, from 14.7% at W012 to 87.1% at

W104 (last post-baseline value 75.9%), vs. for the placebo/agomelatine 10-25 mg group: 12.9% at W012 to 77.6% at W104 (last post-baseline value: 70.6%).

- For the adolescent subset of the sub-MRS data set the corresponding results were: agomelatine 10 or 25 mg/agomelatine 10-25 mg group showed increase from 16.4% at W012 to 83.1% at W104 (last post-baseline value 72.4%) vs. for the placebo/agomelatine 10-25 mg group: 10.1% at W012 to 76.9% at W104 (last post-baseline value: 69.6%).

3.3. Uncertainties and limitations about favourable effects

12-week double blind period

- In the FAS, the absolute difference in mean change in raw CDRS-R total score from baseline to last post baseline between the agomelatine 25 mg group (-22.5 ± 15.2) vs. placebo group (-19.7 ±14.4) was 2.8 points, corresponding to ca. 1/5 of the SD.
- In the adolescent subset, the corresponding difference was 4 points (agomelatine 25 mg group (-23.8 ± 15.4) vs. placebo group (-19.8 ± 13.4), corresponding to around ¼ of the SD.
- The 95% Cis [0.63; 7.82] and [1.03; 9.40] of the primary effect estimate in the FAS and in the adolescent subset, respectively, were wide.
- The outlier analysis reveals the presence of few but significant outliers. These outliers, once removed, seem to lead to even smaller effect sizes for the 25 mg agomelatine group compared to the placebo or 10 mg agomelatine group, which also suggests that overall, outliers may have partly driven the effect and that the efficacy results are not robust.
- None of the pre-planned sensitivity analyses could confirm the robustness of the primary endpoint analysis in the FAS.
- The MMRM model confirming the results achieved in the primary endpoint analysis was adjusted after unblinding of the data and performed *post-hoc.*
- For the adolescent subset, all the sensitivity analyses were performed *post-hoc.*
- Assay sensitivity between fluoxetine and placebo was not formally demonstrated in the adolescent subset for the primary endpoint analysis.
- The secondary endpoints CGI-S and CGI-I scores showed nearly no difference between the treatment groups, including between the placebo group and the agomelatine 25 mg group, for the FAS. The same was observed in the adolescent subset of the FAS, although in this subgroup most of these analyses were unplanned.
- Before inclusion patients received only 2-3 sessions of psychosocial therapy in a 3-week run-in phase (intended to clarify if patients were non-responsive to this treatment). Responders to such therapy have therefore most likely been enrolled in the study, however, the actual number is unknown.
- The proportion of patients in the FAS with response to treatment at last post-baseline value was 48.9% in the agomelatine 25 mg group vs. 44.6% in the placebo group.
- The proportion of adolescents with response to treatment (unplanned analysis) at last post-baseline value was 53.3% in the agomelatine 25 mg group vs. 46.9% in the placebo group.
- The proportion of patients in the FAS with remission at last post-baseline value, defined as a CDRS-R raw total score ≤ 28, was numerically higher in the 25 mg agomelatine group (16.0%) compared

to the placebo group (10.9%). An unplanned analysis comprising only adolescents in the FAS showed similar results; 17.3% in the agomelatine 25 mg group vs. 8.6% in the placebo group.

Extension (W012-W104) period

- Open-label design and no control group (i.e., a comparator placebo group).
- No specific criteria for continuing in the extension phase other than finding it beneficial.
- Due to study design, the true rate of remitters or relapses after long-term use with agomelatine is unknown.
- A flexible dosing regimen (i.e., possibility for adjustments by using 10 mg and 25 mg throughout the period), not in line with applied posology for adolescents, are used.

3.4. Unfavourable effects

The MAH's strategy of the safety evaluation was an analysis of pooled safety data from phase II/III studies (i.e., study CL2-075 and the pivotal study CL3-076) in the adolescent population, and a comparison of this adolescent (Ado) MDE set with the corresponding adult MDE set. There is a large difference in treatment duration in the pooled agomelatine data sets (median 17.9 months in the MDE ado set and 3.7 months in the adult set).

In their response to the 1. RSI, the MAH has also compared short-term data from the double-blind placebo-controlled phase of the CL3-076 study in adolescents (agomelatine 25 mg, duration 12 weeks) with pooled double-blind placebo-controlled studies (agomelatine 25-50 mg, duration 6-8 weeks) from adults.

In general: CL3-076 DB phase: In the Ado MDE DB set no relevant differences in frequencies of EAEs were seen between the groups agomelatine 10 mg and agomelatine 25 mg (63.0% and 62.7%, respectively) and placebo (59.8%). However, frequencies of EAEs considered related to treatment by the investigator were higher in the agomelatine 10 mg and 25 mg group (33.3% and 37.3%, respectively) than in the placebo group (29.3%). The frequency of SEAEs was higher in the agomelatine 10 mg group (6.2%) than in the agomelatine 25 mg g (2.7%) and placebo group (2.4%).

The most frequent EAEs reported in the agomelatine 10 mg and/or 25 mg groups in the DB-phase were: thirst, dry mouth, nausea, headache, increased appetite and fatigue.

The pooled data (MDE ado and adult) set: EAEs, including serious EAEs (SEAEs), were reported with higher frequencies in the adolescent MDE set than in the adult MDE set (67.2% and 10.5% vs. 60.4% and 3.5%, respectively).

When comparing the DB PC phase of the CL3-076 study in adolescents with pooled DB PC studies in adults, the percentage of patients having at least one EAE was similar between adolescents and adults (62.7% and 62.2%, respectively).

Hepatotoxicity is a main safety concern and is stated as an important identified risk in the RMP.

As stated in the SmPC, serious cases of liver injury have been reported in adults, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors) and elevations of liver enzymes exceeding 10 times the upper limit of normal, in the post marketing setting. Therefore, liver transaminases should be monitored before treatment initiation and at specified time-points during treatment.

Based on data from the DB phase of the CL3-076 study, the following frequencies of abnormal liver function tests were observed in adolescents on agomelatine 25 mg: AST > ULN: 2.7%, AST > 3 ULN: 1.47% (one patient) and ALT > ULN: 2.7%, ALT > 3 ULN: 0. Corresponding values in adults based on double-blind

placebo-controlled data were: AST > ULN: 5.79%, AST > 3 ULN: 0.37% and ALT > ULN: 7.6%, ALT > 3 ULN: 0.56%.

In the extension phase in CL3-076, changes for the patients who switched from blinded placebo to the active drug (i.e., agomelatine 10-25 mg) were similar to the observed values (in patients on agomelatine) in the blinded phase, and no further elevations in liver tests were observed.

However, for the pooled data set, in the ado MDE set, the grouping of hepatic adverse events in the TME Hepatic Disorders were reported by 12 (6.3%) adolescents on agomelatine 25 mg group which was considerably higher than in the adult MDE set (1.7%). For instance, the hepatic events ALT and AST increased was both reported in 2.1% in adolescents versus 0.57% and 0.32% in adults, respectively.

Based on data from the DB PC phase of the CL3-076 study in adolescents compared with pooled DB PC studies in adults, the frequency of hepatic EAE (i.e. hepatic EAEs based on Targeted Medical Events (TME) Hepatic events) in adolescents was 4.0% in comparison to 1.8% in the adult population. The frequency in adolescents was lower than reported in the adolescent placebo group (7.3%). The number of adolescents is low, and frequency estimates are uncertain.

Suicidality / Suicide-related events was initially an important potential risk in the RMP, but has later been removed. Suicidal events were reported with an almost 3 times higher frequency in the ado MDE set (3.1%) than in the adult MDE set (1.2%) based on grouping of suicidal events (TME Suicidal events).

Two adolescents on agomelatine presented with three emergent suicidal behaviours (both made suicide attempts). In addition, a case of overdose was registered as a suicide attempt.

Interactions with potent CYP 1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin)

This is an important identified risk in the RMP. No information is available from the adolescent dataset. In adults, fluvoxamine increased agomelatine exposure by 60-fold (range 12-412) and concomitant use of strong CYP1A2 inhibitors is therefore contraindicated.

Serious events and deaths No deaths were reported in the pediatric studies CL2-075 and CL3-076. In the pooled data set, ado MDE set, serious AEs (SEAEs) were reported by 20 patients (10.4%) on agomelatine 25 mg which is three times higher than in the adult MDE set (3.5%). The MAH claims that among the SEAEs, only one, hypothyroidism, was considered as related to the study drug.

Depression and *syncope* are the most frequently reported SEAEs on agomelatine 25 mg in adolescents in the pooled data set (ado MDE set). They were reported by 4 (2.1%) and 3 (1.6%) patients, respectively. Corresponding frequencies in the adult MDE set were 0.34% and 0.04%. All events of (worsening of) depression have been reported in the extension phase, but one adolescent had recently started agomelatine after being treated with fluoxetine in the DB PC phase of CL3-076. Lack of efficacy of agomelatine and/or various stressors may be the most plausible explanation for most of these cases.

All three patients experiencing syncope, continued treatment with agomelatine without any recurrence of syncope.

Suicide attempt, intentional self-injury and platelet count decreased were all reported by 2 patients (1.04%) in the ado MDE set *vs.* 0.53%, 0% and 0% in the adult MDE set.

During the DB phase (W000-W012) in CL3-076, 6.2% adolescents in the agomelatine 10 mg group, 2.7% in the agomelatine 25 mg group versus 2.4% in the placebo group reported at least one SEAE. During the W012-W104 extension period 26 adolescents (9.6%) experienced 38 SEAEs.

The pharmacokinetic variability of agomelatine is large and to a great extent unpredictable, implying an unpredictable therapeutic response, including the safety profile.

Long-term effects in adolescents Assessment of pubertal status by Tanner stage in the CL3-076 study, for pubic hair development in boys and in girls, genitalia development in boys and breast development in girls have been performed. "Continuous Performance Task", measuring parameters like selective attention and vigilance, has been performed. In the extension phase in the CL3-076 study, weight gain was on average 3.5 ± 5.5 kg over the W012-W104 period, which a slight gradual increase of mean BMI (0.50 ± 1.60 kg/m^2) which could be expected, due to muscle gain, in a peri-pubertal population.

3.5. Uncertainties and limitations about unfavourable effects

In general, the Summary of Clinical Safety is not of sufficient quality for assessing the safety data. Data are summarised too briefly, and critical discussions are lacking, for instance regarding suicidality, possible long-term effects when treating depression in the paediatric population, as well as differences in frequencies of adverse events between adolescents and adults. The MAH has addressed most of these issues in their response to the 1. RSI.

- The safety database is limited (N=400 of which 320 adolescents in the pivotal study, CL3-076, N=51 of which 27 adolescents in CL2-075).
- There is a large difference in treatment duration between adolescents and adults in the pooled MDE data set.
- **Hepatotoxicity**: The available data for children and adolescents are scarce. The pivotal DB phase of CL3-076 included 400 patients (320 adolescents) of which 102 (81) and 95 (76) patients received agomelatine 10 mg and agomelatine 25 mg, respectively, which is small given the absolute incidence of liver toxicity associated with the drug. Confidence intervals around the point estimates for liver toxicity for adolescents are likely wide, indicating low precision of the estimate.
- In the adult population non-compliance with the transaminases monitoring programme has been a concern.
- **Suicidality / Suicide-related event** Suicidal events were reported with an almost 3 times higher frequency in the ado MDE set (3.1%) than in the adult MDE set (1.2%) based on grouping of suicidal events (TME Suicidal events).
- **Serious events and deaths** Suicidal attempts as a single term (PT) is reported *twice as frequent* in adolescents compared with adults (see also above), and depression as an SEAE *6 times higher* in adolescents than in adults, which is noteworthy and worrisome. However, the numbers are small and hence, there is an inherent uncertainty in the frequencies.
- Long-term experience on growth, pubertal development and cognitive function is limited.
- The agomelatine dose-exposure-response relationship for safety is to a large extent uncharacterised. It is not known whether systemic exposure of agomelatine following oral administration of a 25 mg dose is comparable in adult and adolescent patients. Data are hampered by uncertainty considering that most paediatric PK data derive from saliva (and not plasma). Therefore, it is not known whether the higher frequency of adverse events observed in adolescents compared to adults could be related to increased agomelatine exposure.
- Frequencies of adverse events in the pooled adolescent MDE set may be diluted due to pooling with data from a study with lower doses and very short duration (CL2-075).
- During the extension phase the agomelatine dose could be adjusted at each visit from 10 mg to 25 mg and *vice versa*. Regarding the dose level received most of the time, the MAH states that 56.5%

(n=153) of the adolescents received agomelatine 25 mg most of the time, while 43.5% (n=118) received agomelatine 10 mg. Accordingly, the number of adolescents exposed long-term to agomelatine 25 mg is limited (n=153). It should be noted that this group was not analysed separately, but together with all patients receiving agomelatine in lower (10 mg) or adjusted doses (10 mg, 25 mg) during treatment. It is therefore a risk of underestimating the true frequencies of adverse events for agomelatine 25 mg in the pooled adolescent MDE data set.

- MAH's causality assessment is questioned (for instance only one serious EAE is considered related to treatment).
- Concomitant use of moderate CYP 1A2 inhibitors (e.g., oestrogens, propranolol, enoxacin) may increase the exposure to agomelatine, and could potentially lead to increased risk of adverse events.

3.6. Effects Table

Effects Table for Valdoxan and treatment of moderate to severe MDE in adolescents unresponsive to psychosocial treatment alone (Data cut-off: Double-blind period: 25 February 2020/Extension period: 29 November 2021)

Effect	Short description	Unit	Treatment Agomelatine 25 mg	Control Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Double-blind phase 12 weeks						
FAS N=396[a]; 94 patients in the agomelatine 25 mg arm and 101 in the placebo arm	Absolute difference in the CDRS-R raw total score from baseline to last post baseline value	Difference last post baseline – baseline Mean ± SD	-22.5 ± 15.2	-19.7 ± 14.4	Modest and non-robust effect size Pre-planned sensitivity analyses not in support of the primary analysis Wide 95% Cis, outliers No support by secondary endpoints	Main study CL3-076
	Adjusted difference in the CDRS-R total score from baseline to W012, using a 3-way ANCOVA model	Estimate	E (SE) = 4.22 (1.83); 95% CI [0.63; 7.82]; Step-Down Dunnett adjusted p-value = 0.040			
Adolescent subset of the FAS N=317[b]; 75 patients in the agomelatine arm 25 mg and 81 in the placebo arm	Absolute difference in the CDRS-R raw total score from baseline to last post baseline value	Difference last post baseline – baseline Mean ± SD	-23.8 ± 15.4	-19.8 ± 13.4		
	Adjusted difference in the CDRS-R total score from baseline to W012, using a 3-way ANCOVA model	Estimate	E (SE) = 5.22 (2.13); 95% CI [1.03; 9.40]; Step-Down Dunnett adjusted p-value = 0.028			
Extension phase W012-W104			Agomelatine 10 or 25	Placebo/ agomelat		

Effect	Short description	Unit	Treatment Agomelatine 25 mg	Control Placebo	Uncertainties / Strength of evidence	References
			mg/10-25 mg*	ine 10-25 mg*		
Sub-MRS N=339[a]; 170 patients in the agomelatine 10 or 25 mg/10-25 mg arm and 85 in the placebo/ agomelatine 10-25 mg arm	Decrease in the CDRS-R Raw score in the period W012-W104	Difference last post baseline – baseline Mean ± SD	-16.3 ± 12.2	-18.9 ± 16.1	Open label design No control group Use of flexible dosing regimen Only descriptive statistics No specific criteria for continuing in the extension phase	
Adolescent subset of the sub-MRS N=271[b]; 134 in the 10 or 25 mg/10-25 mg arm and 69 in the placebo/ agomelatine 10-25 mg arm	Decrease in the CDRS-R Raw score in the period W012-W104	Difference last post baseline – baseline Mean ± SD	-15.2 ± 12.1	-18.4 ± 16.1		
N=339[a]; 170 patients in the agomelatine 10 or 25 mg/10-25 mg arm and 85 in the placebo/ agomelatine 10-25 mg arm	Remission CDRS-R raw total score ≤ 28	Rate of patients (%) in remission in the period W012-W104	Decrease from 14.7% at W012 to 87.1 % at W104 (last post-baseline value: 75.9%)	Decrease from 12.9% at W012 to 77.6% at W104 (last post-baseline value: 70.6%)		
Adolescent subset of the sub-MRS N=271[b]; 134 in the 10 or 25 mg/10-25 mg arm and 69 in the placebo/ agomelatine 10-25 mg arm	Remission CDRS-R raw total score ≤ 28	Rate of patients (%) in remission in the period W012-W104	Decrease from 16.4% at W012 to 83.1 % at W104 (last post-baseline value: 72.4%)	Decrease from 10.1% at W012 to 76.9% at W104 (last post-baseline value: 69.6%)		

Abbreviations: FAS=Full Analysis Set (all efficacy analyses were carried out in this data set in the double-blind period), SD=Standard Deviation, sub-MRS= sub-Modified Randomised Set, i.e., all patients of the MRS carrying on in the extension phase (W012-W014)

Notes: [a] for the double-blind period only results for agomelatine 25 mg vs. placebo is shown, likewise for the extension period only results for the agomelatine 10 or 25 mg/10-25 mg vs. placebo/agomelatine 10-25 mg are shown in the table. [b] the same as stated for [a] is valid for the adolescent subsets. Therefore, the total N does not add up. *agomelatine 10 or 25 mg/10-25 mg and placebo/agomelatine 10-25 mg denote the patients having used either agomelatine 10 mg or 25 mg in the double-blind period and those using placebo in the same period, respectively.

Safety Table for Valdoxan and treatment of moderate to severe MDE in adolescents unresponsive to psychosocial treatment alone (Study CL3-076. Data cut-off: Double-blind period: 25 February 2020)

Safety	Short description of adverse event	Treatment Agomelatine 10 mg	Treatment Agomelatine 25 mg	Control Placebo	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Double-blind Phase, 12 weeks		N=81	N=75	N=82		Main study **CL3-076**
N=319; 81 patients in the agomelatine 10 mg arm, 82 patients in the agomelatine 25 mg arm and 103 in the placebo arm (fluoxetine arm excluded)						Adolescent (ado) subset presented in this table.
EAEs		63.0%	62.3%	59.8%		
EAEs tr-related		33.3%	37.3%	29.3%		
Serious EAEs		6.2%	2.7%	0		
	Most frequent EAEs					
Thirst		18.5%	14.7%	11.0%		
Dry mouth		22.2%	13.3%	12.2%		
Nausea		11.1%	13.3%	14.6%		
Headache		16.0%	9.3%	14.6%		
Increased appetite		6.2%	8.0%	0		
Fatigue		4.9%	8.0%	4.9%		
	EAEs of special interest					
AST > 1 ULN			2.7%	0		
AST > 3 ULN			1.4%	0		
ALT > 1 ULN			2.7%	1.3%		
ALT > 3 ULN			0	0		
ALP > 1 ULN			5.4%	0		
ALP > 3 ULN			0	0		
GGT > 1 ULN			1.4%	2.5%		
GGT > 3 ULN			0	1.3%		
Total bilirubin > 1 ULN			5.4%	7.5%		
Total bilirubin > 3 ULN			0	0		
Dizziness postural		2.5%	6.7%	1.2%		
Blood prolactin increased		3.7%	1.3%	1.2%		
Hypersomnia		1.2%	1.3%	2.4%		
Syncope		1.2%	0	0		

The adolescent Double-Blind Placebo-Controlled set (ado MDE DB PC), including data from the 12-weeks double-blind period of the CL3-076 Phase III study, is an analysis set corresponding to 319 patients. In total paediatric Double-Blind Placebo-Controlled set (paed MDE DB PC) corresponds to in total 399 patients, ie. 319 adolescents and 80 children.

Safety Table for Valdoxan in adolescents (pooled data from CL2-075 and CL3-076) compared to pooled adult MDE data

Safety		Adolescent MDE		Adult MDE		
	Short description of adverse event	Ago 25 mg N=192	Placebo N=13	Ago 25 mg N=5662	Placebo N=1393	Uncertainties / Strength of evidence
Unfavourable Effects						
Adolescent MDE set* vs. Adult MDE set**						Uncertainty of actual dose agomelatine
Adolescent MDE set: 192 patients in ago 25 mg arm, 13 in the placebo arm Adult MDE set: 5662 patients in ago 25 mg arm, 1393 in the placebo arm						Frequencies likely underestimated due to pooling of studies*
EAEs		67.2%	46.2%	60.4%	55.7%	
EAEs tr.related		31.8%	7.7%	32.3%	31.2%	
Serious EAE		10.4%	0	3.5%	3.9%	
	Most frequent EAEs					
Headache		16.15%	23.08%	13.53%	14.21%	
Dry mouth		9.38%	0	3.27%	3.52%	
Thirst		8.33%	0	0.12%	0.43%	
Fatigue		7.29%	0	2.76%	2.01%	
Nasopharyngitis		7.29%	0	5.49%	3.30%	
Nausea		6.25%	7.69%	6.32%	6.82%	
	EAEs of special interest					
Depression		3.13%	0	1.17%	3.23%	
Syncope		1.56%	0	0.07%	0.22%	
Dizziness postural		4.69%	0	0.14%	0	
Hypersomnia		3.13%	0	0.16%	0.07%	
Hepatotoxic reactions						
ALT increased		2.08%	0	0.57%	0.29%	
AST increased		2.08%	0	0.32%	0.14%	
GGT increased		2.08%	0	0.41%	0.29%	
Blood bilirubin increased		1.56%	0	0.09%	0.22%	
Hyperbilirubinaemi		0.52%	0	0.02%	0	
Suicidal related events						
Intentional self-injury		1.56%	0	0.04%	0.07%	
Intentional overdose		1.04%	0	0.12%	0	
Suicide attempt		1.04%	0	0.58%	0.72%	
Self-injurious ideation		0.52%	0	0	0	

Safety		Adolescent MDE		Adult MDE		
	Short description of adverse event	Ago 25 mg N=192	Placebo N=13	Ago 25 mg N=5662	Placebo N=1393	Uncertainties / Strength of evidence
Suicidal behaviour		0.52%	0	0.02%	0	
Suicidal ideation		0.52%		0.25%	0.50%	

*The adolescent MDE set includes data from the CL2-075 phase II study and the pivotal CL3-076 phase III study.

As these two studies have very different design, the CHMP considers that pooling of these data is not acceptable. Data were based on the CL3-076 only. Median treatment duration for the adolescent MDE set was 17.9 months for agomelatine 25 mg and 1.8 months for placebo group.

**The adult MDE set consists of pooled safety data from 35 studies in the indication MDE and two in Bipolar disorders. Median treatment duration for the adult MDE set was 3.7 months for agomelatine 25 mg and 1.9 months for placebo group.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The result of the pivotal study, i.e., the adjusted difference in total score of the CDRS-R, from baseline to W012 (using an ANCOVA model), of 4.22 for the total paediatric population and 5.22 for the adolescent subset, was statistically significant different from placebo for the agomelatine 25 mg dose. Thus, formally, the primary objective was fulfilled. Nevertheless, the resulting efficacy estimates are not considered robust due to several statistical and methodological issues. None of the pre-planned sensitivity analyses confirmed the reliability of the estimate, which, given the large placebo effect observed, may not be clinically relevant. An additional uncertainty pertains to the result in the adolescent subset as assay sensitivity was not formally demonstrated. None of the secondary endpoints supported the primary endpoint. The study failed to discriminate between the agomelatine 10 mg dose and placebo.

The magnitude of the effect size for agomelatine 25 mg is difficult to put into perspective based solely on the estimates. In that respect, the absolute difference in mean change in raw CDRS-R total score from baseline to W012 between the agomelatine 25 mg vs. placebo group (i.e., 2.8 points for all the paediatric patients and 4.0 points for the adolescent subset, respectively) gives a clearer picture of the effect size being small. Another signal of modest efficacy is that the mean last post baseline value on the CDRS-R for all treatment groups was rather high, and not far below the cut-off value of $\geq$ 45 requested for inclusion. The low proportion (total population: 16% in the agomelatine 25 mg group and ca. 11% in the placebo group) of patients considered to be in remission at W012 indicates that many still had moderate to severe depression. The observed l difference between agomelatine 25 mg and placebo implies a considerable placebo response.

Psychosocial therapy was given concomitantly in all groups. All patients were to be unresponsive to psychosocial therapy at inclusion. However, considering the short time period (3 weeks) and the few therapy sessions (2-3) available for deciding responsiveness, it is highly likely that several responders have been included in the study. This is also admitted by the MAH. As a consequence, an even higher response in the placebo group could be expected. The number of included potential responders to psychosocial therapy is unknown. Another critical aspect is that inclusion of such responders violates the prerequisite of the applied indication, i.e., that only patients who no longer respond to psychosocial therapy should be

given agomelatine. However, it is acknowledged that it could be difficult to identify such subjects. Overall, very few patients withdrew from the study due to lack of efficacy, including in the placebo group (2/103 patients).

Most of the included patients were in their first MDE of moderate severity and had relatively few co-morbidities. These factors may also play a role in augmenting the placebo effect. The large placebo response translates into only a modest effect size which, in addition, lacks robustness. The clinical relevance of the effect estimate for agomelatine 25 mg was seriously questioned. The reported effect size in previous adult short-term studies with agomelatine was also small and considered to be of marginal clinical relevance. In order to contextualise the short-term result achieved in adolescents versus in adults, a retrospective meta-analysis was performed. As this analysis is characterised by a selected sample of only positive short-term adult studies of even shorter duration, partly different doses (50 mg also administered in adults), and use of another rating scale (HAM-D) than in Study CL3-076, it is not considered appropriate for concluding that the magnitude of the effect size for agomelatine is similar between adolescents and adults. Likewise, the comparison of results from two older studies conducted in paediatric populations with fluoxetine also suffers from inherent uncertainties associated with across studies evaluations. Data from several meta-analyses (Zhou et al, 2020, Cipriani et al, 2016, Feeney et al, 2022 and Locher et al, 2017) reporting the effect size of fluoxetine, seem to support the notion that the effect size of agomelatine is modest. However, it is very difficult to make comparisons of effect sizes achieved with different substances, studied under various circumstances, and draw any firm conclusions.

Based on the ado and adult MDE sets most adverse events, including serious events (all-causality), are reported with higher frequencies in adolescents than in adults. This applies also to TME Hepatic disorders, TME suicidal events and PT (worsening) of depression. It is not known whether systemic exposure of agomelatine following oral administration of a 25 mg dose is comparable in adult and adolescent patients. Available data could suggest that the systemic exposure of agomelatine in children and adolescents is in the higher end of the adult exposure range following a 25 mg dose of agomelatine but are hampered by uncertainty considering that most paediatric PK data derive from saliva (and not plasma). Therefore, it is not known whether the higher frequency of adverse events observed in adolescents compared to adults could be related to increased agomelatine exposure.

Hepatotoxicity is a main safety concern with agomelatine. For the pooled MDE data set, ALT and AST increased were both reported by 4 adolescents (2.08%) which is higher than in adults (0.57% and 0.32% for ALT and AST increased, respectively). Even if the level of liver toxicity in adolescents seems to be in line with what has been observed in the adult population based on double-blind, placebo-controlled data, this observation, in addition to limited data in adolescents, causes uncertainty related to the risk of hepatotoxicity in adolescents. Hepatotoxicity, which is probably idiosyncratic in nature, is also an important safety concern in adults, and an extensive liver transaminases monitoring programme needs to be followed. Non-compliance with this monitoring programme has been a concern in the adult population. In addition, as the pharmacokinetic variability of agomelatine is large, the risk of adverse events may also be unpredictable.

The observed higher frequencies of all-causality suicidal-related events in adolescents *vs* adults is concerning. In general, causality is difficult to evaluate for these events. Suicidal thoughts or behaviour are listed for agomelatine, but these events can also refer to repetition of previous behaviour, or they can be due to lack of response to agomelatine. Various stressors may also have triggered or contributed to some events. It is considered that monitoring for suicidal events is well-known and adequately handled by psychiatrists treating adolescents with depression. Treatment should therefore be initiated and monitored under specialist supervision in line with fluoxetine MDD treatment in adolescents.

All serious events of depression have been reported in the extension phase, but one adolescent had recently started agomelatine after being treated with fluoxetine in the DB phase (W0-W12) of CL3-076. For some of these events, lack of efficacy may be the most plausible explanation.

Due to the limited safety database, only ADRs with frequency common (> 1/100) can be detected, hence, most uncommon and rare events will not be captured.

Taking into account the questionable short-term efficacy of agomelatine, it is not possible to make valid assumptions regarding the maintenance effect in adolescents. Notwithstanding this, due to the non-optimal design of the extension phase (open-labelled, no control group and allowance of a flexible dosing regimen in contrast to the recommended fixed dose posology of 25 mg agomelatine), firm conclusions of the long-term efficacy and safety of agomelatine cannot be drawn. It has been reported that a high proportion of youth with MDE recover during the first year of illness, implying that patients might feel better primarily due to passage of time. The comparison with long-term efficacy data gathered in an adolescent population for fluoxetine, showed seemingly quite similar improvements in CDRS total scores for agomelatine. It is, however, difficult to directly compare efficacy estimates across studies.

It is acknowledged that agomelatine has demonstrated long-term efficacy in adults. The MAH indicates that similar relapse rates as seen in adults can be expected in adolescents from 12 years. This notion is mainly based on a retrospectively performed *post-hoc* analysis in a very small group of young adult patients (18-30 years), from a former relapse-prevention study in adults, showing that crude relapse rates between the young adult patients and the total population in the study (all ages) were in line. However, to make general assumptions based on these data is not considered valid. The MAH indicated that in addition to the results from the extension phase of the pivotal study, the long-term efficacy of agomelatine in adolescents could be established by extrapolation to corresponding results in adults. However, in order for that to be an acceptable approach, the short-term efficacy has to be found compelling, with respect to both the size of the effect and the robustness of the estimate. Additionally, a reasonable degree of certainty has to be assumed in that critical elements such as disease, progression of disease and prognosis are similar for adolescents and adults. Of special importance in that respect, is the fact that adolescents are not fully developed biologically, cognitively, and socially. The MAH argued that major depression in paediatric population and – especially in adolescents over 12 years old – and major depression in adult population are parts of the same disorder. This is agreed to a certain extent; however, the literature is not fully consistent in this view.

In addition, the proposed dose should lead to comparable exposures and a similar PK/response relationship between adults and paediatric population, and acceptable safety data in the target population. However, with regards to PK, it is not known whether systemic exposure following doses of 10 or 25 mg is overall comparable in children/adolescents and adults.

Long-term effects on growth, pubertal development and cognitive performance have been studied, but data are limited.

Depression in adolescents leads to serious disability and impact negatively on the ability to function and live a rewarding life. It is also a leading risk factor for suicidal behaviour. Considering that only fluoxetine is approved in the EU for treatment of moderate to severe MDE in children and adolescents ≥ 8 years, there is a need for new treatment alternatives which can improve the symptoms and increase the clinician's therapeutic options. However, the short-term efficacy results of agomelatine in adolescents is not convincingly demonstrated, and rather of doubtful clinical relevance. Moreover, the long-term efficacy is uncertain, and the true relapse rate is not possible to assess. When considering agomelatine's modest short-term efficacy and the fact that all participants would receive psychotherapy, it is not agreed with the MAH's view that a well-designed controlled long-term study, for instance a relapse prevention study, in adolescents would be unethical. In conclusion, this type of long-term study is deemed necessary. Long-term safety is also hampered as the reported safety signals may be diluted due to pooling with data from

a study with lower doses and shorter duration (CL2-075). New estimates in adolescents without pooling have not been presented. Flexible dosing (10-25 mg) in the extension phase of study CL3-076 also contributes to diluting frequency estimates of adverse events.

3.7.2. Balance of benefits and risks

A non-robust result of modest effect size and questionable clinical relevance was observed for the short-term efficacy of agomelatine 25 mg compared to placebo: both in the paediatric population as a whole and the adolescent subset. The safety profile for agomelatine in adolescents is characterised by higher frequencies of most adverse events, including serious EAEs, hepatotoxicity and suicide-related events compared to adults. Monitoring for suicidal events is well-known and considered adequately handled by psychiatrists treating adolescents with depression. Treatment should therefore be initiated and monitored under specialist supervision. Regarding the main safety risk, hepatotoxicity, regular monitoring of liver transaminases is mandatory to identify patients with agomelatine-related hepatotoxicity. It is important that the same extensive monitoring regimen as approved for adults is implemented in adolescents. Overall, the risk of hepatotoxicity seems to be manageable when serum transaminases are measured.

Furthermore, it is not possible to make a valid assessment of the long-term efficacy and safety. Due to the non-optimal study design, firm conclusions in adolescents cannot be made based upon the data from the extension phase. Extrapolating the long-term efficacy and safety data from adults to adolescents is not considered appropriate. In addition, it is not known whether the systemic exposure and PK/response relationship is comparable in adults and adolescents. A well-designed controlled long-term study in adolescents is deemed necessary.

Consequently, the benefit-risk balance of agomelatine 25 mg is still viewed as negative by the CHMP for the extension of the indication in adolescents (12 to 17 years).

Initially, the MAH submitted the variation application under category C.I.6 of the variation classification Guideline to extend the indication to the adolescent (12 to 17 years) population. Based on the assessment of the data contained in the application, the CHMP was of the view that the data submitted supported changes to the Product Information with inclusion of the paediatric data. These changes fall under category C.1.4 of the variation classification Guideline. In agreement with the assessment, with their response the MAH informed the CHMP that they withdrew the claim for extension of the indication in adolescents, and instead agreed to reflect the data from Study CL3-20098-076 in various sections of the SmPC and the corresponding section of the package leaflet.

3.8. Conclusions

Based on the assessment of the data contained in this application, the CHMP agrees that the overall benefit/risk of Valdoxan (agomelatine) is negative for the initially proposed extension of the indication to include adolescents (12 to 17 years).

Following the MAH change of scope of the procedure, the CHMP agreed to update sections 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC to reflect the results of the phase 2 (CL2-20098-075) and phase 3 (CL3-20098-076) paediatric clinical studies. The PL has been updated accordingly.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC to reflect the results of the phase 2 (CL2-20098-075) and phase 3 (CL3-20098-076) paediatric clinical studies. The PL has been updated accordingly. In addition, section 6.6 of the SmPC was updated to reflect the Safety Working Party position.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0115/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Valdoxan-H-C-000915-II-0051'

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 30 May 2024