Amsterdam, 21 July 2022
EMA/CHMP/627886/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Valdoxan

agomelatine

Procedure no: EMEA/H/C/000915/P46/032

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 25th April 2022, the MAH submitted a completed paediatric study for Valdoxan (agomelatine), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s).

A short critical expert overview has also been provided.

About the product

Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist.

Valdoxan was first authorised via the centralised procedure in 2009.

Approved indication

Valdoxan is indicated for the treatment of major depressive episodes in adults.

Excerpt of the posology (for a view of the complete posology, please refer to the approved SmPC of Valdoxan):

Adults: The recommended dose is 25 mg once daily taken orally at bedtime. After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e., two 25 mg tablets, taken together at bedtime.

Decision of dose increase has to be balanced with a higher risk of transaminases elevation. Any dose increase to 50 mg should be made on an individual patient benefit/risk basis and with strict respect of Liver Function Test monitoring. Liver function tests should be performed in all patients before starting treatment. Treatment should not be initiated if transaminases exceed 3 X upper limit of normal (see sections 4.3 and 4.4). During treatment transaminases should be monitored periodically after around three weeks, six weeks (end of acute phase), twelve weeks and twenty-four weeks (end of maintenance phase) and thereafter when clinically indicated (see also section 4.4). Treatment should be discontinued if transaminases exceed 3 X upper limit of normal (see sections 4.3 and 4.4). When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment.

Treatment duration: Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.

Elderly: No effect is documented in patients ≥75 years. Therefore, agomelatine should not be used by patients in this age group.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study CL3-20098-076, aiming to evaluate the efficacy and safety of agomelatine in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) with major depressive disorder, is part of a clinical development program. The extension application consisting of the full relevant data package (i.e., containing several studies) is expected to be submitted by the end of September 2022. A line listing of all the concerned studies is annexed.

Of note, previously study CL2-075, aiming at evaluating the pharmacokinetics 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, has been submitted and evaluated (procedure EMEA/H/915-916/P46/027). In the Assessment Report from that procedure, it was considered that the report on the study and the population PK model was sufficient at that stage. The PK database and the modelling approach had some limitations, however the model appeared reasonably robust to describe and predict the PK of agomelatine at the higher dosages > 10 mg.

In the present procedure no SmPC changes are suggested.

2.2. Information on the pharmaceutical formulation used in the study

Oral film-coated tablets of 10 and 25 mg strengths were used for agomelatine, as appropriate to the study population and already tested in the CL2-075 study (procedure EMEA/H/915-916/P46/027).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study CL3-20098-076

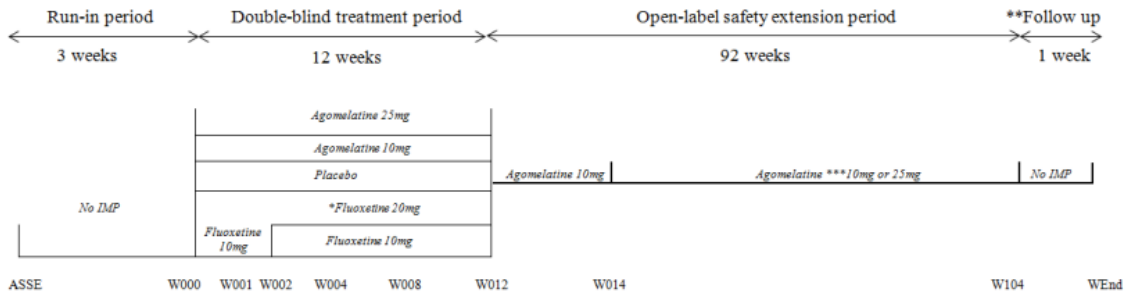
2.3.2. Clinical study

CL3-20098-076

A double blind, 12-week, randomised, multicentre, two dose levels, active and placebo-controlled Phase III trial to evaluate efficacy and safety of agomelatine to treat children from 7 to less than 18 years of age with major depressive disorder. An optional open-label 21-month extension period was also included.

Description

The figure below shows the study plan:



*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.

Methods

Study participants

Excerpt of criteria for inclusion (not exhaustive):

- Male or female, aged from 7 to less than 12 or from 12 to less than 18 years of age.
- Primary diagnosis of MDD, single or recurrent episode, of moderate to severe intensity, as per Diagnostic Criteria for Major Depressive Episode, 4th edition, Text Revision (DSM-IV-TR).
- CDRS-R Raw score ≥ 45.
- Clinical Global Impression - Severity (CGI-S) rating score ≥ 4.
- Patients considered as non-responder to Manualized Psychosocial Counselling during the run-in period.
- Absence of hepatic impairment (e.g., patients with transaminases values [AST and/or ALT] ≥ 2 times the upper limit of normal range [ULN] were excluded).
- Absence of high suicidal risk.

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

Treatments

Test drug:

Agomelatine: 10 mg and 25 mg, one film-coated tablet taken once a day, orally, in the evening at bedtime.
Comparator (reference product and placebo), only during the double-blind period:

Fluoxetine: 10 mg (2.5 mL) with a possible increase to 20 mg (5 mL) at W002, oral solution taken once a day, in the morning at wake-up.

Placebo: one film-coated tablet taken once a day, orally, in the evening at bedtime or oral solution taken once a day, in the morning at wake-up.

Open-label follow-up 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). Finally, there was a follow-up period of 1 week on average (5 to 7 days) without any investigational medicinal product (IMP) after the last IMP intake (after W012, W104 or in case of premature withdrawal from the study at any moment).

Objective(s)

The purpose of the study was to assess the short-term efficacy and the short-term safety of two doses of agomelatine in children and adolescent patients with Moderate to Severe Major Depressive Disorder (MDD).

The primary objective was to demonstrate the antidepressant short-term efficacy of at least one of the two doses of agomelatine compared to placebo after 12 weeks of treatment in children (from 7 to less than 12 years of age) and adolescents (from 12 to less than 18 years of age) suffering from moderate to severe Major Depressive Disorder using Children's Depression Rating Scale – Revised (CDRS-R).

The secondary objectives were:

- to assess the short-term and long-term safety of agomelatine (10 mg, 25 mg).

- to evaluate the long-term efficacy of agomelatine (10 mg, 25 mg). The secondary efficacy endpoints included results from various scores such as Clinical Global Impression-Severity and -Improvement (CGI-S and CGI-I, respectively), Children's Global Assessment Scale (CGAS) total score and Adolescent Depression Rating Scale (ADRS) total score (only in adolescents of the FAS).

- to explore efficacy and safety in children and adolescents separately.

Sample size

After amendment of the protocol, it was planned that overall, at least 390 patients (instead of 484) with at least 312 adolescents (divided in each treatment group) allowed 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.

Randomisation and blinding (masking)

The treatment (agomelatine 10 mg, agomelatine 25 mg, placebo, fluoxetine) was assigned at inclusion (W000) by balanced (non-adaptative) randomisation, with stratification on the country and children/adolescents age set. It was done using an Interactive Response System (IRS).

The 12-week period of the study was conducted in double-blind conditions (i.e., in the agomelatine groups 5 ml oral solution of placebo was given in the morning and 1 tablet of agomelatine in the evening; in the fluoxetine group, 5 ml oral solution of fluoxetine was given in the morning and 1 placebo tablet in the evening while in the placebo group 5 ml placebo oral solution and 1 placebo tablet were given in the morning and evening, respectively).

Statistical Methods

All efficacy analyses were carried out in the Full Analysis Set (FAS). The Last Observation Carried Forward (LOCF) approach was used to handle missing data. For the primary analysis a three-way analysis of covariance (ANCOVA) model was used. The step-down Dunnett procedure was used to control the familywise error rate, since 2 doses of agomelatine were compared to placebo. The estimate of the difference between adjusted treatment group means, associated standard error, two-sided 95% confidence interval and Dunnett-adjusted p-value were provided.
Sensitivity analyses, assessing the robustness of the primary analysis, were performed in addition to subgroup analyses in adolescents (12-17 years). Due to the small sample size in children, no statistical comparison test was performed in this subgroup, only descriptive statistics were provided.

Results

Participant flow and number analysed

Four hundred (400) patients were included; among them, 320 (80.0%) were adolescents and 80 (20.0%) were children. The patients were randomly assigned to one of the 4 groups (Modified Randomised Set; MRS): 102 patients (whereof 81 adolescents) in the agomelatine 10 mg group, 95 (whereof 76 adolescents) in the agomelatine 25 mg group, 103 (whereof 82 adolescents) in the placebo group and 100 (whereof 81 adolescents) in the fluoxetine group.

The FAS consisted of 102 patients in the agomelatine 10 mg group, 94 in the agomelatine 25 mg group, 101 in the placebo group and 99 in the fluoxetine group.

Recruitment

Forty-six (46) centres in 9 countries included 400 patients. The study was initiated on February 23rd, 2016 and completed on October 27th 2021.

Main baseline data (not exhaustive)

Age and gender:

The patients of the MRS were 7 to 17 years old with a mean age of 13.7 (SD: ± 2.7) years. Almost 2 thirds of patients in the study were female (62.5%).

Condition:

Overall, according to the DSM-IV-TR criteria, 286 patients (71.5%) were in their first episode of major depressive disorder (MDD) with a higher rate in the agomelatine 10 and 25 mg groups (78.4% and 74.7%, respectively) than in the placebo (64.1%) and fluoxetine (69.0%) groups.

As required in the selection criteria, all patients had CDRS-R raw total score $\geq$ 45 with a mean of 65.5 $\pm$ 8.4. CGI-S score was $\geq$ 4 with a mean of 4.9 $\pm$ 0.6. The mean CGAS score was 46.5 ± 8.2. The specific adolescents scale, ADRS, showed a mean score at baseline of 33.1 ± 6.0.

According to Columbia-suicide severity rating scale for children, 23.0% of the patients had suicidal ideation in their lifetime (highest in the agomelatine 10 mg group with 25.5%). Overall, 3.5% had suicidal behaviour in their lifetime with a higher rate in the agomelatine 25 mg (6.3%) than in the placebo (1.9%) groups.

The major depressive episode (MDE) was diagnosed (according to DSM-IV-TR criteria) as moderate in most of the patients (61.8%); and as severe without psychotic features in 153 patients (38.3%) with a lower rate in the agomelatine 10 mg group (27.5%) compared to the other 3 groups (between 41.0% and 43.7% according to treatment group).

The mean duration of current episode was 143.4 ± 153.2 days with a median of 96.0 days (range from 29 to 1463 days). This mean duration was higher in the agomelatine 10 mg group (181.2 ± 210.0 days) compared to the other 3 groups (125.2 ± 109.2 to 137.0 ± 130.5 days), mainly due to a maximum equal to 1463 days (~4 years). A total of 114 patients (28.5%) already had a history of previous MDE (recurrent episode), with a lower rate in agomelatine 10 mg and 25 mg (21.6% and 25.3%, respectively) groups than in the placebo (35.9%) and fluoxetine (31.0%) groups. In these patients, the number of episodes in their lifetime before the current episode ranged from 1 to 5 with a mean ± SD of 1.4 ± 0.7 episodes. The duration between the previous episode and the current episode start ranged from 24 to 1817 days (~5 years) (mean ± SD = 428.9 ± 395.4 days). The duration of last episode was between 1 and 852 days (mean ± SD = 150.9 ± 157.2 days).

Efficacy results

The main results of the *primary efficacy endpoint* (change from baseline to last post-baseline value in the CDRS-R raw total score - FAS) are summarised in the table below:

		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 of the change 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 of the change 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)

Age subgroup analysis: change from baseline to W012, in **adolescents** of the FAS is shown in the table below (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)

As can be seen from the table above, the results were statistically significant only for agomelatine 25 mg vs. placebo. Differences between placebo and agomelatine 10 mg and between placebo and fluoxetine were not statistically significant.

In the **children** subgroup; due to the too low number of patients, no statistical inference was performed.

Short overview of some results from the secondary efficacy endpoints:

CGI-S: The difference of the means of CGI-S score of the last post-baseline value between placebo (3.8 ± 1.2) and each agomelatine dose regimen (3.5 ± 1.1 for both agomelatine doses) was only statistically significant in favour of agomelatine 10 mg with the Mann-Whitney test (p = 0.035). In the adolescents of the FAS, no statistically significant difference between treatment groups was observed with any of the statistical tests (unplanned analysis).

CGI-I: Regarding the mean CGI-I score, no statistically significant difference of the last post-baseline value, between placebo (2.7 ± 1.1) and each agomelatine dose (2.6 ± 1.1 in the agomelatine 10 mg group and 2.5 ± 1.0 in the agomelatine 25 mg group) nor between placebo and fluoxetine (2.6 ± 1.0), was observed with any of the statistical tests. Similar results were observed in the adolescents of the FAS.

The proportion of patients with response to treatment (defined as CGI-I score = 1 or 2 as last post-baseline value) was 48.0% in the agomelatine 10 mg group and 48.9% in the agomelatine 25 mg group versus 44.6% in the placebo group and 47.5% in the fluoxetine group without statistically significant difference.

Children's Global Assessment Scale (CGAS): In the FAS, the mean CGAS total score gradually increased with each visit between baseline and W012 to achieve a change from baseline to last post-baseline value of 13.2 ± 11.3 in the agomelatine 10 mg group, 14.4 ± 13.0 in the agomelatine 25 mg group, 12.1 ± 14.0 in the placebo group and 13.9 ± 12.5 in the fluoxetine group.

Adolescent Depression Rating Scale (ADRS): The means of ADRS total score of the last post-baseline value were 18.8 ± 10.1 in the agomelatine 10 mg group, 18.1 ± 10.6 in the agomelatine 25 mg group and 22.2 ± 10.7 in the placebo group. The difference of means between placebo and each agomelatine dose regimen was statistically significant in favour of agomelatine 10 mg with Student t-test (E (SE) = 3.40 (1.65); 95% CI [0.14; 6.67], p = 0.041) but not with Mann-Whitney test (p = 0.064) and in favour of agomelatine 25 mg with both statistical tests (E (SE) = 4.07 (1.72), 95% CI [0.68; 7.46], p = 0.019 and 0.032, respectively). The difference of means between placebo and fluoxetine were not statistically significant.

Some efficacy results – open extension period:

Out of the 400 patients who were included in the study and randomly assigned to one of the 4 groups, 339 patients (analysis-set called Sub-MRS), including 271 adolescents (79.9% of the patients), entered the optional open-label extension period, during which all received agomelatine at flexible dose (10 mg during the first 2 weeks and then 10 or 25 mg). Overall, 187 patients (55.2%) completed the W012-W104 extension period, with a similar frequency in each group. Of the adolescents, 53.5% completed the W012-W104 period. The treatment duration over the extension period ranged between 0.1 and 22.1 months with a mean of 15.5 ± 7.5 months.

The table below summarises the values at baseline (W012), W024, W040, W052, W104 and last post-baseline visit as well as the changes from baseline (W012) to each of these visits:

CDRS-R raw total score - Value at baseline (W012), W024, W040, W052, W104 and last post-baseline visit and changes from baseline (W012) - 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
	Mean ± SD	42.1 ± 12.4	46.2 ± 15.1	42.7 ± 11.7	43.3 ± 13.0
	Median	43.0	47.0	43.0	44.0
	Min ; Max	17 ; 87	17 ; 89	19 ; 66	17 ; 89
W024	n	160	81	78	319
	Mean ± SD	35.1 ± 10.7	36.7 ± 12.1	35.9 ± 11.4	35.7 ± 11.2
	Median	33.5	37.0	35.0	35.0
	Min ; Max	17 ; 57	17 ; 73	17 ; 66	17 ; 73
W024- Baseline [W012-W104 period]	Mean ± SD	-6.8 ± 7.4	-10.1 ± 11.0	-7.5 ± 10.3	-7.8 ± 9.2
	Median	-6.0	-9.0	-8.0	-8.0
	Min ; Max	-39 ; 29	-57 ; 15	-34 ; 30	-57 ; 30
W040	n	137	74	68	279
	Mean ± SD	32.7 ± 10.4	33.1 ± 11.5	32.9 ± 10.5	32.9 ± 10.7
	Median	33.0	32.5	31.5	32.0
	Min ; Max	17 ; 56	17 ; 66	17 ; 57	17 ; 66
W040- Baseline [W012-W104 period]	Mean ± SD	-10.4 ± 8.9	-14.1 ± 13.2	-11.5 ± 9.9	-11.7 ± 10.5
	Median	-11.0	-14.0	-11.5	-12.0
	Min ; Max	-56 ; 26	-65 ; 17	-36 ; 8	-65 ; 26
W052	n	125	63	63	251
	Mean ± SD	30.8 ± 9.6	30.6 ± 12.3	30.8 ± 10.1	30.8 ± 10.4
	Median	30.0	28.0	29.0	30.0
	Min ; Max	17 ; 56	17 ; 79	17 ; 57	17 ; 79
W052- Baseline [W012-W104 period]	Mean ± SD	-12.4 ± 9.8	-16.7 ± 12.8	-14.4 ± 10.2	-14.0 ± 10.9
	Median	-12.0	-16.0	-13.0	-13.0
	Min ; Max	-62 ; 24	-64 ; 19	-42 ; 6	-64 ; 24
W104	n	93	49	46	188
	Mean ± SD	23.0 ± 7.5	24.5 ± 9.4	24.1 ± 9.8	23.7 ± 8.6
	Median	21.0	21.0	20.0	21.0
	Min ; Max	17 ; 49	17 ; 52	17 ; 53	17 ; 53
W104- Baseline [W012-W104 period]	Mean ± SD	-21.0 ± 10.3	-23.6 ± 14.0	-22.2 ± 12.4	-22.0 ± 11.8
	Median	-21.0	-24.0	-23.0	-23.0
	Min ; Max	-46 ; 1	-48 ; 1	-43 ; -2	-48 ; 1
Last post-baseline value	n	170	85	83	338
	Mean ± SD	25.8 ± 10.5	27.3 ± 12.1	26.6 ± 12.2	26.4 ± 11.3
	Median	22.0	22.0	22.0	22.0
	Min ; Max	17 ; 78	17 ; 65	17 ; 66	17 ; 78
Last post-baseline value - Baseline [W012-W104 period]	Mean ± SD	-16.3 ± 12.2	-18.9 ± 16.1	-16.1 ± 15.5	-16.9 ± 14.1
	Median	-15.5	-19.0	-15.0	-16.0
	Min ; Max	-58 ; 29	-57 ; 17	-43 ; 33	-58 ; 33

Baseline: Value at W012 if analysable value

Considering only the **patients receiving agomelatine all along the study**, the mean CDRS-R raw total score decreased along the W000-W104 period. The mean changes from baseline were -29.5 ± 14.0 at W024, -41.6 ± 12.6 at W104 and -38.8 ± 13.2 when considering the last post-baseline value.

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

Regarding **remission**, the table below summarises the rates of patients in remission at baseline (W012), W024, W040, W052, W104 and last post-baseline visit:

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

Safety results

The most frequently reported treatment emergent adverse events in the Safety Set (in at least 2% of the patients in any of the compared groups) are presented in the table below:

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	**206**	**62**	**60.8**	**201**	**60**	**63.8**	**196**	**63**	**61.2**	**172**	**57**	**57.0**
Dry mouth	21	21	20.6	14	13	13.8	12	11	10.7	13	13	13.0
Thirst	16	16	15.7	15	13	13.8	10	10	9.7	15	15	15.0
Nausea	11	10	9.8	14	12	12.8	17	14	13.6	9	9	9.0
Headache	21	16	15.7	15	11	11.7	14	14	13.6	11	11	11.0
Abdominal pain	9	8	7.8	8	7	7.4	10	7	6.8	4	4	4.0
Increased appetite	7	7	6.9	6	6	6.4	-	-	-	3	3	3.0
Fatigue	5	5	4.9	6	6	6.4	9	7	6.8	2	2	2.0
Weight increased	6	6	5.9	5	5	5.3	-	-	-	2	2	2.0
Decreased appetite	3	3	2.9	5	5	5.3	7	7	6.8	5	5	5.0
Nasopharyngitis	3	3	2.9	5	5	5.3	3	3	2.9	1	1	1.0
Dizziness postural	2	2	2.0	5	5	5.3	1	1	1.0	2	2	2.0
Diarrhoea	6	6	5.9	5	4	4.3	7	6	5.8	9	8	8.0
Acne	4	3	2.9	4	4	4.3	2	2	1.9	2	2	2.0
Dizziness	5	4	3.9	3	3	3.2	4	4	3.9	3	3	3.0
Muscular weakness	2	2	2.0	3	3	3.2	6	6	5.8	1	1	1.0
Tachycardia	1	1	1.0	3	3	3.2	3	2	1.9	-	-	-
Somnolence	1	1	1.0	3	3	3.2	1	1	1.0	1	1	1.0
Blood bilirubin increased	3	3	2.9	2	2	2.1	1	1	1.0	-	-	-
Tremor	2	2	2.0	2	2	2.1	1	1	1.0	1	1	1.0
Blood thyroid stimulating hormone increased	1	1	1.0	2	2	2.1	2	2	1.9	2	2	2.0
Insomnia	1	1	1.0	2	2	2.1	1	1	1.0	-	-	-
Rhinorrhoea	1	1	1.0	2	2	2.1	1	1	1.0	-	-	-
Enterocolitis	1	1	1.0	2	2	2.1	-	-	-	-	-	-
Sinusitis	-	-	-	2	2	2.1	1	1	1.0	-	-	-
Dermatitis allergic	-	-	-	2	2	2.1	-	-	-	1	1	1.0
Blood prolactin increased	4	4	3.9	1	1	1.1	1	1	1.0	-	-	-
Vomiting	2	2	2.0	1	1	1.1	1	1	1.0	2	2	2.0
Rhinitis	2	2	2.0	1	1	1.1	-	-	-	-	-	-
Gastrointestinal viral infection	1	1	1.0	1	1	1.1	4	4	3.9	-	-	-
Respiratory tract infection viral	2	1	1.0	1	1	1.1	3	3	2.9	2	2	2.0
Dysmenorrhoea	-	-	-	1	1	1.1	6	4	3.9	2	1	1.0
Anxiety	-	-	-	1	1	1.1	2	2	1.9	3	3	3.0
Aggression	-	-	-	1	1	1.1	1	1	1.0	5	5	5.0
Aspartate aminotransferase increased	-	-	-	1	1	1.1	-	-	-	3	3	3.0
Impulsive behaviour	-	-	-	1	1	1.1	-	-	-	2	2	2.0
Oestradiol increased	-	-	-	1	1	1.1	-	-	-	2	2	2.0
Weight decreased	2	2	2.0	-	-	-	5	5	4.9	2	2	2.0
Blood bilirubin unconjugated increased	2	2	2.0	-	-	-	2	2	1.9	-	-	-
Contusion	2	2	2.0	-	-	-	2	2	1.9	-	-	-
Dyspepsia	2	2	2.0	-	-	-	-	-	-	2	1	1.0
Gastroenteritis	2	2	2.0	-	-	-	-	-	-	1	1	1.0
Hyperprolactinaemia	2	2	2.0	-	-	-	-	-	-	1	1	1.0
Conjunctivitis	2	2	2.0	-	-	-	-	-	-	-	-	-
Rash erythematous	2	2	2.0	-	-	-	-	-	-	-	-	-
Bilirubin conjugated increased	1	1	1.0	-	-	-	3	3	2.9	-	-	-
Suicidal ideation	1	1	1.0				2	2	1.9	2	2	2.0
Gastrointestinal infection	1	1	1.0	-	-	-	1	1	1.0	2	2	2.0
Syncope	1	1	1.0	-	-	-	-	-	-	2	2	2.0
Bronchitis	-	-	-	-	-	-	1	1	1.0	2	2	2.0
Urticaria	-	-	-	-	-	-	1	1	1.0	2	2	2.0
Accidental overdose	-	-	-	-	-	-	-	-	-	2	2	2.0
Pharyngitis bacterial	-	-	-	-	-	-	-	-	-	2	2	2.0
Tension headache	-	-	-	-	-	-	-	-	-	2	2	2.0

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.

Emergent serious adverse events during the treatment period (analysis by system organ class and preferred term – Safety Set) are shown in the table below:

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.

Regarding hepatic safety, 4 patients (one child on agomelatine 10 mg, one adolescent on agomelatine 25 mg and 2 adolescents on fluoxetine) reported high emergent PCSA values (> 3 ULN) of ALAT and/or ASAT.

Regarding suicidality, as evaluated by the Columbia Suicide Severity Rating Scale (CSSRS), no signal was observed, according to the MAH. Few patients presented emergent suicidal ideations on treatment distributed (one patient in each group). Only the case in the agomelatine 10 mg group concerned a child (severity = 1). No emergent suicidal ideation was rated as serious (defined as score of 4 or 5). In addition, a total of 7 patients had a worsening of their suicidal ideation on treatment, without meaningful difference between groups (2 patients and 1 patient in the agomelatine 10 mg and 25 mg, respectively vs. 3 patients in the placebo group and 1 patient 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. A suicide attempt was reported as a serious adverse event in one patient in the agomelatine 25 mg group.

Some safety results – open extension period:

In the extension period (W012-W104, i.e., a 21-month follow-up), a total of 212 patients (62.5%) presented 620 **Treatment-Emergent Adverse Events** under agomelatine: 61.8% of patients in the ago/ago group, 64.7% in the placebo/ago group and 61.9% in the fluox/ago group. Most events were rated as mild (68.9%) or moderate (26%), with more severe events in the placebo/ago group (12.9% of TEAEs) than in the ago/ago and fluox/ago groups (2.3% and 0.8% of TEAEs, respectively).

The most **frequently reported TEAEs** during the W012-W104 period were headache (11.8% of patients), nasopharyngitis (7.1%), nausea (5.3%), weight increased and decreased appetite (3.8% each), abdominal pain, blood prolactin increased, thirst and fatigue (3.5% each) and dizziness (3.2%), without relevant between-group differences. Similar results were observed in the **adolescents** (62.4% presenting TEAEs) with roughly the same most common TEAEs as in the total population.

Overall, 8.6% of patients presented at least one **serious TEAE** during the extension period, with a higher rate in the placebo/ago (14.1%) and fluox/ago (10.7%) groups than in the ago/ago group (4.7%). The most common serious TEAE was depression, reported in 4 patients. Platelet count decreased, pneumonia, syncope, ALAT increased, ASAT increased, and suicidal ideation were reported by 2 patients each. All other serious TEAEs were reported only once. No serious TEAE was considered as related to IMP. Ten serious TEAEs in 6 patients (1.8%) led to IMP withdrawal, mainly Psychiatric disorders.

In the adolescents, 9.6% had serious TEAEs during the W012-W104 period.

Regarding **liver acceptability**, 3 patients (2 adolescents both in the placebo/ago group and one child in the fluox/ago group) reported high emergent PCSA values [> 3 Upper Limit of normal laboratory reference range (ULN)] of ALAT and/or ASAT on treatment. None of these events led to study withdrawal.

Regarding **suicidality**, the analysis of suicide risk using the C-SSRS-C showed that 12 patients (3.6%) [3 patients in the ago/ago group, 4 patients in the placebo/ago group and 5 patients in the fluxo/ago group] presented emergent suicidal ideations on treatment during the W012-W104 period. In addition, one patient (adolescent in the placebo/ago group) had a worsening of his/her suicidal ideation on treatment.

A total of 6 patients (1.8%, all adolescents; 3 patients in the ago/ago group, 1 patient in the placebo/ago group and 2 patients in the fluxo/ago group) reported emergent self-injurious behaviour without suicidal intent on treatment. Two patients (both adolescents; one in each of the placebo/ago and fluxo/ago groups) presented 3 emergent suicidal behaviours: both made emergent actual suicide attempt on treatment; in addition, one of them also undertook emergent preparatory actions toward imminent suicidal behaviour.

2.3.3. Discussion on clinical aspects

In this report only very brief and non-comprehensive information and summaries are given of the data from the submitted study CL3-20098-076.

Furthermore, the data from the study have not been critically assessed by the CHMP in this Art. 46 procedure. This is because the MAH intends to submit an extension of the indication for Valdoxan comprising the paediatric population, based on data from study CL3-20098-076, by the end of September 2022. This intention was notified to EMA 24th March 2022. Consequently, the critical assessment of the data from study CL3-20098-076 is deferred and will be made during the procedure for the extension of the indication for Valdoxan.

3. CHMP's overall conclusion and recommendation

No critical assessment of the data from study CL3-20098-076 has been performed by the CHMP in the current Art. 46 procedure. This will rather be done later during the procedure for the extension of the indication for Valdoxan. The MAH has notified EMA (24th March 2022) that they intend to submit an

application for extension of the indication by the end of September 2022. No changes are proposed in the SmPC in the present procedure.

The current PAM is therefore considered fulfilled **solely** based on the fact that the study data have been provided. However, this conclusion is based on the prerequisite that the MAH applies for an extension of the indication for Valdoxan within a reasonable time frame. Consequently, it is therefore expected that an application for extension of the indication for Valdoxan will be submitted by the MAH within the end of September 2022 (as has already been notified by the MAH to EMA in March 2022).

☒ Fulfilled:

No further action required; however, the data are expected submitted in the context of an extension prior any conclusion on product information amendments is made. The MAH should commit to submit this extension application by the end of September 2022 as has already been indicated by the MAH and notified to EMA on 24th March 2022.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non-clinical studies

Product Name: Valdoxan Active substance: agomelatine

Study title	Study number	Date of completion	Date of submission of final study report
10 weeks toxicity study of Agomelatine in juvenile rats.	901338	February 2009	July 2012

Clinical studies

Product Name: Valdoxan Active substance: agomelatine

Study title	Study number	Date of completion (Last visit Last Patient)	Date of submission of final study report
Open-label, multicentre, three dose levels, trial to evaluate pharmacokinetics of Agomelatine in children from 7 to less than 18 years of age with depressive or anxiety disorder.	CL2-20098-075	14 March 2015	11 September 2015
Double blind, randomised, multicentre, two dose levels, active and placebo controlled, trial to evaluate efficacy and safety of Agomelatine to treat children from 7 to less than 18 years of age with major depressive disorder	CL3-20098-076	27 October 2021	April 2022
Double blind, randomised, multicentre, two dose levels, placebo controlled, trial to evaluate efficacy and safety of Agomelatine in children from 7 to less than 18 years of age with generalised anxiety disorder.	CL3-20098-077	July 2021	Condition "treatment of generalised anxiety disorder" removed on 15 July 2016 (EMA decision)
Double blind, randomised, multicentre, one dose level, placebo controlled, trial to prevent depressive relapse of Agomelatine in children from 7 to less than 18 years of age with major depressive disorder.	CL3-20098-090	March 2023	Study removed from the PIP on 17 January 2021 (EMA decision)
Double blind, randomised, multicentre, one dose level, placebo controlled, trial to evaluate prevention of anxious relapse of Agomelatine in children from 7 to less than 18 years of age with generalised anxiety disorder.	CL3-20098-091	March 2023	Condition "treatment of generalised anxiety disorder" removed on 15 July 2016 (EMA decision)