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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/P46/027

Note

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

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1. Introduction

On 11.09.2015, the MAH submitted a completed paediatric study for Valdoxan and Thymanax (agomelatine), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that 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) with Depressive or Anxiety Disorder. An open-labelled, multicentre, three-dose level, non-comparative study*" is part of a clinical development program. The variation application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by September 2023 (PIP completion March 2023). A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

The oral film-coated tablet available for adults was considered and was retained as the best option also in paediatrics due to the following reasons:

- The film-coating prevents from any issue linked to oromucosal contact (for example if a child does not swallow immediately).

- The dimensions of the agomelatine tablets of 5, 10 and 25mg strengths seem acceptable for the studied population, according to draft guideline on pharmaceutical development (EMA/CHMP/QWP/180157/2011) and Reflection paper on formulation in paediatric population (EMEA/CHMP/PEG/194810/2005). For the 25mg agomelatine strength, the final mass cannot be below 130mg (before film-coating). At this drug/excipients ratio, tableting performance remained indeed optimal, while higher ratio led to poor manufacturability.

- The oblong shape of the agomelatine 25mg tablet (capsule-like shape) is known to pass better the oesophagus (Overgaard et al, 2001).

2.3. Clinical aspects

2.3.1. Introduction

This is an article 46 application concerning study CL2-20098-075. The study was a phase II PK and safety study the antidepressant agomelatine in children aged 7 to <18 years of age. The aim of the study was to obtain exposure and safety data in order to determine the doses for the planned consequent phase II efficacy and safety studies.

The MAH submitted final reports for:

- Study CL2-20098-075
- CL2-20098-044

2.3.2. Clinical studies

Study CL2-20098-075

The CL2-20098-075 study aimed to 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.

It was an open-labelled, multicentre, three-dose level (with intra-subject dose escalation), non-comparative study (Figure 1).

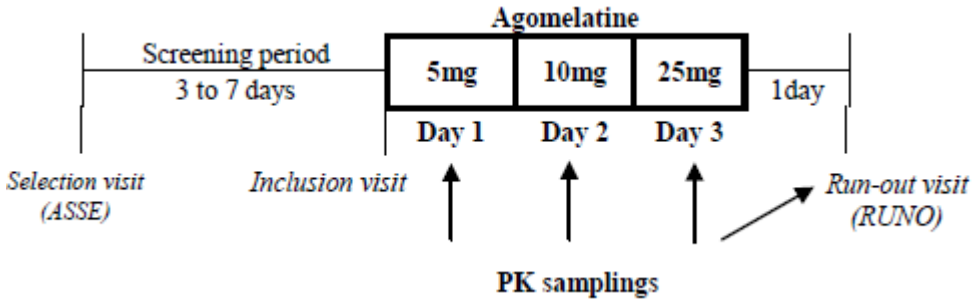

Figure 1 - Study design

The study was going to include:

- At least 24 participants from 7 to less than 12 years of age (at least 6 males and 6 females)

- At least 24 participants from 12 to less than 18 years of age (at least 12 males and at least 12 females).

- With at least 6 pre-pubertal females and at least 6 post-pubertal females in these two subsets, irrespectively of the age.

The **primary objective** was to evaluate the PK characteristics of 3 doses of agomelatine (5, 10 and 25 mg) in the above described paediatric age-sets.

Saliva and plasma were taken at different time points and concentrations of agomelatine were determined using a previously developed method based on liquid-solid extraction and liquid chromatography coupled with tandem mass spectrometry detection (HPLC-MS/MS).

Agomelatine PK parameters to be calculated were: maximum plasma concentration (C_{max}), area under the curve (AUC), terminal half-life ($t_{1/2}$), minimum plasma concentration (C_{trough}), and the time corresponding to C_{max} (t_{max}).

Secondary objectives were to:

Provide safety data of 3 doses of agomelatine (5, 10 and 25 mg).

Main secondary endpoints with times of assessment were:

• Hormonal parameters (prolactin, estradiol, cortisol, thyroid stimulating hormone [TSH], follicle stimulating hormone [FSH], luteinising hormone [LH], testosterone) before inclusion, on D001, D002, D003 and at run-out visit.

• Suicidal ideation and suicidal behaviour using the Columbia Suicide Severity Rating Scale Children's version (C-SSRS-C) assessed before inclusion and at run-out visit.

• Adverse events (AEs) assessed all along the study and collected using the Paediatric Adverse Event Rating Scale (PAERS)

• Physical examination, haematology and biochemistry, including liver function test, 12-lead Electrocardiogram (ECG) recording assessed before inclusion and at run-out visit.

• Height before inclusion; body weight: before inclusion and at run out visit.

• Vital signs (blood pressure and heart rate) at each study visit.

• Vigilance/sedation were via a self-rated visual analogue scale (VAS) and objective measures (Choice Reaction Time (CRT)) at D001, D002 and D003 (at the time point of T0-30min and T0+1h)

• Tablet acceptability of 3 doses of agomelatine (5, 10 and 25 mg). The assessment was performed via the Tablet acceptability questionnaire completed by the patient after the agomaletine intake on D001, D002 and D003.

Results

Pharmacokinetic results

The plasma exposure data are given in Figure 2. The ratio between salvia and plasma was similar to that observed in adults; 0.030 vs 0.033 respectively.

Figure 2 Exposure plasma PK parameters in the population of children form study CL2-20098-75

Exposure plasma PK parameters in the population of children from study CL2-20098-075

	Dose(mg)	N	5th Pctl	Median	95th Pctl	Mean	CV (%)
AUC (ng.h/mL)	5	51	1.97	4.18	19.1	20.8	518
	10	51	3.90	7.09	41.7	29.6	413
	25	49	7.76	19.0	147	42.9	205
C_{max} (ng/mL)	5	51	0.766	1.63	10.8	11.4	550
	10	51	1.10	2.69	19.4	17.1	457
	25	49	1.97	9.68	87.6	23.6	243
t_{max} (h)	5	51	0.325	0.370	0.390	0.366	594
	10	51	0.312	0.380	0.438	0.376	10.3
	25	49	0.284	0.366	0.478	0.369	16.7

Population pharmacokinetics

The pharmacokinetic data from both the performed paediatric studies (CL2-20098-044 and CL2-20098-075) were used for the population PK analysis.

Methodology

PK modelling was performed by nonlinear mixed effects modelling using NONMEM version 7.2 software with Intel Fortran 9.1. Graphs and statistical analyses were performed using SAS pc version 9.3 software (or upgraded version). The First Order Conditional Estimation (FOCE) method with the interaction option was used to estimate model parameters in NONMEM.

The PK model building was performed according to the following steps:

Evaluation of a first model (INITIAL model) describing the PK of agomelatine, investigating age and weight effects, based on the knowledge of adult PK. Possible refinement of the model regarding random effect models, (BASIC model) Covariate model (FINAL model).

Model evaluation was performed for the INITIAL, BASIC and FINAL PK model. Model evaluation was performed for the INITIAL, BASIC and FINAL PK models. The ability of the model to describe and/or predict data was assessed by:

basic evaluation methods such as standard goodness-of-fit (GOF) plots and assessment of uncertainty on parameter estimates and model sensitivity to outliers, advanced evaluation methods, such as and Normalized Prediction Distribution Error (NPDE) and Visual Predictive Check (VPC).

Purpose of use

The PK objectives of the present study were:

- To assess the PK of agomelatine in a paediatric patient population using a population PK approach investigating age and weight effects

- To quantify the variability and identify the sources of variability (pubertal status, smoking habit, gender and oestrogen co-administration)

- To compute derived secondary PK parameters (AUC, Cmax and tmax).

CHMP's comment

The methods used are generally considered appropriate for the described purpose of use. PK was investigated in both plasma and saliva.

Database

A total of 60 subjects (51 from the study CL2-20098-075 and 9 from the study CL2-20098-044) were included in the PK dataset. They were distributed as follows:

- 30 children in age subset 6-12 years

- 30 adolescents in age subset 12-18 years

Pharmacokinetic samples were collected:

in saliva on Day 1, Day 2 and Day 3, PK samples were collected 30 min before agomelatine intake, then 30 min, 1 h, 2 h, 3 h and 4 h after agomelatine intake and then every hour until bedtime and when the patient awoke the following morning. An additional sample was collected at run-out visit.

in plasma: one blood sample was collected 1h after IMP intake on Day 3 after oral administration of agomelatine 25 mg.

Concentrations of agomelatine were determined in plasma and saliva using a previously developed method based on liquid-solid extraction and liquid chromatography coupled with tandem mass spectrometry detection (HPLC-MS/MS). The LLOQ was 0.01 ng/mL for both plasma and saliva.

The dataset comprised 1193 observations including 538 BLQ values which represented 45 % of the overall data. Those BLQ values were removed from the dataset. At a given sampling time in the distribution phase (i.e. after Cmax), if all values were below the limit of quantitation (BLQ), they were removed from the dataset. Only one BLQ value in the distribution phase was retained for each individual. For all other BLQ values, the possibility of considering them as left censored was investigated.

The overall mean weight, BMI, age and height of the participating subjects was 46 kg, 20 kg/m2, 12 years and 152 cm, respectively. The overall percentage of boys and girls in the two studies was 53 and 47 %, respectively. The overall percentage of boys, pre pubertal girls and post pubertal girls in the two studies was 53, 27 and 20 %, respectively. Only 3 % of patients in the two studies had smoking habits, and only 3 % were co-administered oestrogen during the study.

CHMP's comment

The range of demographics of the included patient population seems in line with the aim of the study. The sampling times are considered as tending to be too sparse, as the data only supports a 1-compartment model versus a two-compartment model in adults. The extremely high proportion of observations below the LOQ (45%) is considered a weakness of the study. Further efforts to improve the bioanalytical method should, if possible, have been undertaken.

Assumptions

Presented by the applicant

Assumption	Rationale
ka	*Redacted*
Monocompartmental disposition	*Redacted*
Estimating only apparent parameters	*Redacted*
Weight effects	*Redacted*
Age effect	*Redacted*
BBQ	*Redacted*
Additive error model	Fixed to the LLOQ for both plasma and salvia

Additional assumptions as perceived by the assessor

- Database sufficient with regards to patient population and size as well as the number and timing of PK samples to give a representative model for the PK of the substances in the relevant paediatric age range 7 - <18 years.
- Ranges of co-variates to be explored sufficient to determine effect.
- Parametric distribution for the random effects (log-normal parameter distribution)

CHMP's comment

In general, the model is considered more dependent on some assumptions than need be, if the PK sampling scheme had been more robust and the bioanalytical method improved with regards to the LOQ. The final PK database is much smaller than planned and the model cannot provide robust estimates or predictions of the exposure levels achieved from the 5 mg dose. Even for the 10 mg dose there seems to be an element of under prediction. Co-variate effects observed in adults were not significant in children. As the database is quite small due to the high number of BLOQ excluded, it is likely that the database is too small to allow robust evaluation of potentially significant co-variates.

Results and evaluation

The INITIAL model was a one compartment model parameterised in terms of CL/F, V/F and Ka applied to describe both saliva and plasma concentrations of agomelatine. For identifiability reasons, Ka was from a previous combined population analysis. IIV was retained on Frel and IOV was found on the Frel parameter. The covariate WT was tested on, volume and clearance parameters but was not retained as it did not improve the fit. A similar observation was made for age tested on and CL. Weight effects tested in the model using an allometric power model were not significant. Moreover as the children less than 6 years were not presented in the pool of the data, it is not surprising that the added on Frel and CL was not retained. Two combined error models (one for saliva concentration and one for plasma concentration) were used. Precision of parameter estimation was good, with RSE less than 30 % for fixed-effects and less than 50 % for random effects parameters.

The INITIAL population model was used as a starting point to build the BASIC model. IOV was added on V. IIV on this parameter was removed as it became too low. IIV was also investigated on S/P ratio but not retained.

In the FINAL model analysis, the gender effect and the pubertal status were tested on Frel, but no covariate was retained in the FINAL model. The result on the gender effect was not due to not enough subjects included. Indeed, a power analysis was performed and concluded that the number of subjects included were sufficient to show an effect if similar than in adult (i.e. Frel increased by about a factor 2 in women). Regarding the pubertal status, no differences were expected between boys and pre-pubertal girls. Indeed, the PK characteristics of males and females in children age group is expected to be similar as the oestradiol levels are low and comparable in female and male pre-pubertal subjects (Mahler, 2013). Between pre-pubertal girls and post-pubertal girls, differences were expected as the oestradiol levels are higher in female post pubertal. However, no differences were seen neither between the post pubertal girls and the other ones.

Precision of estimation of parameters was good, with RSE less than 30 % for fixed-effects and less than 50 % for random effects parameters. The data were adequately decribed with a model without dose and time effects which support the assumption that agomelatine is linear in children over the range of dose tested (i.e. from 1mg to 25 mg).

The final parameter estimates for agomelatine is given in **Table 1**. Individual GOF are given in ***Figure 3***, VPC plots are given in Figure 5 and CWRES in ***Figure 4***.

Table 1 Parameter estimates for the final PopPK model

Final population PK parameters

Parameter (unit)	Estimate	IIV (%)	IOV (%)
Ka (1/h)	Redacted	-	-
CL/F (L/h)	1070	-	-
V/F (L)	2170	-	65
Frel	1 fixed	93.3	47
S/P ratio	0.0304	-	-
σ Plasma add (ng/mL)	Redacted	-	-
σ Plasma prop (%)	Redacted	-	-
σ Saliva add (ng/mL)	Redacted	-	-
σ Saliva prop (%)	Redacted	-	-

Figure 19 – FINAL Model - Individual predicted saliva concentrations (ng/mL) (IPRED) *versus* observed saliva concentrations (ng/mL) (DV) after agomelatine administration; blue line represented the trend line; red line represented identy line;

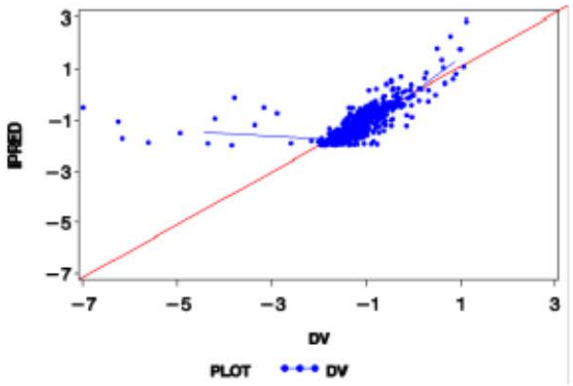

Figure 20 – FINAL Model - Individual predicted plasma concentrations (ng/mL) (IPRED) *versus* observed plasma concentrations (ng/mL) (DV) after agomelatine administration; blue line represented the trend line; red line represented identy line;

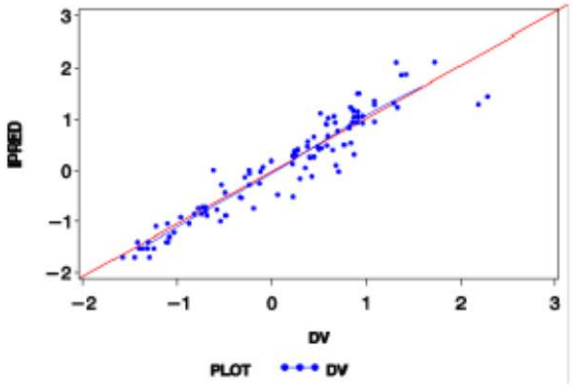

Figure 3 – Individual goodness of fit plots for salvia (Figure 19) and plasma (Figure 20) concentrations for the final model

Figure 21 – FINAL Model - Individual weighted residuals (IWRES) *versus* individual predicted saliva concentrations (ng/mL) (IPRED) after agomelatine administration (left side); Individual weighted residuals (IWRES) *versus* time after administration (h) (TAD) after agomelatine administration (right side) ; blue line represented the trend line;

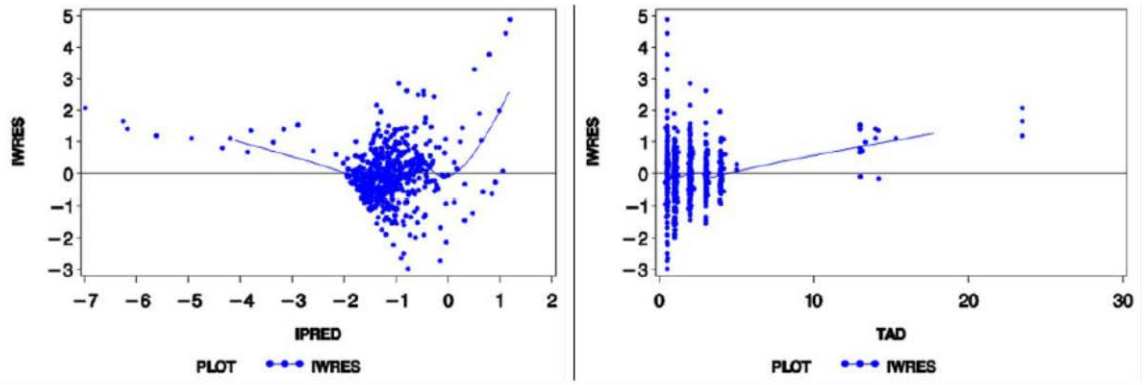

Figure 22 – FINAL Model - Individual weighted residuals (IWRES) *versus* individual predicted plasma concentrations (ng/mL) (IPRED) after agomelatine administration (left side); Individual weighted residuals (IWRES) *versus* time (h) after agomelatine administration (right side) ; blue line represented the trend line;

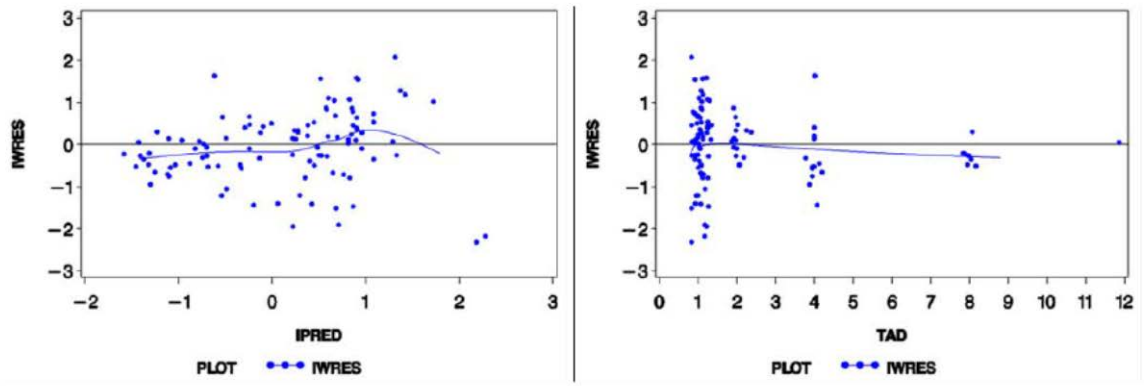

Figure 4 – IWRES versus individually predicted concentrations and time after administration for salvia (Figure 21) and plasma (Figure 22) concentrations for the final model

Figure 25 – FINAL Model - VPC per dose in study CL2-20098-075 : (a) for 5 mg, (b) for 10 mg and (c) fo 25 mg ; the grey areas represented the confidence intervals of the 5th percentile, the median and the 95th percentile of the model predictions; the solid green line represented the median of the observations; the dotted green lines represented the 5th and the 95th percentiles of the observations

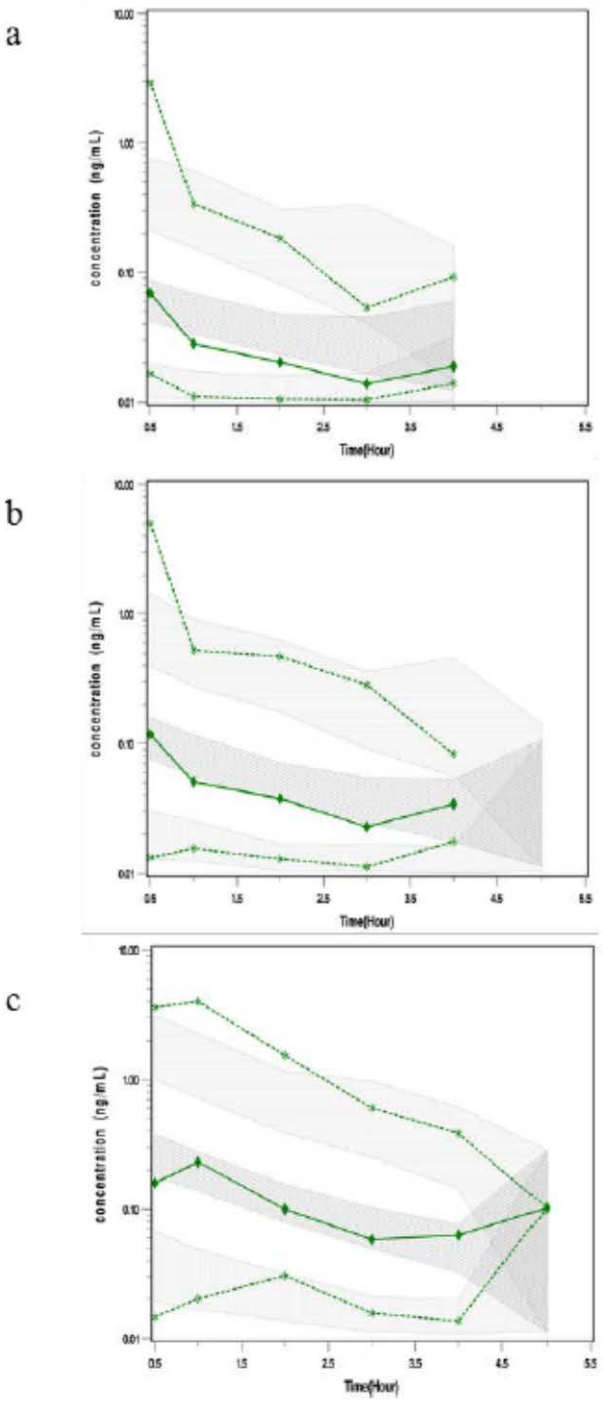

Figure 5 - Visual predictive check of plasma and salvia for the final model split by dose levels; Figure 25 a) 5mg, b) 10mg and c) 25 mg.

For study CL2-20098-044, VPCs performed by dose regimen showed a good predictions at the dose regimen 10 and 25 mg, but overestimated the dose level 5 mg. Indeed at this dose regimen, there is a

large number of BLQ values and suggesting that the population parameters were more likely driven by 10 mg and 25 mg. Nevertheless, the model is not qualified to perform simulations using the population PK parameters at 5 mg.

CHMP's comment

The model is quite simplistic compared to the adult model, and is hampered by the high proportion (45%) of samples below LOQ. A high proportion of the predicted secondary pharmacokinetic exposure parameters are negative, which does not reassure the biological plausibility. However, the model does seem to provide reasonable robust predictions for exposure in the dose range above 10 mg. There is a high variability in the PK parameters, as is also observed in adult, and the data only supports a 1 compartment model versus the 2-compartment model observed in adults. The data did not support any influential co-variates, as opposed to the adult model. However the limitations in the database that were available for the paediatric population analysis, questions the broader validity of such conclusions. The applicant has not provided a direct comparison of the paediatric to the adult data, which would have been useful in order to understand the dosing rationale for the phase III trials.

Due to the aspects discussed above, it could be considered whether it is recommendable to retrieve samples in phase III studies, in order to further explore the potential for significant co-variate relationships as well as the exposure-response relationship in children.

Safety results

The safety analysis set comprised all included patients having taken at least one dose of agomelatine. This set consisted of in total 51 patients which were 100% of the Included Set (i.e. 27 adolescents and 24 children). All except 2 patients received all 3 planned doses of agomelatine (5, 10 and 25 mg); 2 patients received the first 2 doses only (5 and 10 mg), see also further below under Adverse events.

It should be noted that the following assessments were only performed at screening and at the run-out visit (RUNO defined as within 24 hours after the last study drug administration): physical examination, weight, laboratory assessments (haematology, biochemistry, liver function) and ECG. Therefore any emergent adverse events (EAE) reported that was associated with these assessments at RUNO was automatically assigned to the agomelatine 25 mg dose. Consequently, any apparent effects in EAE reporting frequencies related to these assessments were not presented as dose effects.

Hormonal parameters results

For **pre-pubertal females**, mean prolactin, testosterone and thyroid stimulating hormone (TSH) values remained within the reference range throughout the study. Trends over time for each hormonal parameter were variable.

A low proportion of pre-pubertal females experienced out-of-reference-range hormonal values, including: low testosterone (3/14 at baseline; 2 to 4 patients at each post-baseline timepoint); none were reported as EAEs.

For **post-pubertal females**, mean prolactin, testosterone and TSH values remained within the reference range throughout the study. Trends over time for each hormonal parameter were variable. For the following parameters, mean values increased after agomelatine administration: estradiol (values remained above baseline at RUNO) and prolactin (values returned to near baseline at RUNO), the mean prolactin levels remaining in the reference range.

Low testosterone was experienced by 2/11 post-pubertal females at baseline; 4, 2 and 6 after the 5, 10 and 25 mg doses, respectively; and 4 at RUNO. For all other parameters, 1 patient only experienced out-of-reference-range hormonal values (high testosterone, high prolactin and high TSH); none were reported as EAEs.

For **male children**, mean luteinising hormone (LH), prolactin and TSH values remained within the reference range throughout the study. Mean testosterone values at all timepoints were below the reference range (8.4 to 28.7 nmol/L). Trends over time for each hormonal parameter were variable.

However, mean prolactin increased after agomelatine administration (values returned to below baseline at RUNO), the mean prolactin levels remaining in the reference range.

Low testosterone was experienced by the large majority of male children (14/14 at baseline; 14, 13 and 12 patients after the 5, 10 and 25 mg doses, respectively; and 13 at RUNO). For all other parameters, a low proportion of patients experienced out-of-reference-range hormonal values, including: high TSH (3, 1 and 2 patients after the 5, 10 and 25 mg doses, respectively), high prolactin (1 at baseline and 2, 1 and 1 patient after the 5, 10 and 25 mg doses, respectively); none were reported as EAEs.

For **male adolescents**, mean LH, follicle stimulating hormone (FSH), prolactin and TSH values remained within the reference range throughout the study. Mean testosterone values after each dose were below the reference range (8.4 to 28.7 nmol/L). Trends over time for each hormonal parameter were variable. However, mean testosterone values decreased after agomelatine administration (values returned to near baseline at RUNO). Conversely, mean prolactin increased after agomelatine administration (values remained above baseline at RUNO), the mean prolactin levels remaining in the reference range.

Low testosterone was experienced by the majority of male adolescents (6/12 at baseline; 9, 8 and 9 patients after the 5, 10 and 25 mg doses, respectively; and 6 at RUNO). For all other parameters, a low proportion of patients experienced out-of-reference-range hormonal values, including: high LH (1, 1 and 2 patients after the 5, 10 and 25 mg doses, respectively and at 1 at RUNO) and high prolactin (1 patient at baseline, after each dose and 3 patients at RUNO). High prolactin in 1 patient was reported as a mild EAE after the 25 mg dose (not considered related to agomelatine).

As regards cortisol, the decrease observed in mean cortisol after agomelatine administration in all patients regardless of gender and age (pre-pubertal and post-pubertal females or male children and adolescents) is explained by the fact that blood sampling on D1, D2 and D3 were taken in the evening.

Suicidality assessment

No patient completed suicide during the study. Of the patients who had a positive response to one or more Columbia Suicide Severity Rating Scale Children's version (C-SSRS-C) items at baseline (1, 2, 7 and 9 patients according to item, representing suicidal ideation/behaviour over the patient's lifetime before the study), the majority had a negative response at the end of the study (representing suicidal ideation/behaviour during the study). Of the 9 patients (4 adolescents and 5 children) who had previously experienced suicidal ideation (and therefore suicidality), 2 patients (both adolescents) experienced these ideations during the study. No child had a positive response to any of the C-SSRS-C factors during the study.

Adverse events

Overall, 49/51 patients received all 3 planned doses of agomelatine over 3 days: 5 mg on D1, 10 mg on D2 and 25 mg on D3. Two (2) children were withdrawn prematurely (1 patient due to fatigue and

one patient due to withdrawal of consent) and only received the first 2 doses of agomelatine (5 and 10 mg).

Table 2: Overall summary for adverse events in all patients, adolescents and children in the Safety Set

All patients		ALL (N = 51)	Agomelatine 5 mg (N = 51)	Agomelatine 10 mg (N = 51)	Agomelatine 25 mg (N = 49)
Patients having reported					
at least one emergent adverse event	n (%)	17 (33.3)	10 (19.6)	8 (15.7)	11 (22.4)
at least one treatment-related emergent adverse event	n (%)	12 (23.5)	3 (5.9)	4 (7.8)	10 (20.4)

Adolescents		ALL (N = 27)	Agomelatine 5 mg (N = 27)	Agomelatine 10 mg (N = 27)	Agomelatine 25 mg (N = 27)
Patients having reported					
at least one emergent adverse event	n (%)	10 (37.0)	6 (22.2)	5 (18.5)	8 (29.6)
at least one treatment-related emergent adverse event	n (%)	8 (29.6)	2 (7.4)	3 (11.1)	7 (25.9)

Children		ALL (N = 24)	Agomelatine 5 mg (N = 24)	Agomelatine 10 mg (N = 24)	Agomelatine 25 mg (N = 22)
Patients having reported					
at least one emergent adverse event	n (%)	7 (29.2)	4 (16.7)	3 (12.5)	3 (13.6)
at least one treatment-related emergent adverse event	n (%)	4 (16.7)	1 (4.2)	1 (4.2)	3 (13.6)

The most frequently affected system organ class (SOC) overall was nervous system disorders (10 patients [19.6%]) followed by general disorders and administration site conditions (6 patients [11.8%]) and gastrointestinal disorders (5 patients [9.8%]). For each dose received, there were slight differences in the frequency of SOCs affected. The SOC nervous system disorders was the only SOC affected that tended to increase in frequency with agomelatine dose: 4 patients (7.8%) at 5 mg, 5 patients (9.8%) at 10 mg and 6 patients (12.2%) at 25 mg.

The most frequently reported EAEs overall were hypersomnia (5 patients [9.8%]), fatigue (4 patients [7.8%]) and dizziness, dry mouth and somnolence (3 patients [5.9%] each). Hypersomnia was reported at a higher frequency for the 25 mg dose than for 5 or 10 mg (1 patient [2.0%] on 5 mg, 1 patient [2.0%] on 10 mg and 4 patients [8.2%] on 25 mg).

There were no severe EAEs during the study. Overall, the majority of EAEs were of mild intensity (78.9%). Overall, 12 patients (23.5%) had 23 EAEs considered to be related to the treatment: 5.9% at 5 mg, 7.8% at 10 mg and 20.4% at 25 mg (including events assessed at RUNO only and automatically assigned to the 25 mg dose: ECG QT prolonged in 2 patients [4.1%] (not confirmed by the expert), and leukopenia and neutropenia in 1 patient each [2.0%]).

No patient had an EAE leading to dose modification or temporary interruption of agomelatine and 1 patient had 2 mild EAEs of fatigue considered related to treatment that led to withdrawal from the

study on D2. There were no deaths or serious EAEs during the study. One patient experienced 2 severe non-emergent SAEs after the end of the study (13 days post-RUNO; bipolar II disorder and suicidal behaviour).

The majority of the EAEs reported in this population correspond either to those commonly reported in paediatric patients (nasopharyngitis, conjunctivitis bacterial, influenza, acne) or to known EAEs reported with agomelatine in adults (anxiety, headache, dizziness, somnolence, diarrhoea and fatigue). Those not previously reported in adults include ECG QT prolonged (not confirmed by the expert), leukopenia and neutropenia.

Physical examination, laboratory haematology and biochemistry, ECG recording, height, blood pressure and heart rate

Overall, no parameters showed clinically relevant changes in blood pressure, heart rate, weight or BMI during the study for all patients, adolescents or children. One patient (adolescent) experienced moderate blood pressure increased, which was not considered related to agomelatine.

2 patients (1 in children and 1 in adolescent sub-set) experienced ECG QT prolonged, (at RUNO) which were reported as mild EAEs considered related to the agomelatine (both recovering). Both cases were reviewed by an independent cardiologist who stated that the patient had no QT prolongation based on Fridericia correction for QT interval.

Overall, 2 patients (3.9%) had a shift in ECG parameters from normal at baseline to abnormal at RUNO (1 adolescent and 1 child). Both patients experienced ECG QT prolonged, which were reported as mild EAEs considered related to agomelatine:

A 12-year-old female adolescent experienced ECG QT prolonged reported at RUNO, (435 ms at baseline and 444-491 ms at RUNO), which was asymptomatic; the patient was noted to be recovering at the end of the study. The patient did not come for a follow up visit and did not perform any complementary ECG. The case was reviewed by an independent cardiologist who stated that the patient had no QT prolongation based on Fridericia correction for QT interval.

A 9-year-old female child experienced ECG QT prolonged reported at RUNO (444 ms at baseline and 450 ms at RUNO), which was asymptomatic; the patient was noted to be recovering at the end of the study. The patient performed an additional ECG at follow up visit. The investigator confirmed the event was still recovering.

The case was reviewed by an independent cardiologist who stated that the patient had no QT prolongation based on Fridericia correction for QT interval.

Overall, there were no clinically relevant changes in mean or median biochemistry, haematology or liver function values over time for all patients, adolescents or children, except for a slight increase in the mean bilirubin in children.

A low proportion of patients experienced emergent out-of-reference-range biochemistry values on treatment, including 4 patients (8.0%; 2 adolescents, 2 children) with shifts to low HDL cholesterol and 3 patients (6.0%; 3 adolescents) with shifts to high triglycerides. No patient had emergent PCSA biochemistry values on treatment or emergent abnormal non-PCSA values considered as clinically significant by the investigator.

A number of patients experienced emergent out-of-reference-range haematology values on treatment, including: 6 patients (12.2%; 4 adolescents and 2 children) with shifts to low monocytes, 5 patients (10.2%; 3 adolescents and 2 children) with shifts to low neutrophils and 4 patients (8.2%; 3

adolescents and 1 child) with shifts to low white blood cells. One (1) child (2.0% overall) had a PCSA value on treatment: low neutrophils, reported as a moderate EAE of neutropenia (with mild leukopenia and lymphocytosis); the EAE was not considered related to treatment. Non-PCSA abnormal values were reported as EAEs in 1 adolescent: mild neutropenia and leukopenia (both considered related to agomelatine).

A low proportion of patients experienced emergent out-of-reference-range liver function values on treatment, including: 3 patients (6.0%; 2 adolescents and 1 child) with shifts to high ALT, 1 patient (2.0%; adolescent) with a shift to low ALP and 1 patient (2.0%; child) with shifts to high indirect bilirubin associated with high bilirubin. No patient had emergent PCSA liver function values on treatment or emergent abnormal non-PCSA values considered as clinically significant by the investigator.

Vigilance / sedation

For all patients, there was a tendency for a proportion of patients to shift down a VAS category (become less vigilant) after agomelatine intake, which increased with dose: after the 5, 10 and 25 mg dose, 20 (39.2%), 23 (45.1%) and 29 (59.2%) patients, respectively. The percentage of patients 'rather sleepy' increased after agomelatine intake: 7.8%, 9.8% and 14.3% of patients pre-dose versus 29.4%, 33.3% and 36.7% of patients post dose for the 5, 10 and 25 mg doses, respectively. The differences were smaller for the percentage of patients 'very sleepy': 2.0% (1 patient) and 0 patients pre-dose and 3.9% (2 patients) and 6.1% (3 patients) post dose for the 10 and 25 mg doses, respectively (no difference for the 5 mg dose [1 patient]). Conversely, a small percentage of patients became more vigilant after agomelatine intake (11.8%, 5.9% and 8.2% of patients, after the 5, 10 and 25 mg doses respectively).

Median Choice Reaction Time (CRT) motor time and reaction time changes from pre-dose values were increases from baseline in all cases. All median changes were not clinically relevant (within the range of 2.5 to 12.0 ms other than reaction time at 25 mg which showed no change). The small proportion of patients with either incomplete or no reaction did not show any notable trends between tests performed before and after each agomelatine intake or as the dose of agomelatine increased and as time in the study increased.

Compliance and tablet acceptability

All patients were 100% compliant with treatment. The large majority (>90%) found the round 5 and 10 mg tablets "very easy" to swallow. This percentage was lower with the larger, oblong 25 mg tablet (69%). This difference was more marked in children than adolescents. The remaining patients found the tablets "easy" to swallow.

CHMP's comment

The safety results of the study are 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. Based on these scarce data no new safety signals could be detected. Two asymptomatic cases of possible QT prolongation by ECG recording at 25 mg were reported. No ECG recordings were performed at lower doses. Based on the information available, the evaluation made by the external cardiac expert that the 2 cases seem to represent normal fluctuations of ventricular repolarization, is endorsed.

Study CL2-20098-044 – exploratory study in children with Smith-Magenis Syndrome

"Efficacy of co-administration of agomelatine (1 mg or 5 mg) and acebutolol (10 mg/kg) given orally once a day for 6 months (M0-M6) to children suffering from Smith-Magenis Syndrome.

An open, non-randomised Phase II study with a first optional open period of 6 additional months (M6 to M12), a second one of 12 additional months (M12 to M24), and a third one of 24 additional months (M24 to M48)."

The Smith-Magenis Syndrome (SMS) is a multiple congenital anomaly with mental retardation. It is associated with an interstitial deletion on the chromosome 17p11.2, and its estimated prevalence is 1/25000 (Smith 1998). The children suffering from SMS present disability, hyperactivity, and severe sleep and sleep/wake disorders with a major impact on the educational, social, and family life. This includes sleep attacks at the end of the day, severe sleeping difficulties, including early sleep onset, frequent and prolonged night-time awakenings, and early morning awakenings (Smith 1998, Potocki 2000). A clinical study performed in 20 children with SMS showed a phase shift of the circadian rhythm of melatonin with diurnal secretion of the hormone (De Leersnyder 2001a). The children presented tantrums and tiredness when melatonin rose, and naps and sleep attacks when melatonin peaked at midday and in the evening. It has been hypothesized that the hyperactivity and attention deficit problems of these patients could be due to struggle against sleep when the melatonin rose during the day. Furthermore, their sleeping difficulties could also be related to the inversion of the melatonin rhythm.

This study was initiated in 2002 with a duration of 6 months. Later the study was amended to include 3 extension periods. The currently submitted report included the results from the extension periods of the study which was completed in 2007.

Methods

Objectives

The **primary objective** was to assess the activity of agomelatine (1 mg or 5 mg) with a co-administration of β1 adrenergic antagonist acebutolol (10 mg/kg) for 6 months on the sleep disturbances in children suffering from Smith-Magenis Syndrome.

Measured by actigraphy parameters: Mean sleep start/stop time, mean assumed sleep time, mean actual sleep, mean activity score, mean average activity during light/during dark, mean light/dark ratio, mean cosine peak.

The **secondary objective** was to restore the circadian rhythm of melatonin with a nocturnal secretion in children suffering from Smith-Magenis Syndrome.

Measured by sleep diary, Children's sleep questionnaire and Achenbach questionnaire.

The children's sleep questionnaire and the Achenbach questionnaire were filled in by the patient's parents during the whole treatment period.

At the end of the 6-month period, the study was extended by 42 months according to 3 successive amendments based on a wish from the main coordinator, and of claimed very good feedback of the patients' parents in order to dispense treatment to the patients suffering from Smith-Magenis Syndrome for whom there is no satisfactory pharmacological treatment.

Study population

Male or female children aged between 6 and 18 years (inclusive) with a weight > 20 kg, and suffering from Smith-Magenis Syndrome.

Ten patients were included, 9 patients completed the mandatory treatment period (M0-M6) and 8 patients completed at M48.

Treatments

During the whole treatment periods, the patients received doses of agomelatine and acebutolol (Sectral®) adjusted on their weight. Acebutolol has been chosen as a co-administered treatment in the morning for its ability to suppress endogenous melatonin secretion. It is known to suppress rapidly the diurnal secretion of melatonin but does not restore the night time secretion of the hormone (De Leersnyder 2001b).

For patients with a weight ≤ 30 kg:

- Agomelatine: One oral tablet of 1 mg once a day (o.d.) at 20:00 during dinner.
- Acebutolol: 10 mg/kg o.d. at 8:00 during breakfast, given as a syrup (40 mg/ml).

For patients with a weight > 30 kg:

- Agomelatine: One oral tablet of 5 mg o.d. at 20:00 during dinner.
- Acebutolol: 10 mg/kg o.d. at 8:00 during breakfast, oral tablet(s) of 200 mg.

Results

Patient disposition

Ten patients aged 6-17 years were included in this study (mean±SD 10.4±4.1 years, 7 children and 3 adolescents) and nine patients completed the 6-month study (one patient withdrew from the study for non-medical reason before taking any dose of agomelatine). Eight patients entered the extension treatment periods and were treated for a total of 4 years.

Pharmacokinetic results

The pharmacokinetic analysis was performed on 9 patients over the initial 6-month period. Samples were taken at Day 1 for 9 patients and after 6 months on treatment for 8 patients. As the plasma concentrations were comparable at both time-points (indicative of the absence of autoinduction in paediatric population as already observed in adults), they were pooled for calculation of agomelatine pharmacokinetic parameters.

The results show a wide variability on AUC and Cmax (***Table*** 3), as for adults.

Table 3 - Agomelatine pharmacokinetic parameters

Parameters		agomelatine doses	
		1 mg (N = 8)	**5 mg** (N = 9)
AUC (ng.h/ml)	Mean ± SD	0.97 ± 1.5	12 ± 16 (6.9 ± 5.8)*
	Median	0.48	8.4 (5.8*)
C_{max} (ng/ml)	Mean ± SD	0.31 ± 0.35	5.9 ± 7.0 (3.8 ± 3.4)*
	Median	0.20	3.1 (2.5*)
T_{max} (h)	Mean ± SD	0.71 ± 0.34	0.61 ± 0.15
	Median	0.70	0.55
$t_{1/2\,1}$ (h)	Mean ± SD	0.55 ± 0.082	0.47 ± 0.068
	Median	0.51	0.51
$t_{1/2\,Z}$ (h)	Mean ± SD	1.6 ± 0.071	1.6 ± 0.033
	Median	1.6	1.6

**: results without Patient No. 044250000113903 characterised with very high plasma concentrations (AUC=51.6ng.h/ml and Cmax=22.6ng/ml). N: number of pharmacokinetics profiles*

Pharmacokinetic parameters calculated in this study, when adjusted to the dose of 25 mg, were in 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. However, the influence of the weight on the agomelatine pharmacokinetics for paediatrics was to be evaluated with the upcoming paediatrics PK data from study CL2-075.

CHMP's comment

Please refer to the comments on the population PK model under study CL2-20098-075.

Efficacy results

Primary efficacy criteria

Actigraphy parameters

Compared to baseline, no relevant changes over the M0-M6 period were observed in the mean sleep start and stop times, and in the mean cosine peak time.

Compared to baseline, the mean assumed sleep time was prolonged over the M0-M6 period by 0.19 ± 0.58 h (median of 0.25 h) as well as the mean of actual sleep by 6.0 ± 14.6% (median of 1.8%). The mean total activity score decreased between baseline and the last post-baseline value (-43720.2 ± 56622.4, median of -97630.0).

The mean changes from baseline to the last post-baseline value in the mean of average activity during light and during dark were -199.1 ± 192.8 counts/min and -161.7 ± 132.1 counts/min, respectively. The mean light/dark ratio, issued from these two parameters, increased from baseline by 0.68 ± 1.10 (median of 0.46) over the M0-M6 period.

No reliable actigraphy data were recorded during the extension periods. Therefore, these data were not analysed.

Secondary efficacy criteria

Sleep diary, Children's sleep questionnaire, Achenbach questionnaire

Sleep diary:

For the M0-M6 period: The mean actual sleep time increased from baseline by 1.03 ± 2.67 h (median of 1.93 h), whereas no relevant change was observed in the mean assumed sleep time.

The mean ± SD change in nocturnal waking up from baseline to the value at the last post-baseline sleep diary filled in was -0.64 ± 0.80 (median of – 0.33).

The mean number of naps tended to decrease by -0.18 ± 0.31 naps (median of -0.08) compared to baseline.

Children's sleep questionnaire:

No relevant changes from baseline to the last post-baseline value were observed in the go to bed and get up times in the M0-M6 period. This was also the case for the extension periods.

M0-M48 period: The mean ± SD sleep duration was prolonged from baseline to the last post-baseline evaluation under treatment by 1.50 ± 2.35 h (median of 2.00 h, n=6).

Nocturnal waking up was less frequent and shorter over the M0-M48 period (from 2.3 ± 1.1 nocturnal waking up/night (median 2.0, n=7) to 1.5 ± 0.7 (median 1.5, n=2) with a mean duration of 78.3 ± 78.8 min (median 30, n=6) to 20.0 ± 14.1 min (median 20.0 min, n=2).

The mean duration of naps tended to reduce over the M0- M48 period from 65.0 ± 35.1 min (median 60.0 min, n= 6) to 26.7 ± 5.8 min (median 30.0 min, n=3).

Achenbach questionnaire:

M0-M6 period:

Compared to baseline, the activities scale total score slightly increased over the period (mean changes from baseline to last post-baseline value of 0.57 ± 1.21, median of 0.50) whereas no relevant change was observed in the social scale total score.

Among the syndrome scale scores, the internalizing and externalizing scores decreased between baseline and the post-baseline value (mean changes from baseline to last post-baseline value of -3.8 ± 3.7, median of -5.0, and -3.4 ± 3.8, median of -2.0, respectively). The mean total problems score decreased also from 83.2 ± 23.1 with a median 69.0 at baseline (n=5) to 73.8 ± 29.9 with a median 67.0 at M6 (n=4).

The mean activities, and social scales total scores both increased between the baseline and the last post-baseline assessment over the M0-M48 period by 0.81 ± 2.03 (median of 1.75, n = 8), and by 0.88 ± 1.71 (median of 1.25, n = 8), respectively.

The school scale total score and the total competence score were both only analysed in 3 patients between the baseline and the last post-baseline assessment over the M0-M48 period.

Safety results

All patients entering the extension treatment period reported at least one emergent adverse event (24) during the M0-M48 treatment period.

The most frequently affected system organs were infections and infestations (6 patients), and psychiatric disorders (5 patients), mainly anxiety (2 patients).

During the M0-M48 treatment period, 2 patients had 2 emergent serious adverse events, each: pneumonia, and tenotomy for one patient, and medication error (accidental intake of 12 tablets of agomelatine, without any suicidal idea), and orchydopexy for the other one. All serious adverse events resolved. None was considered as treatment-related by the investigator.

Height and weight follow-up during the study showed a normal growth for this population suffering from SMS. Some cases of short stature or obesity were observed, but these features are common in SMS young patients (Elsea & Girirajan, 2008). Blood pressure and heart rate were slightly lowered during the first months of the study, as expected after acebutolol intake, and increased over the 4-year period, probably related to patients' growth.

Liver parameters

Over the M0-M48 period, 3/8 patients entering the extension treatment period had at least one emergent value of liver enzyme above the upper normal limit (corresponding to limit for patients' age at the sample date). According to the MAH, none of the emergent out-of-reference-range values corresponded to potentially clinically significant abnormal values. No abnormal value was considered as clinically significant by the investigator. For 1 patient, it was isolated emergent high ALAT at M36 which returned within the reference range at M48:

Female, 17-year-old at inclusion: M0D0 = 41 IU/L, M36 = 70 IU/L (N = 65 IU/L), M48 = 42 IU/L.

For the other 2 patients, it was emergent high ALAT and ASAT, associated with GGT in one patient. Alkaline phosphatase and total bilirubin were within the reference range for both patients. No follow-up test was performed.

CHMP's comment

This was an open label study including only a total of 10 patients of which 8 completed the extension periods. As Smith-Magenis Syndrome is considered to be a rare condition (1/25000 births) it is acknowledged that it would be difficult to include a sufficient number of patients to make any statistically valid conclusions. Only descriptive measures can be made.

It is noted that in general the standard deviations are large and sometimes larger than the mean/median values, making the results very uncertain. The primary endpoint, actigraphy parameters, is the only objective measure for efficacy in this study and it failed to show any relevant changes of the treatment with agomelatine for the first 6 months. In addition, no reliable data in this respect could be recorded during the extension period. The secondary endpoints showed slight improvements in some of the parameters, but overall, the difference from baseline was minor and is considered to be of doubtful clinical relevance.

No new safety signals were detected as could be expected from a study of this small size, although it is acknowledged that the total study duration was long, up to 4 years. Three patients had at least one emergent value of liver enzyme above the upper normal limit. Increases in ALAT and/or ASAT are a common AE for agomelatine and monitoring of the liver function is mandatory for all patients taking agomelatine for the approved indication "treatment of major depressive episodes". Patients in the present study took lower doses of agomelatine (based on their weight either 1 mg or 5 mg) as compared to the dose recommended for depressed adult patients (25 mg). It is unclear if/when the liver cases reported in the current study resolved as they were not followed further.

Overall, study CL2-20098-044 can only be viewed as an exploratory/hypothesis generating study with possible interesting results for individual patients, but cannot be used for drawing any general conclusions for a larger number of patients.

2.3.3. Discussion on clinical aspects

To characterize the PK of agomelatine in paediatric patients, a population modelling approach was used based on pooled PK data from two clinical studies (CL2-20098-075 and CL2- 20098-044). Contrary to adults, no covariates showed a significant effect on agomelatine PK and thus none was retained in the model. The individual PK parameters were used for the computation of individual plasma concentration-time profiles and derived parameters (AUC, Cmax and tmax). As in adults, a high variability on pharmacokinetics parameters has been observed. Results of this analysis were used to support the dose selection for the efficacy study in children based on the assumption that the exposure/efficacy relationship is the same between adults and paediatric population.

The report on the study and the population PK model is considered sufficient at this stage. The PK database and the modelling approach have some limitations as previously discussed, however the model appears reasonably robust to describe and predict the PK of agomelatine at the higher dosages > 10 mg.

The safety results of study CL2-20098-075 are 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. Based on these scarce data no new safety signals could be detected.

Study CL2-20098-044 can only be viewed as an exploratory/hypothesis generating study with possible interesting results for individual patients, but cannot be used for drawing any general conclusions for a larger number of patients.

3. CHMP's overall conclusion and recommendation

The report on study CL2-20098-075 is considered sufficient at this stage. The reports on the additional studies will be submitted according to article 46 procedures and the full data package will be submitted after the development in children has been completed.

No information is presently deemed necessary to include in the SPC.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

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/Thymanax 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/Thymanax Active substance: Agomelatine

Study title	Study number	Date of completion	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	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	*Redacted*	
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 generalized anxiety disorder.	CL3-20098-077	*Redacted*	
Double blind, randomised, multicentre, one dose level, placebo controlled, trial to prevent depressive relapse of gomelatine in children from 7 to less than 18 years of age with major depressive	CL2320098-090	*Redacted*	

disorder.			
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 generalized anxiety disorder.	CL3-20098-091	*Redacted*	