European Medicines Agency
Evaluation of Medicines for Human Use

London, 27 July 2006
Doc.Ref.: EMEA/CHMP/87018/2006

REFUSAL CHMP ASSESSMENT REPORT FOR Valdoxan

International Nonproprietary Name:
Agomelatine

Procedure No. EMEA/H/C/656

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TABLE OF CONTENTS

1 BACKGROUND INFORMATION ON THE PROCEDURE 3

1.1 Submission of the dossier 3

1.2 Steps taken for the assessment of the product 3

2 SCIENTIFIC DISCUSSION 4

2.1 Introduction 4

2.2 Quality aspects 5

2.3 Non-clinical aspects 7

2.4 Clinical aspects 13

2.5 Pharmacovigilance 36

2.6 Overall conclusions, risk/benefit assessment and recommendation 36

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Les Laboratoires Servier submitted on 11 March 2005 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Valdoxan, through the centralised procedure. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 15 December 2004.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 30 July 1999. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: C. Sampaio
Co-Rapporteur: E. Skovlund

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 11 March 2005.
- The procedure started on 28 March 2005.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2005. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2005.
- During the meeting on 25-27 July 2005, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 July 2005.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 January 2006.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 March 2006.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 March 2006.
- During the CHMP meeting on 20-23 March 2006, the CHMP agreed on a list of outstanding issues to be addressed in an oral explanation and/or in writing by the applicant. The list of outstanding issues was sent to the applicant on 22 March 2006.
- The applicant submitted the responses to the CHMP list of outstanding issues on 19 May 2006.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 June 2006.
- During the CHMP meeting on 26-29 June 2006, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 24-27 July 2006 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for Valdoxan.

- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 16 January 2007.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Major Depressive Disorder (MDD) is reported to be the most common mood disorder, with a lifetime prevalence of about 15% and as high as 25% in women. Despite the availability of effective treatments, many persons with depressive disorders are disabled, and risk of suicide is considerable. Depressive disorders tend to be chronic and both relapse and recurrence are seen frequently.

A number of options are currently available for the treatment of MDD, including psychological therapies such as cognitive behavioural therapy and psychoanalytic psychotherapy, antidepressant medications, and electro-convulsive therapy.

Initial treatment objectives in the treatment of depression include: 1) Symptom remission (acute phase), 2) Prevention of relapse (continuation phase) and 3) Prevention of recurrences, or new episodes in patients with recurrent depressions (maintenance phase).

The presumed mechanism of action of the majority of antidepressants in the treatment of MDD is thought to be via inhibition of neuronal reuptake of monoamines (mainly serotonin and noradrenaline), with a resultant increase in monoamine neurotransmission in the central nervous system (CNS). The major classes of medicinal products used to treat depression are the tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine and sertraline), selective noradrenaline reuptake inhibitors (NRIs, e.g. reboxetine), serotonin and noradrenaline reuptake inhibitors (SNRIs, e.g. venlafaxine, duloxetine), heterocyclics (e.g., bupropion), monoamine oxidase (MAO) inhibitors, and a few other compounds such as mirtazapine and mianserin. No single antidepressant medication is clearly more effective than another and no single medication results in remission for all patients. In many occasions the choice of the medication is made looking at the side effect profile.

A significant percentage of patients develop sexual side effects after several weeks or months of SSRI and SNRI therapy, especially a decreased ability to have an orgasm. In addition, these medicinal products exert a negative influence on paradoxical sleep, thereby modifying sleep architecture in treated patients. A withdrawal syndrome may also occur upon cessation of treatment. Another inconvenience with SSRIs and SNRIs are that they are generally considered to be less potent than tricyclics for the treatment of severe depression. Furthermore, with all antidepressant drugs currently available, only 60-70% of depressed patients improve. Finally, another major limitation in the therapeutic value of MAOIs, tricyclics as well as SSRIs and SNRIs is the 3-4 weeks latency which unavoidably elapses from starting treatment with any one among these medicinal products to appearance of the first convincing signs of clinical improvement. This delay in their therapeutic efficacy is often a difficult period for the clinician to manage because of the behavioural disinhibition that these medicinal products can induce before raising mood. In particular, for depressed patients with suicidal ideas, suicide attempts can actually occur during the very first weeks of antidepressant treatment.

For all these reasons, it is obvious that there is still a need for new antidepressants which would preserve the quality of life and whose therapeutic action would be more efficient than that of medicinal products currently available.

About the product

Agomelatine is a new chemical entity intended for treatment of major depressive disorder (MDD). Agomelatine has a new pharmacological mechanism of action, which combines melatonin MT_1 and MT_2 agonist properties with a serotonin 5-HT_{2C} antagonist effect. The 5-HT_{2C} receptors are considered a relevant target with regard to antidepressant therapy, as several currently used antidepressant drugs are endowed with 5-HT_{2C} receptor antagonist properties (e.g. mianserin and mirtazapine).

The proposed posology is one oral 25 mg tablet taken in the evening. After two weeks of treatment, if further clinical improvement was required, the dose may be increased to 50 mg once daily, taken as a single dose of two tablets in the evening.

The clinical development programme focused on providing evidence for efficacy of agomelatine 25 mg and 50 mg in the major depression disorder indication. Supportive studies were performed to demonstrate efficacy in the elderly and clinical safety.

The applicant obtained scientific advice from the EMEA on 30 July 1999 (CPMP/1807/99) on the following issues concerning the clinical development: The investigation of a higher dosage than the 25mg dose and the designs of studies evaluating this higher dose of 50mg, and a specific efficacy study in elderly patients. This advice was partly taken into account in the design of subsequent studies.

2.2 Quality aspects

Introduction

The product is presented as film-coated tablets containing 25 mg of agomelatine as active substance. Other ingredients are lactose monohydrate, maize starch, povidone, sodium starch glycolate type A, stearic acid, magnesium stearate and silica colloidal anhydrous in the core tablet and hypromellose, yellow iron oxide (E172), glycerol, macrogol 6000, and titanium dioxide (E171).

The film coated tablets are packaged in aluminium/polyvinylchloride blister pack.

Drug Substance

- Agomelatine is a non-hygroscopic white or almost white powder practically insoluble in purified water and contains no asymmetric carbon atoms. Agomelatine has the chemical name N[2-(7-methoxy-1-naphthyl)ethyl] acetamide.

- Manufacture

The manufacturing process is carried with adequate in-process controls. The specifications and control methods for intermediate products, starting materials and reagents, have been presented.

Batch analysis data is provided on 16 batches produced with the defined synthetic route, and the batch analysis data show that the active substance can be manufactured reproducibly.

- Specification

The active substance specification includes tests for appearance, solubility (Ph Eur.), identification (IR, LC), assay (potentiometric titation), chemical purity (LC), loss on drying (Ph Eur), sulphated ash (Ph Eur), heavy metals (Ph Eur), particle size distribution, residual catalyst content. The specifications reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitably described and validation studies are in accordance with the ICH Guidelines. Impurity limits in the specifications are justified by toxicology studies.

- Stability

Three industrial-sized batches of agomelatine synthesized according to the synthesis process were placed under ICH storage conditions and at 30°C under 70% relative humidity for up 3 years. The results indicate that agomelatine drug substance is stable, and a practical re-test period has been established.

Drug Product

- Pharmaceutical Development

The intrinsic physico-chemical properties of the active substance were taken into account for the development of an oral solid formulation. A conventional immediate release tablet was selected as the dosage form and the excipients were selected based on compatibility testing of a number of excipients with the drug substance.

Several formulations were developed during clinical trials phases and judged to be bioequivalent. The excipients lactose monohydrate, macrogol 6000, magnesium stearate, maize starch, povidone, colloidal anhydrous silica, sodium starch glycolate (type A), stearic acid meet the Ph Eur specifications.

Lactose monohydrate is the only excipient of animal origin, derived from milk sourced from healthy animals in the same conditions as milk collected for human consumption.

Aluminium/polyvinylchloride blister are used as primary packaging. The materials comply with the Ph Eur and are adequate to support the stability and use of the product.

- Manufacture of the Product

A conventional wet granulation process is used. The in process controls are adequate for this film-coated preparation.

The batch analysis data show that the film-coated tablets can be manufactured reproducibly according to the defined finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The product specifications include tests by validated methods for appearance, identification of the active substance (HPLC, TLC), average mass, microbial quality (Ph Eur), assay (HPLC), degradation products (HPLC), uniformity of content (Ph Eur), dissolution (Ph Eur)

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for its intended purpose.

Batch analysis data on three pilot-scale and two production batches confirm satisfactory uniformity of the product at release.

- Stability of the Product

Stability studies were carried out on three primary batches according to defined stability protocols, which follow the ICH guidelines on stability at 25°C/60% RH and at 30°C/70%RH during 18 months, at 30°C/60%RH during 12 months and 40°C/75%RH during 6 months.

Physical and chemical parameters tested did not show significant signs of modifications in relation to the initial controls and comply with the shelf-life specifications.

The available stability data allow a practical shelf life and storage conditions to be defined.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-clinical aspects

Introduction
Regarding safety pharmacology, studies of cardiovascular, respiratory and gastrointestinal safety were generally conducted in accordance with Good Laboratory Practice (GLP) standards, while studies assessing CNS safety and follow-up studies did not fully comply with the GLP standards. The majority of the pharmacokinetic studies and all pivotal toxicology studies were conducted in accordance with GLP standards.

Pharmacology

- Primary pharmacodynamics

Agomelatine is a melatonin agonist with high affinity binding to human melatonine MT_1 and MT_2 receptors. Agomelatine is also a serotonin antagonist at the 5-HT_{2C} receptor from man and several animal species, although with low affinity. Two of the three main metabolites of agomelatine showed some pharmacological activity at the melatonin receptors, while a third metabolite (dihydrodiol-agomelatine, DHDP) was not pharmacologically active at either receptor families. In particular, 3H7DP (3-hydroxy-7-desmethyl agomelatine), the major metabolite in man, and also present in monkey and possibly in rat, showed low affinities for both human melatonin and serotonin receptors. In addition, due to the high degree of conjugation, 3H7DP may have minimal pharmacological effect in vivo.

Agomelatine had anti-depressive like activity in a number of animal models of depression (depression induced by stress, i.e. the despair test, the learned helplessness test, the model of unavoidable aversive light stimulus, the prenatal stress model, and the chronic mild stress which is a model of anhedonia; the antidepressant activity was also studied in models related to a hyperactivity of the hypothalamus-pituitary-adrenals axis). The anti-depressant effect was related both to activation of melatonin receptors and inhibition of 5-HT_{2C} receptors, and putatively to increased levels of extracellular noradrenaline and dopamine.

The pharmacological effects of agomelatine seemed to be related to the time of dosing, and highest effect levels were seen at dosing in the evening (light/dark transition), in accordance with the circadian fluctuation of endogenous melatonin, and with the applied clinical posology.

- Secondary pharmacodynamics

Agomelatine showed chronobiotic activity related to the melatonin activity, and anxiolytic effects while no indication of antipsychotic properties was seen.

- Safety pharmacology programme

Safety pharmacology studies carried out in mouse, rat and monkey with the dose up to 1024 mg/kg showed that agomelatine and the metabolite 7DP (7-desmethyl-agomelatine) caused significant CNS depression at high doses and induced slight-to-moderate sedation in several models.

In dog isolated cardiac Purkinje fibres, in the presence of agomelatine (10^{-6}M and 10^{-5}M), there was a small, but dose dependent and significant decrease in action potential duration, while in Cynomolgus monkey treated with agomelatine a prolongation of QT interval was observed, although QTc remained unchanged. No significant effect on recombinant HERG current was observed. In vivo agomelatine did not modify QTc in spontaneously breathing monkey up to a high intravenous dose and in human at doses up to 4-fold the therapeutic doses. Furthermore, the high concentrations used in the dog Purkinje fibres study largely exceeded the therapeutic concentrations.

No biologically relevant effects were seen on renal function or respiratory system. Agomelatine resulted in a slightly increased gastrointestinal motility. Endocrine studies in rat showed that agomelatine reduced basal and stress-related prolactin and LH levels in males and the surge of prolactin and LH in potentially pro-oestrus females, and corticosterone in both genders. Equivocal effects were observed on ACTH, GH, TSH. Further, during a 28-day endocrine study, exposure to agomelatine was in the range of the exposure in the carcinogenicity study, showing adequate exposure to demonstrate the lack of prolactine and oestradiol increase at the high dose of the carcinogenicity study in the rat.

Conventional studies of drug discrimination and self-administration (cocaine discrimination, diazepam discrimination, self-administration) in rats and monkeys did not indicate any dependence potential of agomelatine.

Pharmacokinetics

An LC-Fluorescence assay was validated in animal plasma samples from several species and human plasma samples, and used for all toxicokinetic analyses and for the first clinical studies. A sensitive LC/MS-MS technique was developed later and mainly used for analysis of agomelatine in human plasma and saliva samples.

- Absorption

Agomelatine was rapidly and almost completely absorbed after oral administration, but with a low absolute bioavailability caused by a high level of first-pass metabolism; following both single and repeated oral dosing, agomelatine exhibited non-linear kinetics in the oral dose range 2.5-750 mg/kg and 10-720 mg/kg for the rat and monkey, respectively, as both C_{max} and AUC increased more than dose proportionally. This non-linearity was related to saturation of the first-pass/ pre-systemic metabolism at higher doses. (Table 1 below)

Table 1: Absorption parameters for agomelatine in rats, in monkeys and in human following various single oral doses of agomelatine (gavage)

Species	Strain	Dose (mg/kg) *	n	Gender	t_{max} (h)	C_{max} (ng/mL)	AUC (ng.h/mL)	$F_{(\%)}$ (%)	Report number
Rat	Wistar	2.5	27	M	0.25	44.9	40.9	7.2	NP03218
		100	27	M	0.25	4900	14740	65	
Monkey	Macaca fascicularis	10	2	M	1	6.1	10.4	0.15	NP03216
		250	2	M	5	7310	27975	10	
Human	Caucasian	25mg	52	32M/20F	1	8.8	15	5.3	NP15749/ NP08350
		50mg	18	M	1	21	43	7.9	NP15794 NP15695

** unless indicated otherwise*

The exposure levels of unchanged agomelatine in plasma, especially in monkey, were characterised by a high inter- and intra-individual variability. The underlying mechanisms explaining most of the observed variability in plasma levels could be saturation of the solubility of the drug at high doses, as well as a high and saturable hepatic first-pass effect. The level of dissolution and saturation of first-pass metabolism could vary depending on the individual gastrointestinal status (stomach and gut fluid content, food, gut motility, etc.) at feeding time.

The single dose absorption studies were performed on males only, thus a gender-related effect on single dose pharmacokinetics was not assessed. In the repeated dose studies both genders were represented. In rats the exposure levels tended to be higher in females than in males, while in monkeys the exposure levels tended to be higher in males than in females**.**

- Distribution

Distribution studies were performed in the rat. Agomelatine and/or its metabolites were rapidly and extensively distributed throughout the body, with a rather moderate volume of distribution (2l/kg in rat, 1L/kg in monkey), in accordance with the lipophilic properties of agomelatine. The levels in the CNS were low and quickly eliminated. Initially, there were high levels of radioactivity in organs related to excretion, in adrenal glands, and in the uveal tract indicating possible affinity to melanin. The binding to melanin was considered weak (half life: 6-10h) and rapidly reversible in comparison of melanin turn-over measured in years. At late sampling times (48-96 h), highest levels were seen in the gastrointestinal system and this was explained by gastric secretion. In pregnant rats, agomelatine passed into placenta and foetuses. The level of radioactivity in maternal uterus was higher than plasma levels at 72 h post dosing.

The plasma protein binding of agomelatine and its 4 main metabolites (7DP; 3HP, 3-hydroxy-agomelatine; DHDP; and DAPACID, desacetamide-agomelatine-carboxylic acid) was moderate (75-85%) in different species, and the unbound fraction was independent of agomelatine plasma concentration. The in vitro blood to plasma concentration was close to 1 in rat, 0.9 in monkey and 0.7 in man, indicating an almost equal distribution of agomelatine in blood (erythrocytes) and plasma in rat and monkey, but slightly more distributed to plasma in man. In an in vitro blood-brain barrier model, agomelatine and 7DP crossed at a high grade, 3HP at an intermediate and DAPACID at a low grade.

- Metabolism, excretion

The main routes of metabolism in rat, monkey and man were as 3-hydroxylation, 7-desmethylation and oxidation of the naphtyl moiety at position 7, leading to the main metabolites 3HP, 7DP, and DHDP. The combination of 3-hydroxylation and 7-desmethylation lead to formation of the 3H7DP, a major metabolite in man, a moderate metabolite in monkey and a minor metabolite in rat. DHDP was most likely formed after hydrolysis of a 3,4-epoxide-agomelatine intermediate. Both rat and monkey were found to be representative toxicological species, and the metabolites identified in humans were found in at least one of these species.

Enzyme induction was observed to different degrees in rodent and monkey at oral doses ≥ 125 mg/kg, with a subsequent decrease in exposure of unchanged agomelatine. Agomelatine caused a time and dose-related induction of CYP2B, CYP1A, CYP3A and UGT in rodents. In monkey, only a minimal induction of CYP2B and CYP3A was observed, while CYP2C and CYP4A was slightly down-regulated. The enzyme induction was associated with a dose-dependent increase in liver weight in rodents. There was a dose-dependent increase in monkey liver weight (up to 40%), and the total P450 levels and microsomal hepatic protein concentration in the monkey were slightly increased at high doses.

The metabolites of agomelatine were conjugated and excreted via urine and faeces, and only low levels of unchanged agomelatine were excreted. About 80 % of the administered dose was excreted after 120 and 168 h for low and high oral doses (2.5 and 100 mg/kg, respectively). In rats, approximately 50-75 % of administered radioactive agomelatine was recovered in the urine and 20-40 % in faeces, while in monkey a larger proportion (60-80 %) was excreted in urine, similar to man. In general, the urinary excretion was slightly increased at high oral doses, and slightly higher in female than male rats. Studies performed in bile-cannulated rats demonstrated that most of the radioactivity detected in faeces was due to biliary excretion. Agomelatine and/or its metabolites was readily excreted into rat milk.

Toxicology

- Single dose toxicity

Single-dose toxicity was studied in mouse (465-1157 mg/kg po; 46-150mg/kg iv), rat (804-2000mg/kg po; 72-150mg/kg iv) and monkey (500-1500mg/kg po).

The studies indicated a rather low acute toxicity. All studies showed dose-related sedative effects. In rodents, the lowest maximal non-lethal dose was 465 mg/kg, while in monkeys no mortality was observed up to the highest dose of 1500 mg/kg. After iv administration to rodents, the maximal non-lethal dose was 59-72 mg/kg; cause of death was most likely due to excessive CNS depressive effect.

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicology was studied in rats (4-, 13-, 26-week studies; 25-750mg/kg po or 4-60mg iv) and monkeys (4-, 13-, 26- and 52-week studies; 60-720 mg/kg po or 2-32 mg/kg iv). In all studies a body weight reduction was observed without change on the feed intake.

In rat, there was a dose-related incidence of reduced body weight gain, CNS depression and liver discoloration from the lowest dose. Enlarged livers were seen in both males and females. Liver enzyme levels were only assessed in males, showing P450 induction in accordance with reduced exposure levels for agomelatine. In addition, thyroid findings in males were observed and related to hepatic enzyme induction. Also discoloration of urine, increased protrombin and activated partial thromboplastin time were seen.

In monkey, dose-related emesis, enlarged livers and increased urinary levels of porphyrins were observed. The effect on liver and porphyrinuria was likely related to the induction of hepatic enzymes. Single cases of loss of conscience occurred at all dose levels in the 13 weeks repeated dose toxicity studies immediately or shortly after dosing, causing 2 deaths; due to lack of dose-relationship, unchanged ECG and blood pressure, and lack of similar findings in other monkey studies these episodes, were considered related to misdosing based on necropsy data.

Toxicokinetic data were presented from all repeated dose toxicity studies in rat and cynomolgus monkey. There was considerable inter-individual variability in exposure in both rats and monkeys. The monkeys also demonstrated a considerable intra-individual variability. In monkey, there was sub-proportional relation between dose and exposure at low doses, while a marked increase in exposure

and increased t_{max} was observed with the highest doses. A time and dose related reduction in exposure was seen, which is in accordance with an enzyme induction.

In rat, there was a rather proportional relation between the lower doses and exposure, while at high doses the exposure level was sub-proportional to dose. This sub-proportionality was more pronounced in longer studies, and most likely reflected the increased metabolism due to enzyme induction. Exposure levels for agomelatine were reduced after repeated dosing, especially at the highest doses.

In Table 2 the exposure levels to agomelatine at NOAEL in the different repeated dose toxicity studies have been presented together with the human exposure after 4 weeks repeated daily administration of the intended clinical dose (50 mg/day). Exposure levels in animals are presented as mean and range AUC_{24}, unless otherwise noted.

Table 2: Exposure levels to agomelatine at NOAEL

Species	Report N°	Duration (weeks)	NOAEL[a] (mg/kg/d)	Mean plasma AUC_{24} (ng·h/mL)	
				Males	Females
				Mean AUC_{24} (min-max)	Mean AUC_{24} (min-max)
Rat	NP03207	4	40	615 (400-830)	349 (310-388)
	NP03204	13	25	1755 (1300-2210)	1555 (1490-1620)
	NP05355	26	25	2647 (2485-2809)	2166 (1606-2726)
Monkey	NP03193	4	240	4011 (1473-6234)	1519 (1016-2008)
	NP05172	13	< 80	<119 (21-263)	263 (60-850)
	NP06151	26	60	153 (60-293)	116 (49-193)
	NP08367	52	60	154 (74-281)	301 (76-1091)
Human[b]	NP15939	4	50 mg/d	116 ± 224	

a: unless otherwise noted; b: AUC level presented as mean ± SD

- Genotoxicity

The genotoxic potential of agomelatine was evaluated in a battery of tests including multiple bacterial reverse mutation assays, mouse lymphoma cell gene mutation assays, cytogenetic assays on peripheral human lymphocytes and in vivo bone marrow micronucleus and Unscheduled DNA synthesis (UDS) assays performed either after single or repeated oral dosing, as mechanistic experiments for carcinogenicity studies. All studies were conducted with concomitant positive controls. In vivo, no genotoxic potential of agomelatine was found. However, equivocal results were obtained in a mouse lymphoma assay in vitro, without performing an additional assay to clarify the equivocal results. Positive results at cytotoxic doses were seen in a chromosomal aberration assay with human lymphocytes. The applicant performed under CHMP request an additional mouse lymphoma assay, which was negative.

- Carcinogenicity

The carcinogenic potential of agomelatine was studied in mice (125-2000 mg/kg/day) and rats (40-360 mg/kg/day) by oral administration of a dietary admixture for 104 weeks after 13-weeks dose-finding toxicity and toxicokinetic studies in both species. A summary of the pivotal studies and their major findings are presented in Tables 3 and 4.

In mice, the males in the highest dose group had significantly increased number of intra-abdominal masses. Both sexes had increased occurrence of hepatocellular adenomas (at ≥ 500 mg/kg for females and at 2000 mg/kg for males) and carcinomas (at 2000 mg/kg for both sexes), associated with basophilic and eosinophilic cell foci and hepatocellular hypertrophy (Table 3).

Table 3: Incidence of main neoplastic and non-neoplastic findings in mice (NP07134).

	Males	Females

Dose level (mg/kg)	0	0	125	500	2000	0	0	125	500	2000
Number at start[a]	50	50	50	50	50	50	50	50	50	50
Survival (%)	90	84	90	80	82	78	80	80	80	76
Hepatocellular adenoma	7	2	1	7	18**/°°	3	3	3	9*/°	22**/°°
Hepatocellular carcinoma	9	11	11	15	32**/°°	2	1	3	2	14**/°°
Basophilic cell foci	3	3	7	7	21**	1	1	6*	1	16**
Eosinophilic cell foci	2	5	6	13**	32**	4	4	3	7	36**
Hepatocellular hypertrophy	0	0	0	0	42**	0	0	0	0	12**

*a : main groups; each tumour is counted once per animal; */**:p<0.05/0.01 (Fisher's test);°/°°:p<0.05/0.01 (Peto's test)*

In rats, males had increased occurrence of hepatocellular adenomas (≥ 120 mg/kg) and carcinomas (360 mg/kg), associated with increased incidences of foci of hepatocellular alterations and hepatocellular hypertrophy. At the highest dose, both sexes had increased incidences of mammary gland fibroadenomas (Table 4 below).

Table 4: Incidence of main neoplastic and non-neoplastic findings in rats (NP06859).

	Males					Females				
Dose level (mg/kg)	0	0	40	120	360	0	0	40	120	360
Number at start[a]	50	50	50	50	50	50	50	50	50	50
Survival (%)	56	56	80	76	60	68	78	68	72	64
Liver										
Hepatocellular adenoma	1	4	3	9*/°	9*/°°	1	0	1	1	1
Hepatocellular carcinoma	0	0	0	1	14**/°°	0	0	1	0	1
Basophilic cell foci	25	21	32*	32*	18	41	41	43	43	40
Eosinophilic cell foci	26	28	37*	42**	46**	17	12	8	6	13
Clear cell foci	12	9	26**	32**	24**	4	3	4	1	4
Atypic cell foci	0	0	1	6**	12**	0	0	0	0	3*
Hepatocellular hypertrophy	0	0	0	0	17**	0	0	0	0	27**
Mammary glands										
Fibroadenoma (be)	0	1	0	1	4*/°	10	6	14	13	19**/°°
Adenoma	0	0	0	0	0	5	0	1	1	0

*a : main groups; each tumour is counted once per animal; */**:p<0.05/0.01 (Fisher's test);°/°°:p<0.05/0.01(Peto's test)*

Due to the high extent of the first-pass metabolism seen in both rodents and humans, calculations of safety margins based on dose (mg/kg) were justified for the agomelatine-induced hepatic tumours: the safety margins (expressed as dose, mg/kg) for the rodent tumours were 150- and 50-fold in the mouse and rat, respectively.

- Reproduction Toxicity

Reproduction and developmental toxicity studies were performed in rat (15-240 mg/kg) and rabbit (50-450 mg/kg). Adequate paternal and/or maternal toxicity was confirmed in the high dose. Pharmacokinetic studies demonstrated that agomelatine and/or its metabolites pass the placenta and are excreted into rat milk, resulting in exposure in utero and through lactation. Agomelatine had no teratogenic potential, and no adverse effects on sperm count or viability, fertility, embryo-foetal development or pre- or postnatal development at doses up to 640 mg/kg/day in rat and 450 mg/kg/day in rabbit, although maternal toxicity was seen at the high doses in all studies.

- Other toxicity studies

Immunotoxicity

The 4 weeks immunotoxicity study in rat with doses 25-625 mg/kg/day was performed. Agomelatine at doses ≥ 125 mg/kg/day caused significant decrease in T-helper cell counts and a slight decrease in

the cytotoxic T-cells in females, lower spleen weight without affecting the T-cell dependent immune response. In males, there was a significant increase in B-cells without any histomorphological correlate. The long-term biological relevance of these effects, especially in females, is not known.

Mechanistic studies

Agomelatine revealed tumorigenic potential in rodents, leading to hepatic tumors in rats and mice and mammary benign fibroadenomas in rats (see above). Set of mechanistic studies were carried out to address this. Toxicokinetic studies showed that males were exposed higher than females, especially at 104 weeks. The gender-related differences in occurrence of hepatic tumours could be related to gender-related differences in exposure. Overall the results allowed to confirm a liver enzyme induction profile for agomelatine in rats, with some concordance with liver enlargement and the expected thyroid changes. However, a major increase in the level of ^{32}P incorporation in DNA bases was observed following 28 days agomelatine exposure in rat in vivo at exposure levels 8-fold human therapeutic exposure at 50 mg/day. The relevance and the meaning of these DNA adducts is unknown.

Although studies indicated that neither agomelatine nor its metabolites were forming DNA adducts in vitro, the identity of the in vivo adducts was not established. The applicant speculated that the DNA modifications might be related to the enzyme induction, without presenting any supporting data. Further evidence was considered necessary to demonstrate the proposed mechanism of adduct formation. Furthermore, elucidation of the adduct nature should also be performed. The applicant has planned to carry out a dietary study in Fisher rats to address the possible adduct formation after single and 28-day repeated administration of agomelatine. If formed after single dose administration, the adducts characterisation would be also performed. Overall, the potential clinical relevance of these findings remained unknown.

Ecotoxicity/environmental risk assessment

The predicted environmental concentration (PEC) in surface water was calculated to be 0.25 µg/l. This was above the action limit of 0.01 µg/l, and a phase II tier A assessment was therefore performed.

In the phase II tier A assessment the acute toxicity of agomelatine to fish and daphnids, and the inhibition of growth of algae, were determined and a predicted no effect concentration (PNEC) was calculated based on the most sensitive species. The ratio $PEC_{SURFACE\ WATER}$: $PNEC_{AQUATIC}$ was determined to be 0.33. Since the ratio was below 1, agomelatine was unlikely to represent a risk for the aquatic environment. The effect of agomelatine on micro-organisms present in sewage treatment plant was determined, and PNEC was calculated. The ratio $PEC_{MICRO\text{-}ORGANISMS}$: $PNEC_{MICRO\text{-}ORGANISMS}$ was determined to be 0.0001875. Since the ratio was below 1, agomelatine was unlikely to represent a risk for sewage treatment plants. No further assessment in a phase II tier B was therefore required.

2.4 Clinical aspects

Introduction

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

Pharmacokinetics

Methods for the analysis of agomelatine in human samples involved liquid or solid phase extraction followed by reverse phase liquid-chromatography (LC) and native fluorescence detection, and liquid chromatography/mass spectrometry/mass spectrometry method (LC/MS-MS). The LC/MS-MS method was adapted for the simultaneous determination of agomelatine and some of its metabolites in human plasma (3-OH-A, 3,4-dihydrodiol-A and 7-O-desmethyl-A). Metabolite identification was

achieved by comparison with authentic reference compounds and using on-line LC/MS-MS and nuclear magnetic resonance spectroscopy.

- Absorption

In vitro the intestinal transport of agomelatine across a Caco-2 cell monolayer was high through passive diffusion and corresponded to a predicted *in vivo* human rapid and total absorption of the compound. *In vivo*, as reflected by the urinary recovery of radioactivity following oral administration of [^{3}H]-agomelatine and [^{14}C]-agomelatine gastrointestinal absorption was at least 81 ± 4.2% of the dose, and rapid (Tmax < 1h). Agomelatine was rapidly and well (≥80%) absorbed after oral administration.

No formal bioavailability study with oral and i.v. administration of agomelatine in the same subject was performed. Absolute bioavailability was estimated to be (by a population pharmacokinetic approach on pooled phase I data from oral and i.v. administration) 3.4% with high variability (160%) and influenced by covariates (sex, dose and time of administration). The peak concentration was reached within 1 to 2 hours after administration.

Food intake did not modify the extent of bioavailable agomelatine for elderly subjects but it increased the delay and possibly decreased the rate of absorption as compared with administration of the drug under fasted conditions. In young volunteers a slight decrease of mean Cmax (20%) between fasted and fed conditions without modification in AUC was observed. However, this decrease was not clinically relevant, taking into account the variability of agomelatine pharmacokinetics. Therefore agomelatine can be administered with or without meals.

- Distribution

Steady-state volume of distribution (Vss) was determined as about 35L after i.v. administration of agomelatine and was dose independent.

Agomelatine was bound to plasma proteins at 95% mainly to serum albumin (about 35%) and alpha$_{1}$-acid glycoprotein (about 36%).

- Elimination

Agomelatine was mainly catalysed by CYP1A2; CYP2C9 and CYP2C19, at equal levels, also participated in elimination, but as minor secondary enzymes. CYP1A1 (mainly extrahepatic in human) was also shown to metabolise agomelatine.

Agomelatine was a relatively potent competitive CYP1A2 inhibitor, but 40-fold less potent than fluvoxamine.

The potential of induction by agomelatine of CYP1A2, CYP2C9 and CYP3A4 was also compared with known inducers (rifampicin and dioxin). Agomelatine was not an inducer of the CYP450-related monoxygenase activities tested: acetanilide hydroxylase (CYP1A2), tolbutamide 4-hydroxylase (CYP2C9) and cyclosporin A oxidase (CYP3A4).

Overall, dihydrodiol metabolite formation, 3-hydroxy-7-desmethylation and 3-hydroxylation were found to be the major circulating metabolic pathways of agomelatine in human with respectively 28.3%, 27.5% and 10.3% of the circulating radioactivity.

The non conjugated metabolites having some pharmacological activity (3-hydroxy (S 21540) and 7-desmethyl (S 21517) were not detected in plasma at therapeutic doses.

Urinary excretion of unchanged agomelatine was negligible (0.01% of an intravenous dose). Following oral administration, urine was the main route of excretion of metabolites (mainly glucuronides): 80.6 ± 3.6% of the [^{14}C]-agomelatine dose (PKH-012) and 78 ± 4.7% of the [^{3}H]-agomelatine dose. Elimination of agomelatine was rapid with a mean Cl ~1100mL/min and a mean $t_{1/2}$ ~1h, thus accumulation is not foreseeable.

- Dose proportionality and time dependencies

A clear dose dependency was observed for oral doses above 50 mg, consistent with saturation of the first pass effect. Upon repeated dose administration, no accumulation effect was observed, consistent with the short terminal half-life of agomelatine.

The inter-individual variability of agomelatine exposure was large (CV between 40 and 160%), probably due to the individual variation of CYP 1A2 activity. The intra-individual variability was also large (123%) probably due to the variation of the first-pass effect.

There was no difference between healthy volunteers and patients pharmacokinetic parameters.

- Special populations

Impaired renal function: In subjects with severe renal impairment the pharmacokinetic parameters C_{max} and AUC were slightly higher than in healthy subjects. However, due to the high interindividual variability (90% Confidence Intervals for Cmax and AUC were 0.397 – 5.02 and 0.407 – 3.78, respectively) of agomelatine pharmacokinetics, this result was not clinically relevant. Renal impairment did not affect the protein binding of agomelatine.

Impaired hepatic function: Following a single oral dose of 25mg agomelatine in patients with hepatic impairment, C_{max} increased by a factor of ~60 and ~110, while AUC increased by ~70-times and ~140-times, in mild (Child-Pugh score of 5 or 6) and moderate (Child-Pugh score of 7 to 9) hepatic impairment, respectively. Both mild and moderate liver impairment increased the half-life of agomelatine by a factor of ~3. The unbound fraction of agomelatine was also increased in subjects with hepatic insufficiency. The interindividual variability decreased with mild hepatic impairment, with a further decrease in moderate hepatic impairment, suggesting a progressive saturation of the hepatic first-pass effect. Agomelatine should therefore be contraindicated in patients with hepatic insufficiency.

Gender, smoking and age: No significant difference in exposure was shown between the young and the elderly as well as between males and females. Nevertheless, females were more exposed than men. A 3.7-fold decrease in mean exposure was observed in heavy smokers; this decrease was larger in young volunteers (factor 7-9.5) than in elderly ones (factor 1.3-2.4) suggesting that cigarette smoke could induce CYP 1A2 involved in the metabolism of agomelatine.

- Pharmacokinetic interaction studies

The use of specific inhibitors of various CYP450 isoenzymes in human liver microsomes showed that CYP1A and CYP2C were the main enzymes responsible for the metabolism of agomelatine. In human, the principal isoenzymes were CYP1A2 together with CYP2C9, CYP2C19 and CYP1A1 (extrahepatic) to a lesser extent.

Based on *in vitro* results, pharmacokinetic interaction studies in human volunteers were performed with fluvoxamine, theophylline paroxetine, fluconazole, lorazepam lithium and ethanol. The only significant interaction found was with fluvoxamine, which was a strong inhibitor of agomelatine metabolism, increasing the plasma C_{max} and AUC of agomelatine by 47-fold and 61-fold, respectively and by a factor of 2.5 for $t_{1/2}$.

Pharmacodynamics

- Mechanism of action

Agomelatine is a potent agonist of melatonin (MT1 and MT2) receptors with 5-HT_{2C} antagonist properties. It is also a 5-HT_{2B} antagonist. Agomelatine does not interact with adenosine, adrenergic, dopamine, GABA, muscarinic, nicotinic, histamine, excitatory amino acid, benzodiazepine and sigma receptors, nor with sodium, potassium or calcium channels.
Through its 5-HT_{2C} antagonist effect, agomelatine increases dopamine and noradrenaline release specifically in the prefrontal cortex.

- Primary and Secondary pharmacology

The rationale for the use of agomelatine in major depression is based not only on melatonin agonist properties of agomelatine but also on its 5-HT_{2C} antagonist properties. A pure melatoninergic action is not necessarily antidepressant and the combination with the 5-HT_{2C} antagonist action in agomelatine may be needed. Agomelatine showed only minor biological effects in the phase I and II pharmacodynamic studies. Sleep EEG indicated a possible sleep improvement and an advance in sleep onset at low doses of agomelatine. Wake EEG after morning administration of agomelatine pointed towards a mild sedative effect. The results of wake EEG after evening administration were inconclusive. Different subjective rating scales indicated no powerful sedative or activating effect in healthy volunteers. As an adverse event, sedation was observed in healthy volunteers independently of

administration time (morning or evening). For the core body temperature, a slight, but not consistent temperature decrease was seen. Comparing venlafaxine and agomelatine with regard to sexual function and sexual dysfunction, there was a numerical trend in favour of agomelatine on all scores; only some of the secondary measures showed statistically significant differences.

Clinical efficacy

The efficacy and safety of agomelatine in major depressive disorder were studied in a clinical development programme in which agomelatine was administered to more than 2400 patients and 400 healthy volunteers in 25 countries in Europe, Africa, South America, Australia and North America.
The development programme for short-term efficacy consisted of one pilot study (CL2-007) and six short-term placebo-controlled efficacy studies in MDD [one dose-finding study (CL2-014) and five other studies (CL3-022, -023, -024, -042 and -043)]. One placebo-controlled study in an elderly population (CL3-026) and one dose response study in partial responders (without placebo) (CL3-025) were also performed. Long-term efficacy was examined in a relapse prevention study (CL3-021), and three double-blind placebo-controlled extensions of short-term studies (CL3-022, -023, -024 extensions).

Long-term safety was investigated for 1-year treatment exposure in three studies, one double-blind, placebo-controlled (CL3-021) and two open-label (CL3-025 and CL3-029) and, for 6-month treatment exposure in five placebo-controlled studies (CL3-022, -023, -024, -026 and -027).

Five clinical studies were designed to evaluate particular aspects of safety. Three studies were performed in healthy volunteers, two assessed safety on gonadotrophic function (CL1-032, CL1-034) and one cardiovascular safety (CL1-033). Two active controlled studies investigated specific aspects of safety in MDD patients *i.e.* possible discontinuation syndrome (CL3-030) and impact on sexual function (CL3-036). Two other pilot studies which aimed at evaluating agomelatine in largely resistant hospitalised depressed patients (CL3-027) and Bipolar I depressed patients (CL3-029) were also conducted.

Five studies in MDD were on-going at the time of submission: an active-controlled study evaluating the efficacy on subjective sleep (CL3-035), an open polysomnography study (CL3-038), two double-blind 46-week agomelatine extension studies (CL3-042, CL3-043 extensions) and a relapse prevention study (CL3-041). In addition, a recurrence prevention study in seasonal affective disorder (CL3-037) and a pilot study in generalised anxiety disorder (CL2-040) were ongoing at the time of submission.

In the early agomelatine development programme, studies in patients with other diseases, such as sleep/wake disorders (delayed sleep phase syndrome, primary insomnia, sleep/wake disorders in blind patients or in demented patients) and schizophrenia as add-on therapy, were performed. A pilot open study was also performed in children suffering from Smith-Magenis syndrome, a rare genetic disease of which a characteristic feature is an inversion of melatonin rhythm (CL2-044).

Table 5 below describes the clinical efficacy studies on agomelatine.

Table 5: Summary clinical efficacy studies on agomelatine

Study ID	Design	Study Posology	Study Objective	No of Subjects	Duration	Diagn.	Primary Endpoint	Extension
CL2-007	Randomised parallel groups	Agomelatine 5 and 100 mg o.d.	Pilot study - Efficacy	28	4 weeks	MDD	MADRS	4 weeks
CL2-014	Double blind Placebo controlled	Agomelatine 1, 5 and 25 mg o.d. vs placebo. Active control paroxetine 20 mg o.d.	Efficacy and safety	711	8 weeks	MDD Bipolar II	HAM-D	
CL3-025	Randomised double blind parallel groups	Agomelatine 25, 25-50 mg o.d.	Efficacy and safety Dose escalation Partial responders	448	4 + 4 weeks	MDD with partial response to 4 weeks / 25 mg	HAM-D	16 weeks + optional 24 weeks open
CL3-042	Randomised double blind parallel groups	Agomelatine 25-50 mg o.d. vs placebo	Efficacy and safety	238	6 weeks	MDD	HAM-D	46 weeks
CL3-043	Randomised double blind parallel groups	Agomelatine 25-50 mg o.d. vs placebo	Efficacy and safety	212	6 weeks	MDD	HAM-D	46 weeks
CL3-022	Randomised double blind parallel groups	Agomelatine 25 mg Fluoxetine 20 mg Placebo	Efficacy and safety	419	6 weeks	MDD	HAM-D	18 weeks
CL3-023	Randomised double blind parallel groups	Agomelatine 25 mg Paroxetine 20 mg Placebo	Efficacy and safety	418	6 weeks	MDD	HAM-D	18 weeks
CL3-024	Randomised double blind parallel groups	Agomelatine 25-50 mg Fluoxetine 20 mg Placebo	Efficacy and safety	607	6 weeks	MDD	HAM-D	18 weeks
CL3-026	Randomised double blind parallel groups	Agomelatine 25 mg Placebo	Efficacy and safety in elderly patients	220	6 weeks	MDD	MADRS	18 weeks
CL3-021	Randomised double blind parallel groups	Agomelatine 25 mg vs. placebo	Relapse prevention	367	34 weeks	MDD	HAM-D	18 weeks
CL3-036	Randomised double blind parallel groups	Agomelatine 50 mg Venlafaxine 150 mg	Sexual function of remitted patients	277	12 weeks	MDD	SEX FX	12 weeks
CL3-035	Randomised double blind parallel groups	Agomelatine 25-50 mg Venlafaxine 75-150 mg	Sleep function	344	6 weeks	MDD	LSEQ	18 weeks

METHODS

Treatments

The treatments in different studies are presented in Table 5 above.

Objectives

Objective of all the main studies was to study efficacy and safety of agomelatine in the treatment of major depressive disorder (or related areas, like sleep, sexual function).

Study Participants
Patients entering the placebo-controlled efficacy studies on agomelatine were required to satisfy the DSM-IV diagnostic criteria for Major Depressive Disorder (MDD), single or recurrent episode (American Psychiatric Association, 1994). A minimum severity of depression on the HAM-D (17-item HAM-D total score ≥ 22) was defined for entry into all protocols except for the study in elderly (CL3-026) where a severity was defined on the MADRS (MADRS total score ≥ 24). In addition in two studies (CL2-014 and CL3-022) patients were required to have a minimum severity of ≥ 4 (moderate severity of illness) on the clinical global impression severity scale (CGI-S). Patients with a significant risk of suicide judged by the clinician were excluded from all studies and, in most of the placebo-controlled studies patients with a score of three or more on the HAM-D suicide item were also excluded. A washout was required for patients treated previously with psychotropic medications that were contra-indicated in the protocols. Concomitant treatment with drugs thought to interfere with study evaluations (central α blockers, systemic corticosteroids and exogenous melatonin) was also not allowed. Stabilized (at least one month) benzodiazepines (BZDs) were allowed at limited doses in most studies except study CL3-043 where the use of any BZDs was contra-indicated. Short-term use of an occasional limited dose (single tablet) of hypnotics (zolpidem or zopiclone) was allowed for the first two weeks of most studies.

Outcomes/endpoints
The primary efficacy outcome measure was the 17-item HAM-D total score for all protocols, except for protocol CL3-026 where the MADRS total score was used to avoid an overrating of somatic complaints in elderly patients. Secondary efficacy outcome measures for depression were the MADRS and HAM-D total scores (where they were not used as primary) except for studies CL3-042 and CL3-043, and the clinical global impression of severity (CGI-S) and improvement (CGI-I). StudiesCL3-036 and CL3-035 addressed sexual and sleep functions, respectively.

Statistical methods
Different patients sets were defined according to ICH E9 Guideline (CPMP/ICH/363/96, 1998). The definitions of the main patients sets were mainly the same in all the studies:
- Randomised set (RS): all patients included and randomised.
- Full analysis set (FAS) (in accordance with the intention-to-treat principle (CPMP/ICH/363/96, 1998)): Randomised patients having taken at least one dose of study medication and having at least one post-baseline value for the primary efficacy criterion (for any efficacy criterion for studies CL3-042 and CL3-043) over the mandatory double-blind period.

Details of the statistical methods used are given in Table 6 below.

Table 6: Statistical methods for short-term placebo-controlled efficacy studies used in main and assay-sensitivity (if applicable) analyses (on the primary efficacy criterion-main analytical approach)

Study	Objective	Comparison	Main analysis set	Statistical methodology	Significance level
CL2-014	Dose finding (difference *vs* placebo)	Three agomelatine doses (1, 5, 25mg *o.d.*) *vs* placebo	FAS	One-way analysis of variance on factor treatment One-way analysis of covariance on factor treatment with baseline as covariate Dunnett's test for comparison with placebo (multiplicity correction)	Two-sided type I error = 0.05
	Assay-sensitivity	Active control *vs* placebo		Two-sided Student's t test for independent samples	Two-sided type I error = 0.05
CL3-022 CL3-023 CL3-024	Superiority *vs* placebo	Agomelatine 25mg *vs* placebo	FAS	Two-sided Student's t test for independent samples Two-way analysis of covariance on factors treatment and centre (random effect) with baseline as covariate and without interaction	Two-sided type I error = 0.05
	Assay-sensitivity	Active control *vs* placebo		Same analyses	Two-sided type I error = 0.05
CL3-026	Superiority *vs* placebo	Agomelatine 25mg *vs* placebo	FAS	Two-sided Student's t test for independent samples Analysis of variance on factors treatment, age, sex and geographic zone	Two-sided type I error = 0.05
CL3-042 CL3-043	Superiority *vs* placebo	Flexible dose agomelatine (25-50mg *o.d.*) *vs* placebo	FAS	Two-sided Student's t test for independent samples Two-way analysis of covariance on factors treatment and centre (random effect) with baseline as covariate and without interaction	Two-sided type I error = 0.05

RESULTS

- Dose response studies

Study CL2-007: Pilot double-blind, randomised, non-placebo-controlled, parallel group study on safety and efficacy of agomelatine at a dose of 5mg or 100mg once a day for one month in patients with a Major Depressive Episode.

Repeated administration of agomelatine 5mg or 100mg once daily for four weeks had similar antidepressant activity, with no impairment of the vigilance and performances. Both doses were well tolerated.

Study CL2-014: Dose-finding study. Efficacy and safety of 3 doses of agomelatine (1, 5 and 25mg) given orally once a day for 8 weeks versus placebo in patients with Major Depressive Disorder or bipolar depression (bipolar II). Double-blind, placebo controlled study (using paroxetine 20mg as positive control).

Baseline data

No relevant between-group differences were observed at baseline. The mean age of the patients was 42.3 years [19-65]; two thirds of them were female patients. They had a diagnosis of Major Depressive Disorder according to DSM-IV criteria, single (31.1%) or recurrent episode (67.1%) or a diagnosis of Bipolar II Disorder according to DSM-IV criteria (1.8%). They had a mean number of 2.7 MDE and the mean duration of their current episode was 5.0 months. At selection, 19.3% of the patients were hospitalized.

Outcomes and estimation

There was a statistically significant difference between the 25mg agomelatine dose and placebo ($p < 0.034$), as well as between paroxetine and placebo in the HAM-D total score (see Table 7 below). No difference was seen with the doses of 1 and 5mg.

Table 7: Agomelatine – Primary efficacy result (8 weeks): 17-item HAM-D total score (FAS) (CL2-014, NP07859)

Week	Treatment group	No. of patients	Mean score	SD	p-value[1]	Difference from placebo			
						Estimate	SE	95% CI	p-value[2]
HAM-D total score									
Baseline	agomelatine 1mg	136	27.9	3.0					
	agomelatine 5mg	146	27.3	2.6					
	agomelatine 25mg	135	27.4	2.7					
	placebo	136	27.4	3.1					
W8	agomelatine 1mg	112	11.6	7.1					
	agomelatine 5mg	107	13.0	7.4					
	agomelatine 25mg	105	11.3	6.9					
	placebo	105	13.2	7.4					
Final	agomelatine 1mg	136	13.2	8.2		2.17	1.03	[-0.25; 4.58]	0.089
	agomelatine 5mg	146	14.7	8.5	0.037	0.64	1.01	[-1.73; 3.01]	0.861
	agomelatine 25mg	135	12.8	8.2		2.57	1.03	[0.15; 4.99]	0.034
	placebo	136	15.3	8.9					

[1] One way ANOVA with replications *SD: standard deviation; SE: standard error; CI: confidence interval*
[2] Dunnett's test vs placebo

Table 8 below presents an overview of the other efficacy variables.

Table 8: Agomelatine – Overview of placebo comparisons (p-value) on efficacy criteria (8 weeks) (CL2-014, NP07859)

Criteria		Agomelatine[1]			Paroxetine[2]
		1mg	5mg	25mg	20mg
Primary					
HAM-D total score	non adjusted	NS	NS	0.034	0.030
	adjusted	0.038	NS	0.030	0.030
Secondary					
MADRS total score		NS	NS	0.016	0.012
CGI-S		NS	NS	0.049	0.005
CGI-I		NS	NS	NS	NS
HAM-D responder		0.021	NS	0.036	NS
HAM-D remitter		NS	NS	0.010	0.034
HAM-A total score		NS	NS	0.011	0.004

[1] Dunnett's test vs placebo
[2] Student's t test vs placebo
NS: not significant

The 25 mg dose was the best dose, although dose response relationship was not clear: the 1 mg had some markers of efficacy, while the 5 mg had none.

- Main studies

Study CL3-022: Efficacy and safety of fixed dose agomelatine (25mg) given orally once a day for 6 weeks versus placebo in patients with Major Depressive Disorder. A randomised double-blind, placebo-controlled 3 parallel group study (using fluoxetine 20mg as positive control) with a further 18-week double-blind extension treatment period.

The primary objective of the study was to assess the efficacy of agomelatine comparing to placebo using the HAM-D rating Scale in patients with MDD treated for 6 weeks. Secondary objective was to assess the safety on long-term use of agomelatine.

Baseline data
No relevant between-group differences were observed for demographic data or baseline characteristics. The mean age of the patients was 42.4 years [19-60]; two thirds of them were female. They had a mean of 2.7 MDE and the median duration of their current episode was 72 days. At selection, 13.4% of the patients were hospitalised. About 50% of the patients received concomitant benzodiazepine treatment during the acute period.

Outcomes and estimation
Short-term efficacy results: There was no statistically significant difference between the agomelatine and the placebo groups on the HAM-D total score. There was a statistically significant difference between the agomelatine and the placebo groups on the CGI-I. There were no statistically significant differences between agomelatine and placebo groups with respect to MADRS total score, response (53% versus 47%, respectively) or remission (14% versus 16%, respectively) rates.

There was a statistically significance difference between the fluoxetine and the placebo group on the HAM-D total score, CGI-I and MADRS total score. There were no statistically significant differences between the fluoxetine and the placebo groups with respect to response (58% versus 47%, respectively) and remission (19% versus 16%, respectively) rates.

Efficacy results of the extension period: A total of 299 patients entered the extension period (73% of FAS patients). Among them, 198 patients (66.2%) were responders at the end of the acute period. The mean final HAM-D total score over the W6-W24 period were 10.0 ± 8.4, 10.7 ± 8.5 and 8.4 ± 6.5 in the agomelatine, placebo and fluoxetine groups, respectively.

Sustained response analysis: Among acute period responders in extension period 19.0%, 36.1% and 20.3% in the agomelatine, placebo and fluoxetine groups, respectively, had a loss of response over the W6-W24 period, and the survival curve analysis showed a statistically significant difference in favor of agomelatine compared to placebo ($p = 0.033$). Fluoxetine was also significantly different from placebo on this analysis ($p = 0.039$).

Relapse analysis: Among acute period responders in extension period with HAM-D total < 16 at W6, 14.3%, 33.3% and 17.8% in the agomelatine, placebo and fluoxetine groups, respectively, had a relapse over the W6-W24 period, and the survival curve analysis of the time to relapse showed a statistically significant difference in favour of agomelatine ($p = 0.017$) and fluoxetine ($p = 0.045$) compared to placebo.

Study CL3-023: Efficacy and safety of fixed dose agomelatine (25mg) given orally once a day for 6 weeks versus placebo in patients with Major Depressive Disorder. A randomised, double-blind, placebo-controlled, parallel groups study (using paroxetine 20mg as positive control) with a further 18-week optional double-blind treatment period.

Baseline data
No relevant between-group differences were observed for demographic or baseline characteristics.
The mean age of the patients was 40.9 years [18-60]; 75% were female. They had a mean of 3.0 MDE and the mean duration of their current episode was 4.4 months. At selection, 12.0% of the patients were hospitalised. About 22% of patients received concomitant benzodiazepine treatment during the acute period.

Outcomes and estimation
Both agomelatine and the active control paroxetine failed to show statistically significant differences from placebo over the 6-week acute period on the primary outcome criterion. Over the 18-week extension period (with 289 patients of which 208 were responders at the end of the acute period) no difference in maintenance of response could be shown between either agomelatine or paroxetine and placebo.

Study CL3-024: Efficacy and safety of fixed dose agomelatine (25mg and 50mg) given orally once a day for 6 weeks versus placebo in patients with Major Depressive Disorder. A randomised, double-blind, placebo-controlled, parallel group study (using fluoxetine 20mg as positive control), with a further optional 18-week double-blind extension period.

Baseline data
No relevant between-group differences were observed for the main demographic or baseline characteristics. The mean age of the patients was 40.9 years [18-65]; 72.5% of patients were female.
The mean number of Major Depressive Episodes was 3.0 and the mean duration of the current episode was 3.3 months. At selection, 3.6% of the patients were hospitalised. About 25% of the patients received benzodiazepines during the acute period.

Outcomes and estimation
Both agomelatine 25mg or 50mg, and the active control fluoxetine failed to show a statistically significant difference from placebo over the 6-week acute period on the primary outcome criterion. Over the 18-week extension period (with 449 patient of which 327 were responders at the end of the acute period), there was no statistically significant difference between either of the doses of agomelatine or fluoxetine and placebo at maintaining response in acute period responders and placebo was associated with very low relapse rate.

Study CL3-042: Efficacy and safety of fixed dose agomelatine (25mg with double-blind potential adjustment at 50mg) given orally once a day for 6 weeks in patients with Major Depressive Disorder. A randomized flexible dose double-blind, placebo-controlled parallel group study.

Baseline data
No relevant between-group differences were observed regarding demographic or baseline characteristics. The mean age of the patients was 45.0 years [18-65]; 73.5% of them were female.
The mean number of Major Depressive Episodes was 2.7 and the mean duration of the current episode was 3.9 months. The majority (95%) of the patients were out-patients. Treatment duration over the W0-W6 period was on average 39.0 days in the randomized set (RS), with a median of 42 days (range from 1 to 56 days) and no relevant differences between groups were observed. A total of 66 patients (27.7% of the RS) received benzodiazepine during treatment.

Outcomes and estimation
<u>Efficacy results in the total population:</u>

There was a statistically significant difference in favor of agomelatine, as compared to placebo, on the primary outcome criterion, HAM-D total score in the full analysis set (FAS), see Table 9 below.

Table 9: Agomelatine – Primary efficacy result (6 weeks): 17-item HAM-D total score (FAS) (CL3-042, NP15928)

Week	Treatment group	No. of patients	Mean score	SD	Difference from placebo			
					Estimate*	SE	95% CI	p-value*
HAM-D total score								
Baseline	agomelatine 25-50mg	116	27.4	2.7				
	placebo	119	27.2	2.7				
W6	agomelatine 25-50mg	104	12.8	6.9	3.44	0.91	[1.65; 5.24]	< 0.001
	placebo	106	15.8	7.4				
Final	agomelatine 25-50mg	116	13.9	7.7	3.44	0.92	[1.63; 5.26]	< 0.001
	placebo	119	17.0	7.9				

*adjusted on baseline and centre SD: standard deviation; SE: standard error; CI: confidence interval

In the analysis of the CGI scale, the agomelatine group differentiated significantly from placebo on both the CGI-severity of illness score and the CGI-Improvement score (see Table 10 below).

Table 10: Secondary efficacy result (6 weeks): rate of responders (FAS) (CL3-042, NP15928)

Week	Treatment group	No. of patients	% of responders	Difference from placebo			
				Estimate	SE	95% CI	p-value
Final	agomelatine 25-50mg	116	54.3	19.02	6.37	[6.53; 31.50]	0.003
	placebo	119	35.3				

Most agomelatine patients remained with the initial 25mg dose. In patients with poor improvement after 2 weeks with agomelatine 25mg who had a dose increase to 50mg, the improvement at endpoint was better than in patients on placebo.

Study CL3-043: Efficacy and safety of fixed dose agomelatine (25mg with double-blind potential adjustment to 50mg) given orally once a day for 6 weeks in patients with Major Depressive Disorder. A randomised flexible dose double-blind, placebo-controlled parallel group study.

Baseline data

No relevant between-group differences were observed for demographic or baseline characteristics.
The mean age of the patients was 42.5 years [18-65]; 59.9% of them were female. The mean number of Major Depressive Episodes was 2.6 and the mean duration of the current episode was 6.0 months. All patients were ambulatory. Treatment duration over the W0-W6 period was on average 40.3 days, with a median of 42 days (range from 1 to 48 days).

Outcomes and estimation

There was a statistically significant difference in favor of agomelatine, as compared to placebo, on the primary outcome criterion, HAM-D total score in the FAS, see Table 11 below.

Table 11: Agomelatine – Primary efficacy result (6 weeks): 17-item HAM-D total score (FAS) (CL3-043, NP15840)

Week	Treatment group	No. of patients	Mean score	SD	Difference from placebo			
					Estimate*	SE	95% CI	p-value*
HAM-D total score								
Baseline	agomelatine 25-50mg	106	26.5	2.8				
	placebo	105	26.7	3.0				
W6	agomelatine 25-50mg	100	13.7	7.6	2.10	1.04	[0.04; 4.16]	0.046
	placebo	94	15.9	7.3				
Final	agomelatine 25-50mg	106	14.1	7.7	2.30	1.02	[0.28; 4.31]	0.026
	placebo	105	16.5	7.4				

adjusted on baseline and centre SD: standard deviation; SE: standard error; CI: confidence interval

The results on the HAM-D total score were confirmed on the analysis of the response rate and CGI-Severity of illness score, which showed statistically significant differences in favor of agomelatine. There was no statistically significant difference between the agomelatine and placebo groups with respect to remission rates (20.8% *versus* 13.3%, respectively). Most agomelatine patients remained with the initial 25mg dose; in patients with poor improvement after 2 weeks with agomelatine 25mg who had a dose increase to 50mg, the improvement at endpoint was better than in patients on placebo.

Study CL3-021: Maintenance therapy with agomelatine (25mg) given orally once a day for the prevention of relapse in patients with recurrent depression. A randomised double-blind, placebo-controlled, parallel group, 6-month study following a 2-month open treatment with an optional 4-month double-blind extension period.

Baseline data

No relevant between-group differences in demographic or baseline characteristics were observed. The mean age of the patients of the RS was 45.7 years [19-67]; 77.9% of them were female. They had a mean number of 4.4 MDE (including the current episode) and the mean duration of their current episode was 2.5 months. At selection, 3.1% of the patients were hospitalised. A total of 26.2% of the patients received a psychotropic treatment at least once during mandatory double-blind period. The mean baseline (W8) HAM-D total score was 6.1 ± 2.9 in the agomelatine group and 6.4±3.4 in the placebo group. Treatment duration ranged from 1 to 226 days with a mean of 149.4 days over the W8-W34 period.

Outcomes and estimation

Open period results (8 weeks): The mean HAM-D total score decreased from 26.3 ± 2.9 at baseline to 8.4 ± 6.1 at W8. A total of 85.3% of patients showed response to treatment (decrease of baseline HAM-D total score ≥ 50%) at W8. The majority of patients (83.3%) also met the protocolled criterion for randomization (HAM-D total score ≤ 10 at W8).

Relapse prevention results: In the main analysis, the treatment periods W8-W34 and W10-W34 were considered, the latter allowing distinguishing rapid discontinuation signs or rebound phenomenon from early depressive relapse. 25.9% and 23.5% of patients had a relapse on agomelatine and placebo, respectively; the time to relapse showed no statistical difference between groups over the W8-W34 period. (See Table 12 below.)

Table 12: Efficacy results: Overview of time to relapse analyses (CL3-021, NP15851)

Group	No. of patients	Relapses		Cumulative incidence of relapse at W34	Cox model RR	Logrank
		N	%	E (SE) %	E (SE)	p-value
Period W8-W34 (26 weeks)						
Total population						
agomelatine 25mg	185	48	25.9	25.9 (3.36)	0.956 (0.202)	0.833
placebo	179	42	23.5	24.8 (3.40)		
Patients with baseline [HAM-D total > 25 and CGI-S ≥ 5]						
agomelatine 25mg	89	19	21.3	22.4 (4.61)	1.588 (0.484)	0.125
placebo	80	25	31.3	32.6 (5.60)		
Period W10-W34 (excluding the first 2 weeks after randomisation)						
Total population						
agomelatine 25mg	176	41	23.3	23.0 (3.31)	0.993 (0.225)	0.976
placebo	167	37	22.2	22.6 (3.36)		
Patients with baseline [HAM-D total > 25 and CGI-S ≥ 5]						
agomelatine 25mg	84	14	16.7	17.8 (4.39)	2.017 (0.685)	0.034
placebo	77	23	29.9	30.8 (5.61)		

E: Estimate; SE: Standard Error; RR: relative risk

Optional double-blind extension period (4 months) results: A total of 225 patients entered the optional double-blind extension period (118 on agomelatine and 107 on placebo). The secondary analyses of the primary criterion over the W8-W52 period did not show significant differences between treatment groups in the total population: 54 (29.2%) patients had a relapse in the agomelatine group versus 51 (28.5%) in the placebo group. In an additional analysis in the subgroup with baseline HAM-D total score > 25 and CGI-S score ≥ 5 (169 patients: 89 agomelatine, 80 placebo), the difference observed on time to relapse over W8-W52 between agomelatine and placebo was statistically significant (Logrank, p = 0.046; Cox RR = 1.749).

Overall, this relapse prevention study failed to show a significant effect of agomelatine 25mg compared to placebo on the primary criterion in the total population.

- Analysis performed across trials (pooled analyses and meta-analysis)

The efficacy of agomelatine in Major Depressive Disorder (MDD) was evaluated primarily on short-term in six randomised, double-blind, placebo-controlled, multicentre studies in adults using the 17-item HAM-D total score as pre-specified primary endpoint (CL2-014, CL3-022, -023, -024, -042 and -043). One additional specific randomised double-blind placebo-controlled study evaluated the antidepressant efficacy of agomelatine on short-term in elderly patients, using the MADRS total score (CL3-026).

Meta-analyses were conducted on three different pools of placebo-controlled adult studies in order to examine the overall effect of agomelatine, to evaluate the efficacy of agomelatine on specific criteria (anxiety and sleep items of HAM-D, CGI scores) or in subpopulations and to evaluate the effect of agomelatine on sleep symptoms using the Leeds Sleep Evaluation Questionnaire (LSEQ).

The antidepressant efficacy of agomelatine 25 or 25-50mg was investigated in three placebo-controlled studies (CL2-014, CL3-042, -043), that showed statistically significant differences from placebo on the primary outcome criterion HAM-D total score and consistent results across secondary criteria (see Tables 13-16). Two studies (CL-023, CL-024) were inconclusive studies (also positive control failed), and in CL-022 agomelatine failed to show efficacy whereas fluoxetine showed positive effect.

Table 13: Overview of short-term primary effect results for the study primary outcome criterion HAM-D total score in placebo-controlled studies (FAS) W0-W6/W0-W8

Study (duration) Treatment group	No. of patients	Baseline score		Final score		Difference from placebo [1] (FAS, LOCF)			
		Mean	SD	mean	SD	Estimate	SE	95% CI	p-value
CL2-014 (8 weeks) [2]									
agomelatine 1mg	136	27.9	3.0	13.2	8.2	2.17	1.03	[-0.25; 4.58]	0.089
agomelatine 5mg	146	27.3	2.6	14.7	8.5	0.64	1.01	[-1.73; 3.01]	0.861
agomelatine 25mg	135	27.4	2.7	12.8	8.2	2.57	1.03	[0.15; 4.99]	0.034
placebo	136	27.4	3.1	15.3	8.9				
paroxetine 20mg	144	27.3	3.4	13.1	8.4	2.25	1.03	[0.22; 4.28]	0.030
CL3-042 (6 weeks)									
agomelatine 25-50mg	116	27.4	2.7	13.9	7.7	3.44	0.92	[1.63; 5.26]	< 0.001
placebo	119	27.2	2.7	17.0	7.9				
CL3-043 (6 weeks)									
agomelatine 25-50mg	106	26.5	2.8	14.1	7.7	2.30	1.02	[0.28; 4.31]	0.026
placebo	105	26.7	3.0	16.5	7.4				
CL3-022 (6 weeks)									
agomelatine 25mg	129	27.6	2.9	14.5	8.2	1.17	0.90	[-0.59; 2.94]	0.193
placebo	147	28.0	3.6	15.9	8.6				
fluoxetine 20mg	133	27.5	2.8	13.3	7.6	2.55	0.89	[0.80; 4.31]	0.005
CL3-023 (6 weeks)									
agomelatine 25mg	141	25.7	2.8	13.0	8.0	0.63	0.93	[-1.21; 2.46]	0.504
placebo	137	26.0	2.7	13.8	8.0				
paroxetine 20mg	137	26.1	2.9	12.2	8.1	1.58	0.94	[-0.27; 3.43]	0.095
CL3-024 (6 weeks)									
agomelatine 25mg	148	26.4	3.0	12.0	8.2	0.90	0.86	[-0.78; 2.58]	0.291
agomelatine 50mg	147	26.5	3.4	13.4	8.2	-0.41	0.86	[-2.10; 1.27]	0.629
placebo	158	26.9	3.4	13.4	8.4				
fluoxetine 20mg	146	26.5	3.4	12.5	7.4	0.53	0.86	[-1.16; 2.22]	0.538

SD: standard deviation; SE: standard error; CI: confidence interval

[1] Covariance analysis with adjustment for centre and baseline except for study CL2-014

[2] Study CL2-014: treatment effect (agomelatine doses and placebo: analysis of variance (p=0.037)); Dunnett's test for pairwise comparison of agomelatine with placebo; two-tailed Student's t test for comparison of paroxetine and placebo

In the pool of all placebo-controlled studies (positive, negative and failed studies), including all tested agomelatine doses, treatment effects were in favour of agomelatine (heterogenicity test, p = 0.131) and the meta-analysis demonstrated a significant difference of 1.55 (95% CI [0.61; 2.48]) in favour of agomelatine on the primary outcome criterion HAM-D total score.

In the positive placebo controlled studies at therapeutic doses (25, 50 mg, see table 14) the treatment effects were in favour of agomelatine. The meta-analysis demonstrated a significant difference of 2.86 (95% CI [1.75; 3.97]) in favour of agomelatine on the primary outcome criterion HAM-D total score, as well as on secondary efficacy criteria compared to placebo (see Tables 15 and 16).

Table 14: Agomelatine – Placebo comparisons on primary and secondary efficacy criteria in studies CL2-014, CL3-042, CL3-043 (FAS) W0-W6/W0-W8

Study (duration)	Primary criterion	Secondary criteria				
	HAM-D total	CGI-S	CGI-I	HAM-D responder	HAM-D remission	MADRS total
CL2-014 (8 weeks) agomelatine 25mg	+	+	NS	+	+	+
CL3-042 (6 weeks) agomelatine 25-50mg	+	+	+	+	not done	not used
CL3-043 (6 weeks) agomelatine 25-50mg	+	+	NS	+	NS	not used

Placebo comparisons: +: significant difference in favour of agomelatine (p < 0.05) NS: not significant

Table 15: HAM-D total score, W0-W6/W0-W8, meta-analysis of the positive placebo-controlled studies (CL2-014, CL3-042, CL3-043) (FAS)

		Baseline		Final		Difference from placebo (LOCF)		
	N	mean	SD	mean	SD	E	SE	95% CI
HAM-D total								
agomelatine 25-50mg	358	27.1	2.8	13.6	7.9	2.86	0.56	[1.75; 3.97]
placebo	363	27.1	3.0	16.5	8.4			

Table 16: Secondary efficacy criteria, W0-W6/W0-W8, meta-analysis of the positive placebo-controlled studies (CL2-014, CL3-042, CL3-043) (FAS)

		Baseline		Final		Difference from placebo (LOCF)		
	N	mean	SD	mean	SD	E	SE	95% CI
CGI-S								
agomelatine 25-50mg	358	4.8	0.7	3.0	1.4	0.47	0.10	[0.26; 0.67]
placebo	363	4.9	0.7	3.5	1.4			
CGI-I								
agomelatine 25-50mg	358	-		2.3	1.2	0.35	0.09	[0.17; 0.52]
placebo	362	-		2.6	1.2			
HAM-D response (↓ HAM-D total ≥ 50%)								
agomelatine 25-50mg	358	-		55.3%		16.51	3.65	[9.37; 23.66]
placebo	363	-		38.8%				
CGI-I response (CGI-I = 1 or 2)								
agomelatine 25-50mg	358	-		63.1%		16.84	3.64	[9.72; 23.97]
placebo	362	-		46.4%				
HAM-D remission (HAM-D total ≤ 6)								
agomelatine 25-50mg	358	-		22.9%		8.66	2.82	[3.13; 14.19]
placebo	363	-		13.8%				

SD: standard deviation; E: estimate; SE: standard error; CI: confidence interval - Meta-analytic estimation (without adjustment)
LOCF values over W0-W6 except for study CL2-014 (W0-W8)

The efficacy of agomelatine in the elderly was evaluated in comparison with placebo in the meta-analysis performed on data from the elderly patients aged 60 and above in three placebo-controlled studies (CL2-014, CL3-042 and CL3-043). Agomelatine revealed significantly greater efficacy than placebo in the elderly subgroup, as measured on the primary HAM-D measure. The magnitude of the agomelatine placebo difference in the elderly was 4.50 points (p=0.033).

- Clinical studies in special populations

Study CL3-026: Efficacy and safety of fixed dose agomelatine (25mg) given orally once a day for 6 weeks in elderly (>60 years) patients with Major Depressive Disorder. A randomised double-blind, placebo-controlled parallel groups study with a further 18-week double-blind extension period.

Short-term efficacy results: No statistically significant difference was observed between the agomelatine and the placebo groups on primary outcome criterion MADRS total score, nor in the secondary efficacy criteria HAM-D total score, CGI scores or MADRS secondary expressions (responder and remission rates).

Efficacy results of the double-blind extension period: A total of 127 patients entered the extension period; 94 (74.0%) were responders at the end of the acute period. The mean final MADRS total score over the W6-W24 period were 10.6 ± 9.4 in the agomelatine group and 9.6 ± 8.7 in the placebo group.

- Supportive studies

Study CL3-025: Efficacy and safety of agomelatine 50mg/day in patients with Major Depressive Disorder with partial response to 4-week treatment with agomelatine 25mg/day. A randomised double-blind, parallel groups, 4-week study, with a further 4-month double-blind extension period and with a 12-month open study for responder patients.

Baseline data
The demographic and baseline characteristics of partial responder patients randomised in the acute double-blind period showed no relevant between-group differences. The mean age of the patients was 43.8 years [18-69] and 75.0% were female.

Outcomes and estimation
The primary analysis of the response on HAM-D total score over the W4-W8 period showed no statistically significant difference between agomelatine 25mg and agomelatine 50mg groups (see Table 17 below).

Table 17: Primary efficacy result (acute double-blind period): response on HAM-D total score (FAS) (CL3-025, NP15926) W4-W8

Week	Treatment group	No. of patients	Response rate (%)	agomelatine 25mg minus agomelatine 50mg			
				Mean	SE	95% CI	p-value
W8	agomelatine 25mg	78	64.1				
	agomelatine 50mg	100	64.0				
Final	agomelatine 25mg	86	59.3	-3.55	7.09	[-17.46; 10.35]	0.616
	agomelatine 50mg	105	62.9				

SE: standard error; CI: confidence interval

Additional long-term data became available during the procedure from two 6-month venlafaxine comparative studies:

Study CL3-035: Efficacy of agomelatine (25 mg with potential adjustment at 50 mg) given orally for 6 weeks versus venlafaxine on subjective sleep evaluation of patients with Major Depressive Disorder. A randomized double-blind parallel group study, with an optional continuation for 18 weeks.

Baseline data
No relevant between-group differences were observed for the main demographic data and baseline characteristics. The mean age ± SD was 40.1 ± 10.5 years and 71.1% of the patients were female. On average 2.2 ± 1.9 depressive episodes, including the current one, were reported; the median duration of the current episode was 2.8 months.

Outcomes and estimation
The primary objective of this study was to demonstrate that agomelatine improved subjective sleep faster than venlafaxine in patients suffering from major depressive disorder. The mean LSEQ getting off to sleep score decreased over the week 0 –week 6 period in both treatment groups showing a continuing improvement in the patients' falling asleep. From the week 1 the mean score was statistically significantly lower in agomelatine group than in venlafaxine group and remainedlower up to week 6 visit as well as the last value (p=0.008).

In the analyses of the long-term efficacy (secondary objective), agomelatine 25-50 mg was shown to be superior to venlafaxine 75-150mg (p=0.025) over 6 months. The magnitude of the difference on CGI-I in favour of agomelatine at 6 months (0.32 points) was similar to the difference observed between agomelatine and placebo in the meta-analysis of the three pivotal short-term, placebo-controlled studies (CL2-014, CL3-042, CL3-043). This result was supported by trends in favour of agomelatine in the long-term analysis on the remitters (60.0% versus 50.3% respectively, p=0.076).

Study CL3-036: Sexual function after 3 months of treatment with agomelatine (50 mg/day) in stable remitted depressed patients. A 3-month, randomised, double-blind study, versus venlafaxine (150 mg/day) with an optional period of additional 3 months.

Baseline data
No relevant between-group differences were observed for the main demographic data and baseline characteristics. The mean age ± SD was 40.9 ± 10.2 years and 71.8% of the patients were female. On average 2.4 ± 1.4 depressive episodes, including the current one, were reported; the median duration of the current episode was 3.0 months.

Outcomes and estimation
The primary objective of the study was to compare the global sexual function, assessed by the Sex Effects scale (SEX FX total core) of remitted depressed patients treated with agomelatine 50 mg with that of remitted depressed patients treated with venlafaxine 150 mg from baseline to week 12. The dose of venlafaxine was raised in all patients from 75mg to 150mg at 2 weeks but the dose of agomelatine was fixed from the beginning of the study. The SEX FX-results are presented in Table 18 below.

Table 18: SEXFX: Sexual dysfunction – Analysis at the end of the 12-week period in remitted patients with sexual activity at baseline – Study CL3-036 (N=276)

SEXFX sub-score	Treatment group		Patients with dysfunction		Difference between groups venlafaxine minus agomelatine	
		N	n	%	95% CI	p-value
Drive-Desire/Arousal	agomelatine 50mg	60	12	20.0		
	venlafaxine 150mg	51	21	41.2	[4.30; 38.05]	0.015
Orgasm	agomelatine 50mg	60	12	20.0		
	venlafaxine 150mg	51	24	47.1	[10.03; 44.09]	0.002

CI: confidence interval
N: number of remitted patients
n: number of remitted patients with dysfunction at W12
%: (n/N) x 100

In the analyses of the long-term efficacy (secondary objective), agomelatine 50mg was not inferior to venlafaxine 150mg (p=0.006) over 6 months using -2 points on the total MADRS as the non-inferiority margin.

- Discussion on clinical efficacy

The clinical development programme of agomelatine was large and well-conducted, and also GCP-compliant according to the applicant.

The demonstration of efficacy of agomelatine in the treatment of major depression was not conclusive. The issues identified were the following:

The dose-finding process for agomelatine was not optimal. In the overall clinical program it was difficult to distinguish greater efficacy with the dose of 50 mg in comparison to the initial recommended dose 25 mg, although a fraction of the patients improved from this dose increase.

Demonstration of short-term efficacy: At short-term (6 weeks) three trials (including the dose-finding one) were able to discriminate agomelatine from placebo. In the flexible dose design trials the rate of responders in agomelatine was superior to placebo. Out of these 3 trials only one (CL2-014) had an active comparator arm (paroxetine 20 mg). The effect size of agomelatine and paroxetine were in the same range. Four other trials including the trial on elderly patients failed to discriminate from placebo. One of these trials had assay sensitivity because fluoxetine, used as a comparator, did discriminate from placebo, which suggests that the effect size of agomelatine was smaller than fluoxetine 20 mg. It is noteworthy that in all trials fairly severe patients were enrolled excluding the explanation that the failure was due to a "flooring effect". The effect size measured

from baseline to endpoint was large in both active- and placebo-treated groups. Taken together, the data from the short-term efficacy trials could indicate that agomelatine 25 to 50 mg in the treatment of major depression exerted a clinical effect the magnitude of which could not lead to firm conclusion of clinical efficacy.

Demonstration of long-term efficacy: There was only one pivotal long-term trial (relapse prevention trial) and this failed to discriminate agomelatine from placebo. Data on long-term efficacy could also be derived from a) a double-blind extension of a short-term trial and b) two double-blind venlafaxine-controlled trials conducted in MDD patients to study sleep disturbances or sexual dysfunction. However, even though the applicant analysed all the available data in various ways, and even though these data may have pointed towards maintenance of efficacy, none of these analyses were conclusive (studies were not primarily designed to evaluate long-term efficacy). Further, the data from venlafaxine-controlled trials had major methodological shortcomings, e.g. they did not have depression as the primary variable, and the evaluation of depression was based only on CGI score in CL3-035 and on MADRS score in CL3-036-study. Thus, these data were suggestive of a beneficial effect of agomelatine in the long-term treatment of major depression, but could not be considered conclusive.

Clinical safety

The safety of agomelatine was investigated in 51 completed studies and 6 on-going studies at the time of submission. Among these studies, 26 studies were conducted in healthy or patient volunteers.

- Patient exposure

A total of 3476 patients were exposed to agomelatine. Of these, 2757 were suffering from Major Depressive Disorder. 200 patients received agomelatine 25 mg for 350 days or more.

The short-term, double-blind, placebo-controlled, MDD Safety Set included 1120 patients receiving agomelatine at 25/50 mg doses. The long-term, double-blind, placebo-controlled, MDD Safety Set included 511 depressed patients treated up to 24 weeks with agomelatine 25/50 mg. 273 patients in the MDD population were 60 years or older.

Table 19: Number of individuals who received at least one dose of agomelatine

No. of individuals	Healthy or patient volunteers	MDD patients[1]	Non depressed patients	All exposed
Completed studies	476	2757	719[2]	3952[2]
On-going studies	-	708	-[2]	708[2]

[1] *including bipolar and largely resistant hospitalised patients*
[2] *in addition, 9 children with Smith-Magenis Syndrome exposed to agomelatine and 33 patients of cross-over studies who have not received agomelatine in the first treatment period were not taken into account, according to OSA rules*

- Adverse events

The short-term, double-blind placebo-controlled MDD safety set.
The commonly reported adverse events (> 1%) in the pooled group of agomelatine 25/50 mg, placebo and active comparators are detailed in Table 22.

Of the most commonly reported adverse events, dizziness (exc vertigo) was observed with a significantly higher frequency in the agomelatine 25/50 mg group than in the placebo group. Other frequently reported emergent adverse events were nausea, dry mouth, somnolence, diarrhoea NOS and abdominal pain upper.

In addition, the following less commonly reported adverse events had a higher incidence in the agomelatine 25/50 mg group than in the placebo group: paraesthesia NEC, migraine NOS, sweating increased, blurred vision, anxiety NEC, pruritus NOS, abnormal dreams, aggravated anxiety, irritability.

Table 20. Common emergent adverse events by SOC and PT (≥ 1% in the agomelatine group) in the short-term double-blind placebo-controlled MDD safety set (W0-W6/W8).

Primary SOC Preferred term	agomelatine 25/50mg (N=1120)		placebo (N=998)		fluoxetine 20mg (N=284)		paroxetine 20mg (N=283)	
	n	%	n	%	n	%	n	%
ALL	**591**	**52.8**	**515**	**51.6**	**140**	**49.3**	**191**	**67.5**
Nervous system disorders	**297**	**26.5**	**232**	**23.2**	**63**	**22.2**	**85**	**30.0**
Headache NOS	153	13.7	140	14.0	34	12.0	38	13.4
Dizziness (exc vertigo)	61	5.4	31	3.1	8	2.8	10	3.5
Somnolence	32	2.9	23	2.3	10	3.5	21	7.4
Insomnia NEC	24	2.1	21	2.1	10	3.5	12	4.2
Migraine NOS	12	1.1	4	0.4	2	0.7	1	0.4
Gastrointestinal disorders	**217**	**19.4**	**185**	**18.5**	**66**	**23.2**	**88**	**31.1**
Nausea	86	7.7	71	7.1	20	7.0	45	15.9
Dry mouth	37	3.3	30	3.0	16	5.6	16	5.7
Diarrhoea NOS	32	2.9	22	2.2	11	3.9	14	4.9
Abdominal pain upper	26	2.3	13	1.3	5	1.8	1	0.4
Constipation	19	1.7	21	2.1	3	1.1	5	1.8
Dyspepsia	18	1.6	15	1.5	3	1.1	3	1.1
Infections and infestations	**120**	**10.7**	**94**	**9.4**	**22**	**7.7**	**30**	**10.6**
Nasopharyngitis	25	2.2	25	2.5	2	0.7	6	2.1
Influenza	22	2.0	18	1.8	5	1.8	4	1.4
Psychiatric disorders	**95**	**8.5**	**69**	**6.9**	**19**	**6.7**	**31**	**11.0**
Anxiety NEC	14	1.3	8	0.8	4	1.4	5	1.8
Depression aggravated	13	1.2	12	1.2	1	0.4	3	1.1
General disorders and administration site conditions	**66**	**5.9**	**61**	**6.1**	**11**	**3.9**	**28**	**9.9**
Fatigue	28	2.5	21	2.1	4	1.4	12	4.2
Skin and subcutaneous tissue disorders	**56**	**5.0**	**37**	**3.7**	**17**	**6.0**	**18**	**6.4**
Sweating increased	15	1.3	7	0.7	8	2.8	8	2.8
Musculoskeletal, connective tissue and bone disorders	**51**	**4.6**	**55**	**5.5**	**13**	**4.6**	**10**	**3.5**
Back pain	15	1.3	13	1.3	3	1.1	2	0.7
Ear and labyrinth disorders	**16**	**1.4**	**17**	**1.7**	**11**	**3.9**	**3**	**1.1**
Vertigo NEC	12	1.1	12	1.1	6	2.1	3	1.1

SOC: System Organ Class, PT: Preferred Term, NOS: Not Otherwise Specified, NEC: Not Elsewhere Classified
N: number of patients by group
n: number of patients with at least one emergent AE in a given preferred term or in a given SOC
%: (n/N) x 100

Agomelatine at the 50 mg dose appeared to cause a slightly higher rate of AEs than at the 25 mg dose.

In the short-term double-blind placebo-controlled MDD studies, the most frequent emergent adverse events on agomelatine 25/50mg occurred mainly within the first 2 weeks of treatment, with a secondary peak of frequency after 3 to 4 weeks of treatment for diarrhoea and upper abdominal pain. Therefore, the majority of patients experienced emergent adverse events within the first month of treatment.

The long-term double-blind placebo-controlled MDD safety set.
Adverse events reported by at least 1% of patients are listed in Table 21.

Table 21. Common emergent adverse events by SOC and PT (≥1% in the agomelatine group) in the long-term double-blind placebo-controlled MDD safety set (W6-W24).

Primary SOC Preferred Term	agomelatine 25/50mg (N=511)		placebo (N=406)		fluoxetine 20mg (N=222)		paroxetine 20mg (N=105)	
	n	%	n	%	n	%	n	%
ALL	**198**	**38.7**	**156**	**38.4**	**71**	**32.0**	**47**	**44.8**

Nervous system disorders	**69**	**13.5**	**47**	**11.6**	**29**	**13.1**	**15**	**14.3**
Headache NOS	42	8.2	28	6.9	18	8.1	3	2.9
Insomnia NEC	12	2.4	2	0.5	3	1.4	2	1.9
Dizziness (exc vertigo)	6	1.2	4	1.0	-	-	1	1.0
Infections and infestations	**47**	**9.2**	**54**	**13.3**	**20**	**9.0**	**11**	**10.5**
Influenza	13	2.5	14	3.4	4	1.8	4	3.8
Nasopharyngitis	11	2.2	11	2.7	3	1.4	1	1.0
Sinusitis NOS	7	1.4	-	-	-	-	1	1.0
Gastrointestinal disorders	**42**	**8.2**	**31**	**7.6**	**15**	**6.8**	**10**	**9.5**
Diarrhoea NOS	8	1.6	4	1.0	2	0.9	3	2.9
Nausea	8	1.6	3	0.7	4	1.8	-	-
Dyspepsia	7	1.4	6	1.5	1	0.5	2	1.9
Abdominal pain upper	6	1.2	2	0.5	1	0.5	1	1.0
Constipation	6	1.2	2	0.5	-	-	-	-
Psychiatric disorders	**33**	**6.5**	**17**	**4.2**	**13**	**5.9**	**7**	**6.7**
Anxiety NEC	7	1.4	1	0.2	5	2.3	1	1.0
Musculoskeletal, connective tissue and bone disorders	**26**	**5.1**	**25**	**6.2**	**10**	**4.5**	**3**	**2.9**
Back pain	14	2.7	8	2.0	3	1.4	1	1.0

SOC: System Organ Class, PT: Preferred Term, NOS: Not Otherwise Specified, NEC: Not Elsewhere Classified
N: number of patients by group
n: number of patients with at least one emergent AE in a given preferred term or in a given SOC
%: (n/N) x 100

Of the most common emergent adverse events (≥1% in the agomelatine group) reported over the long-term treatment period, insomnia NEC and sinusitis were observed with a significantly higher frequency in the agomelatine 25/50 mg group compared to placebo. Other AEs with a higher reporting rate in the agomelatine group were headache NOS and back pain.

In addition, the following less common adverse events had also a higher incidence in the agomelatine 25/50 mg group than in the placebo group: anxiety NEC, nausea, aggravated depression, gamma-glutamyl transferase increased, abdominal pain upper, constipation, diarrhoea, abdominal pain NOS, liver function tests NOS abnormal.

- Serious adverse event/deaths/other significant events

Deaths: In the Overall Safety Set there were a total of 26 deaths, of which 9 occurred in the All MDD set and 17 in studies in other indications. In the All MDD set all deaths on agomelatine and placebo were due to suicide.

Other Serious Adverse Events: The most common SEAEs in the agomelatine group were:
- suicide attempt (0.6% *vs* 0.4% in the placebo group),
- depression aggravated (0.5%, same rate as in the placebo group),
- fall (0.4 % *vs* 0.2% in the placebo group).

Suicides and attempts

Table 22: Patients reporting completed suicide or attempted suicide under agomelatine in all agomelatine open and controlled MDD studies (excluding suicidal thoughts)[*]

Preferred term n (%)	agomelatine all doses N=2757	agomelatine 25/50mg N=2441
Completed suicide	4 (0.1)	4 (0.2)
Suicide attempt	24 (0.9)[a]	20 (0.8)
All	28 (1.0)	24 (1.0)

N: total number of patients in the treatment group
n: number of patients reporting a suicidal act in the treatment group
%: (n/N) x 100
* *placebo results are not displayed in this table since the "all MDD set" includes double-blind non-placebo-controlled and open studies, making comparison difficult to interpret*
[a] *the 4 additional suicide attempts in the all agomelatine doses group as compared to the 25/50mg group occurred in patients treated with subtherapeutic doses of agomelatine (1 under 1mg and 3 under 5mg)*

The frequency of suicides in the agomelatine treated patients appeared similar to that of the comparator drugs. Data from the total database was somewhat higher than in the placebo group. In the MDD group, however, the rates were similar in the placebo and agomelatine groups. The small number of deaths makes it difficult to judge the real rates, and suicides/suicidality should be specially monitored in post-marketing surveillance. In view of the recent referral of paroxetine and the recommendations of the CHMP, patients should be closely monitored during initial treatment.

- Laboratory findings

Vital signs
No difference between agomelatine 25mg, 50mg and placebo was observed in respect of the mean changes in heart rate, systolic or diastolic blood presssure from baseline. No obvious influence of agomelatine dose on orthostatic hypotension was observed.

ECG
Five cases of QT interval prolongation were reported as emergent adverse events on agomelatine in the Overall Safety Set: in 2 cases the existence of concomitant ECG abnormalities (bigeminy, flat T waves) prevented a reliable evaluation; in one case, the baseline ECG had shown a prolonged QT and Bazett correction overcorrected the QTc interval; in one case the direct assessment of the tracings did not confirm the existence of a prolongation; in one case, the patient was treated with antiarrhythmic drugs prone to induce QT disorders.

Specific study on QT-interval: the study CL1-033 was performed in young healthy male or female volunteers to study the effect of agomelatine at supratherapeutic doses (100 and 200mg, single administration) on QT interval. This was a placebo controlled study using a latin square design.
The administration of 100 or 200mg of agomelatine did not significantly prolong the ventricular repolarisation time in healthy volunteers. Agomelatine-induced variations of QTc interval were similar to those observed during the placebo period. None of the subjects reported a change in QTc from baseline > 60 ms.

Blood biochemistry
No relevant differences between agomelatine doses and placebo were observed as regards the incidence of patients with emergent out-of-reference range values.

Gonadotrophic hormonal safety
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). The studies showed that chronic administration (3-4 months) of agomelatine 50mg did not modify the hypothalamo-hypophyseal axis in male and female healthy volunteers.

Urinary Porphyrins

Urinary porphyrin measurements were carried out in two clinical studies; no clinically relevant changes over time and no dose-related changes in urinary porphyrin excretion were observed.

Changes in Body Weight
A low percentage of patients presented clinically significant weight gain of at least 7% during long-term treatment period, without major differences between treatment groups: 3.7% in the agomelatine 25/50mg group versus 4.5%, 5.9% and 7.6% in the placebo, fluoxetine and paroxetine groups, respectively.
Results were similar for weight loss < 7%: 3.2% in the agomelatine 25/50mg group versus 4.5%, 3.7% and 2.7% in the placebo, fluoxetine and paroxetine groups, respectively.

- Special safety assessments

Emergent symptoms after treatment discontinuation
Study CL3-030 was specifically designed to compare, in outpatients with remitted depression after a 12-week treatment period, the total number of discontinuation-emergent symptoms assessed by the DESS Check-list, occurring during a 2-week agomelatine 25mg treatment discontinuation with the number occurring in patients having carried on agomelatine treatment.
Results showed the absence of discontinuation symptoms after abrupt agomelatine cessation. In the same conditions, clear discontinuation symptoms were observed in patients previously treated with paroxetine 20mg, stating the assay sensitivity of the study.

Hepatic effects
There was a trend towards an increase in transaminases from baseline to the last value under treatment in the agomelatine 50mg group, whereas no change was detected in the placebo and the agomelatine 25mg groups. This increase was likely to be due to the high values observed in three patients treated with agomelatine 50mg.
One case of sustained potentially clinically significant values in liver parameters was reported: a 24 year-old male volunteer developed elevated liver enzyme concentrations (ALAT at 1.7 x ULN and ASAT at 1.5 x ULN) after 8 treatment weeks with agomelatine 50mg. In addition, during the procedure a new case was seen in a clinical study: a 57-year old man had been treated with agomelatine for circa 10 weeks and had increased ALT-value at 230 IU/l and AST 124 IU/l.

Effects on skin and subcutaneous tissue
The higher frequency of skin and subcutaneous tissue disorders in the agomelatine 25/50mg group (5.7%) as compared to the placebo group (4.0%) was mainly related to a higher frequency of pruritus NOS (1.1% versus 0.5%, respectively) and sweating increased (1.3% versus 0.9%, respectively).

Overdose
From studies in healthy volunteers, it was shown that agomelatine was well tolerated up to 800mg/day orally. Clinical studies were conducted, even in the elderly, with doses up to 100mg/day. During the clinical development of agomelatine 7 cases of intentional overdose were reported under agomelatine.

- Safety in special populations

Hepatic Impairment
Compared with healthy subjects, the systemic exposure to agomelatine was increased by 71-fold in mild liver failure and 140-fold in moderate failure; however, a single oral dose of 25mg of agomelatine was not associated with unusual pattern of adverse events in subjects with liver failure.

Renal Impairment
The open study, carried out in 8 volunteers with severely impaired renal function (creatinine clearance < 30 mL/min) and 8 healthy matched volunteers, showed that mean exposure to agomelatine was slightly greater in patients with impaired function than in healthy volunteers. Nevertheless, this increase was within the range of the inter-individual variability.

Pregnancy and lactation
During the clinical development of agomelatine, 9 pregnancies occurred under agomelatine, including 1 pregnancy in a phase I study and 1 pregnancy in an ongoing study. Pregnancies were followed by induced abortion in 6 patients. In the three other patients, pregnancy and delivery were normal and newborns were in good health with no dysmorphic features.

- Safety related to drug-drug interactions and other interactions

No clinically relevant interactions were identified.

- Discontinuation due to adverse events

Percentages of patients having reported at least one emergent adverse event leading to premature discontinuation of study drug were comparable in the agomelatine and placebo groups: In the short-term double-blind placebo-controlled MDD set, there were 61 (5.4%) patients with such adverse events on 25/50mg agomelatine and 15 (1.1%) on 1/5mg. There was no obvious dose effect among agomelatine groups on the percentage of patients with EAE leading to treatment discontinuation: 5.5% on 25mg vs 5.2% on 50mg.

Adverse events leading to premature discontinuation in the short-term MDD safety set, analysed by organ class are presented in Table 23.

Table 23: Emergent adverse events leading to premature discontinuation of study drug in the short-term double-blind placebo-controlled MDD set (reported by more than one patient in the agomelatine 25/50mg group)

Primary SOC HLT	**agomelatine 25/50mg N=1120 n (%)**	**placebo N=998 n (%)**	**fluoxetine 20mg N=284 n (%)**	**paroxetine 20mg N=283 n (%)**
Psychiatric disorders	**25 (2.2)**	**25 (2.5)**	**3 (1.1)**	**3 (1.1)**
Depressive disorders	10 (0.9)	12 (1.2)	1 (0.4)	1 (0.4)
Suicidal or self-injurious behaviour	6 (0.5)	5 (0.5)	1 (0.4)	2 (0.7)
Anxiety symptoms	5 (0.4)	4 (0.4)	1 (0.4)	-
Behaviour or socialisation disturbances	2 (0.2)	2 (0.2)	-	-
Nervous system disorders	**24 (2.1)**	**17 (1.7)**	**4 (1.4)**	**4 (1.4)**
Neurological signs and symptoms NEC	8 (0.7)	1 (0.1)	1 (0.4)	2 (0.7)
Headaches NEC	7 (0.6)	9 (0.9)	1 (0.4)	1 (0.4)
Disturbance in initiating or maintaining sleep	5 (0.4)	3 (0.3)	2 (0.7)	1 (0.4)
Paraesthesias and dysaesthesias	2 (0.2)	-	1 (0.4)	-
Gastrointestinal disorders	**8 (0.7)**	**13 (1.3)**	**3 (1.1)**	**4 (1.4)**
Nausea and vomiting (all forms)	7 (0.6)	11 (1.1)	1 (0.4)	2 (0.7)
Gastrointestinal and abdominal pain (exc oral and throat)	3 (0.3)	2 (0.2)	1 (0.4)	1 (0.4)
General disorders and administration site conditions	**3 (0.3)**	**3 (0.3)**	**1 (0.4)**	**1 (0.4)**
Asthenic conditions	3 (0.3)	-	-	-
Skin and subcutaneous tissue disorders	**4 (0.4)**	**1 (0.1)**	**-**	**1 (0.4)**
Dermatitis and eczema	2 (0.2)	1 (0.1)	-	-

N: total number of patients by treatment group
n: number of patients with at least one AE leading to premature discontinuation of study drug
%: (n/N) x 100

In the long-term double-blind placebo-controlled MDD set (W6-W24), the rate of adverse events leading to study drug discontinuation was similar in the agomelatine 25/50mg and placebo groups (6.7% versus 5.2%, respectively).

- Post marketing experience

Not applicable.

- Discussion on clinical safety

Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were dizziness and nausea. Other adverse reactions included: anxiety, abnormal dreams, irritability, somnolence, migraine, paraesthesia, blurred vision, dry mouth, diarrhoea, upper abdominal pain, pruritus, sweating increased, dermatitis, eczema, erythematous rash, fatigue. These adverse reactions were usually transient and did not generally lead to cessation of therapy.

Increases (>3 times the upper limit of the normal range) in ASAT and ALAT were reported in about 0.6% of patients treated with agomelatine 25/50 mg. The CHMP was of the opinion that this issue could have been addressed by careful monitoring of subjects included in the ongoing and future agomelatine clinical trials (monitoring carefully patients with ALAT, ASAT, ALP, or total bilirubin values > 3 ULN).

Overall the safety profile of agomelatine did not pose particular concerns. The most common adverse events were consentaneous with the medicinal product and with the disease.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfilled the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in a satisfactory way and there are no unresolved quality issues which might have negative impact on the benefit/risk balance.

Non-clinical pharmacology and toxicology

Agomelatine is a melatonin agonist with high affinity binding to human melatonin MT_1 and MT_2 receptors. Agomelatine is also a serotonin antagonist at the $5\text{-}HT_{2C}$ receptor from man and several animal species, although with low affinity. Agomelatine had anti-depressive like activity in a number of animal models of depression. The anti-depressant effect was related both to activation of melatonin

receptors and inhibition of 5-HT_{2C} receptors, and putatively to increased levels of extracellular noradrenaline and dopamine. Safety pharmacology studies showed that agomelatine and the metabolite 7DP caused significant CNS depression at high doses and induced slight-to-moderate sedation in several models. No biologically relevant effects were seen on renal function, respiratory system or cardiovascular system. No effect of agomelatine on hERG current or on dog Purkinje cells action potential was seen. Agomelatine resulted in a slightly increased gastrointestinal motility. Agomelatine did not show proconvulsive properties before electroconvulsive shock threshold test in mice and rats.

Agomelatine and/or its metabolites were rapidly and extensively distributed throughout the body; kinetics were non-linear. The main routes of metabolism were 3-hydroxylation, 7-desmethylation and oxidation; the metabolites of agomelatine were conjugated and excreted via urine and faeces. Agomelatine passed into the placenta and foetuses of pregnant rats.

Single-dose toxicity studies indicated a relatively low acute toxicity, with dose-related sedative effects. The repeated dose toxicity studies showed that liver was the target organ. In rodents, a marked induction of CYP 2B and a moderate induction of CYP 1A and CYP 3A were seen, whereas in monkeys the induction was slight for CYP 2B and 3A. No hepatotoxicity was observed in the repeat dose toxicity studies in rodents and monkeys. Reproduction studies in the rat and the rabbit showed no effect of agomelatine on fertility, embryofoetal development and pre- and post natal development.

A battery of *in vitro* and *in vivo* standard genotoxicity assays concluded to no mutagenic or clastogenic potential of agomelatine. In a 4-week ^{32}P-postlabelling study in rats DNA adduct formation was seen at exposure levels below human therapeutic exposure at 50 mg/day. The clinical relevance of these findings is not known.

In carcinogenicity studies agomelatine induced an increase in the incidence of liver tumours in the rat and the mouse and mammary fibroadenomas in the rat**,** at a dose at least 110 and 400 fold higher than the therapeutic dose respectively. Liver tumours were most likely related to enzyme induction; however, the final clinical relevance of these findings remains unknown.

Efficacy conclusions

The short-term antidepressant efficacy of agomelatine 25 or 25-50mg was investigated in three randomised, double-blind, placebo-controlled, multicentre studies in adults, that showed statistically significant differences from placebo on the HAM-D total score and consistent results across secondary criteria. Two additional studies were inconclusive (also positive control failed), and in one study agomelatine failed to show efficacy whereas fluoxetine showed positive effect. In addition, the study in elderly patients failed to show statistically significant difference between agomelatine and placebo treated patients. On the short-term efficacy data of agomelatine controversy arouse regarding its actual effect size and how it compared with alternative therapies; arguments suggested that the effect size was in line with the expectations in the field.

The long-term efficacy was studied in a relapse prevention trial, which failed to discriminate agomelatine from placebo. Data on long-term efficacy could also be derived from a double-blind extension study: two of the three double-blind extension studies failed to discriminate agomelatine from placebo, whereas in one study some secondary analyses were positive. Two double-blind venlafaxine-controlled trials were conducted to evaluate sleep disturbances or sexual dysfunction in MDD patients; no firm conclusions could be made, because the studies were not primarily designed to evaluate long-term efficacy on depression. In fact no depression score was obtained during the follow-up in one of these studies. The suggestion of efficacy was extrapolated from the CGI score in the CL3-035 study and from MADRS score in the CL3-036 study.

Thus, the efficacy, especially the long-term efficacy, has not been conclusively demonstrated.

Safety

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

Increases (>3 times the upper limit of the normal range) in ASAT and ALAT were reported in about 0.6% of patients treated with agomelatine 25/50 mg. The CHMP was of the opinion that this issue could have been addressed by careful monitoring of subjects included in the ongoing and future agomelatine clinical trials (monitoring carefully patients with ALAT, ASAT, ALP, or total bilirubin values > 3 ULN).

Overall the safety profile of agomelatine did not pose particular concerns. The most common adverse events were consentaneous with the medicinal product and with the disease.

Risk-benefit assessment

Agomelatine revealed tumorigenic potential in rodents, leading to hepatic tumours in rats and mice and mammary benign fibroadenomas in rats. The mechanistic explanation was extensively studied. The clinical relevance of some of these findings remained still unknown.

Oral bioavailability of agomelatine was low and the inter-individual variability substantial. From a clinical point of view, this is an unfavourable aspect of a medicinal product implying an unpredictable therapeutic response. In addition, bioavailability was increasing non-proportionally with dose, which contributed further to therapeutic unpredictability.

The demonstration of efficacy of agomelatonine in the treatment of major depression was not conclusive. The issues identified were the following:

The dose-finding process for agomelatine was not optimal. In the overall clinical program it was difficult to distinguish greater efficacy with the dose of 50 mg in comparison to the initial recommended dose 25 mg, although a fraction of the patients improved from this dose increase.

Demonstration of short-term efficacy: At short-term (6 weeks), three trials (including the dose-finding one) were able to discriminate agomelatine from placebo. In the flexible dose design trials the rate of responders in agomelatine was superior to placebo. Out of these 3 trials only one (CL2-014) had an active comparator arm (paroxetine 20 mg). The effect size of agomelatine and paroxetine were in the same range. Four other trials including the trial on elderly patients failed to discriminate from placebo. One of these trials had assay sensitivity because fluoxetine, used as a comparator, did discriminate from placebo, which suggests that the effect size of agomelatine was smaller than fluoxetine 20 mg. It is noteworthy that in all trials fairly severe patients were enrolled excluding the explanation that the failure was due to a "flooring effect". The effect size measured from baseline to endpoint was large in both active- and placebo-treated groups. Taken together, the CHMP concluded that data from the short-term efficacy trials could indicate that agomelatine 25 to 50 mg in the treatment of major depression exerted a clinical effect the magnitude of which could not lead to firm conclusion of clinical efficacy.

Demonstration of long-term efficacy: There was only one pivotal long-term trial (relapse prevention trial) and this failed to discriminate agomelatine from placebo. Data on long-term efficacy could also be derived from a) a double-blind extension of a short-term trial and b) two double-blind venlafaxine-controlled trials conducted in MDD patients to study sleep disturbances or sexual dysfunction. However, even though the applicant analysed all the available data in various ways, and even though these data may have pointed towards maintenance of efficacy, none of these analyses were conclusive (studies were not primarily designed to evaluate long-term efficacy). Further, the data from venlafaxine-controlled trials had major methodological shortcomings, e.g. they did not have depression as the primary variable, and the evaluation of depression was based only on CGI score in the CL3-035 study and on MADRS score in the CL3-036 study. Thus, these data were suggestive of a beneficial effect of agomelatine in the long-term treatment of major depression, but could not be considered conclusive. Based on the available

data, the CHMP was of the opinion that there was insufficient evidence to demonstrate the long-term efficacy of agomelatine.

Overall the safety profile of agomelatine did not pose particular concerns; increases in liver enzyme values could have been addressed by a risk management plan.

Taking all that above into consideration, the CHMP concluded that the benefit-risk balance for Valdoxan in the proposed indication is unfavourable, especially given that the long-term efficacy was not demonstrated.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Valdoxan in the treatment of major depressive disorder was unfavourable and therefore did not recommend the granting of the marketing authorisation.

Grounds for refusal

Efficacy has not been sufficiently demonstrated:

- Long term efficacy has not been demonstrated.

- Short-term efficacy trials indicated that agomelatine exerted a clinical effect the magnitude of which could not lead to firm conclusion of clinical efficacy.