European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Thymanax

International Nonproprietary Name: agomelatine

Procedure No. EMEA/H/C/000916

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Servier (Ireland) Industries Ltd submitted on 06 September 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Thymanax, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 26 April 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

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 tests or studies.

The applicant applied for the following indication: treatment of major depressive disorder in adults.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 29 July 1999. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status:
Thymanax has been given a Marketing Authorisation in Ukraine on 28 August 2006.
A new application was filed in the following countries: Australia, Brazil, Russia, South Africa and Turkey.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Eva Skovlund** Co-Rapporteur: **Tomas P Salmonson**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 06 September 2007.
- The procedure started on 27 September 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 December 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 December 2007. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 21-24 January 2008, 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 25 January 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 April 2008.
- The Integrated Inspections Report of the routine inspections carried out at the sponsor site in France and two investigators sites, one in Portugal and one in South Africa between 15 January and 21 February 2008, was issued on 18 April 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 06 June 2008.
- During the CHMP meeting on 23-26 June 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant..

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 September 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 06 October 2008.
- During the CHMP meeting on 20-23 October 2008, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 17-20 November 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Thymanax on 20 November 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 November 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Major Depressive Disorder (MDD) is reported to be the most common mood disorder. Depressive disorders tend to be chronic and both relapse and recurrence are seen frequently.

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).

Agomelatine is claimed to bring a new concept into the antidepressant treatment area. The agomelatine molecule possesses a new pharmacological mechanism of action, which combines its melatonin MT_1 and MT_2 agonist properties with a serotonin 5-HT_{2C} antagonist effect. The 5-HT_{2C} receptors is 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 recommended dose proposed by the applicant in the SPC is 25 mg once daily (taken at bedtime). After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets together at bedtime. Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.

The clinical development programme focused on showing efficacy of agomelatine 25 mg and 50 mg in the rather wide MDE indication. Supportive studies were performed to demonstrate relapse prevention, efficacy in the elderly and clinical safety.

The applicant obtained scientific advice from the EMEA on 30 July 1999 (CPMP/1807/99).

The applicant submitted in March 2005 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Thymanax, through the centralised procedure. Major objections regarding the doubtful clinical relevance of the effect size in the short-term studies and the fact that long-term efficacy and relapse prevention had not been demonstrated were raised. A negative opinion was adopted by the CHMP in July 2006, and the applicant requested a re-examination of the application. However, in January 2007 the Commission of the European Communities adopted the negative decision of the CHMP and issued a negative Commission Decision refusing marketing authorisation for Thymanax – agomelatine.

In September 2007, the applicant submitted to the EMEA a complete new Marketing Authorisation application based on a full documentation dossier for Thymanax through the Centralised Procedure, according to Article 8(3).

The new application has been completed by additional data including a new study aiming to demonstrate the efficacy of agomelatine in preventing relapse of depression (CL3-041).

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) and indigotine (E132).

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

Active 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 out in two main steps and adequate in-process controls are applied during the synthesis. Adequate in-process controls are applied. The specifications and control methods for intermediate products, starting materials and reagents, have been presented.

The manufacturing process of agomelatine has been validated on consecutive production scale batches, 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, HPLC), assay (potenciometric titration), chemical purity (HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), particle size distribution (Laser granulometry), 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. The validation studies are in accordance with the ICH Guidelines.

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

- Stability

Stability studies have been conducted in accordance with ICH Q1A (R) on three reduced-sized industrial container closure systems. Data provided cover 6 months stored at 40 ºC/75 % RH, one year stored at 30 ºC/60 % RH and three years stored at 25 ºC/60%RH and 30 ºC/70 % RH. The stability parameters tested were appearance, identification (IR), assay (HPLC and potentiometry), water content and related substances.

Stress testing at different temperatures was performed for one industrial size batch in powder form . Testing parameters were appearance, water content, IR and determination of agomelatine and related substances (HPLC).

Photostability was also tested according to ICH Q1B of the active substance.

Based on these stability results, the retest period proposed for agomelatine was considered acceptable.

Medicinal 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 pharmaceutical form and the excipients were selected based on compatibility testing of a number of excipients with the drug substance. A wet granulation formulation was chosen for this product.

Several formulations were developed during clinical trials phases. The dissolution studied results showed that the different formulations were similar.

The excipients lactose monohydrate, macrogol 6000, magnesium stearate, maize starch, povidone, colloidal anhydrous silica, sodium starch glycolate (type A), stearic acid meet the specifications of European Pharmacopoeia. Certificates of analysis of one batch of dry premix for orange coating containing the colouring agents titanium dioxide and yellow iron oxide and one batch of blue ink for printing containing the colouring agent indigo were presented and were analysed according to the specifications and analytical procedures

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

- Adventitious Agents

Lactose monohydrate is the only excipient of animal origin. The lactose manufacturers certifies that: lactose derives from milk sourced from healthy animals in the same conditions as milk collected for human consumption, which excludes this excipient from the scope of the "*Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*"; calf rennet used for production of the raw material whey is in accordance with the Public Statement "*Lactose prepared using calf rennet: risk assessment in relationship to bovine spongiform encephalopathies (BSE)*".

- Manufacture of the Product

The manufacturing process for the tablets is adequately described and consists of a conventional wet granulation. The manufacturing process and in-process controls are adequate for this tablet preparation..

The batch analysis data and process validation data show that the tablets can be manufactured reproducibly according to the agreed 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.

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

Batch analysis data confirm satisfactory uniformity of the product at release.

- Stability of the Product

Stability data are presented for 3 primary batches packed in the immediate container closure system proposed for marketing i.e. heat-sealed aluminium/polyvinyl chloride blister pack. The stability testing conditions are in accordance with ICH Q1A (R).

The parameters tested during stability study are identical with the release specifications. Additional test results for resistance to crushing, water content (Ph.Eur.) and disintegration were performed.

Results have been generated by validated, stability indicating methods and indicate satisfactory stability. These results support the shelf life and storage conditions stated in the SPC.

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

The applicant submitted extensive documentation concerning the non-clinical pharmacology, pharmacokinetics and toxicology of agomelatine. One non-clinical major objection and a number of points for clarification were raised and subsequently resolved during the previous procedure. The major objection concerned findings in the carcinogenicity studies.

The majority of the non-clinical studies were generally conducted in accordance with Good Laboratory Practice (GLP) standards, while studies assessing CNS safety and follow-up studies were non-GLP standards. All pivotal toxicity studies were conducted according to the principles of Good Laboratory Practice.

Pharmacology

- Primary pharmacodynamics

Agomelatine is a melatonin agonist with high affinity binding to the human melatonin MT_1 and MT_2 receptors. It also acts as a serotonin antagonist at the 5-HT_{2C} receptor from man and several animal species, although with lower affinity. In vitro the 3HD metabolite has a moderate affinity for human cloned MT_1 ,MT_2 receptors and the 7DP has a moderate affinity for human cloned $5HT_{2C}$ receptors . The other metabolites have weak or no affinity for MT_1 ,MT_2 and $5HT_{2C}$ receptors.

Although formal *in vitro* studies have not been submitted to demonstrate affinity for MT receptors in other species than man, the applicant adequately demonstrated that agomelatine has anti-depressive like activity in a number of animal models of depression, with effects similar to imipramine and fluoxetine. The anti-depressant effect is related both to activation of melatonin receptors and inhibition of 5-HT_{2C} receptors, and putatively to increased levels of extracellular NA and DA. Additionally, agomelatine showed anxiolytic effects and chronobiotic activity related to the melatonin activity, while no indication of antipsychotic properties is seen. The pharmacological effects of agomelatine seems to be related to the time of dosing, and highest effect levels are 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

Secondary pharmacodynamics studies explored the effects of agomelatine on memory, learning and vigilance in mice, as well as its effects on sleep and EEG spectra in rats when administered in the morning or in the evening. All studies were performed in males only.

Agomelatine had no adverse effects on the performed spatial learning and memory studies in mice, or on EEG recordings in rats at doses ≤ 10 mg/kg (ip, iv). Agomelatine (0.1 mg/kg, i.p.) enhanced the acquisition of discrimination. At the highest doses (1 and 10 mg/kg, i.p.), agomelatine improved retention, particularly when administered in the evening. However no effect of agomelatine on vigilance states and EEG power spectrum is observed at a dose (3mg/kg, i.p.) efficient for resynchronisation of circadian rhythms. Blood levels of agomelatine lower than 10µg/mL (corresponding to the high dose group) are unlikely to alter the EEG spectral power.

- Safety pharmacology programme

Studies of safety pharmacology showed that agomelatine and the metabolite 7DP causes significant CNS depression at high doses. No abuse potential for agomelatine was observed. No biologically relevant effects were seen on renal function, the respiratory system, the cardiovascular system or the gastrointestinal 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, while a potential effects on the oestrus cycle was not properly assessed.

- Pharmacodynamic drug interactions

No studies were performed in animals except the diazepam and barbital interaction studies in the rat. Interaction studies were performed in healthy volunteers (see Clinical Primary and Secondary Pharmacology section).

Pharmacokinetics

The pharmacokinetics of agomelatine was studied in the B6C3F1 mouse, the Wistar rat, the pigmented LE rat and the cynomolgus monkey, the same animal species and strains used in the toxicology studies. Absorption, distribution, metabolism and elimination characteristics were assessed following single and repeated oral administration, which is the intended route for human use. The absolute bioavailability, distribution and elimination were determined after intravenous administration in the Wistar rat and the monkey. A non-compartmental analysis was used. Data obtained with SD or Fischer rat strains and in cynomolgus monkeys in oral toxicology studies, were included for pharmacokinetic interpretation. The pigmented LE rat was selected for the assessment of whole body distribution of agomelatine.

Agomelatine was rapidly and almost completely absorbed after oral administration, but with a low absolute bioavailability (7 % and 0.2 % in rat and monkey, respectively) 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 proportional. This non-linearity is by the applicant related to saturation of the first-pass/ pre-systemic metabolism at higher doses. In rats, the first-pass metabolism is assumed to be of hepatic origin. In monkeys, however, the gut wall also contributes significantly to the low bioavailability.

The exposure levels of unchanged agomelatine in plasma, especially in monkey, was characterised by a high inter- and intra-individual variability. The underlying mechanisms explaining most of the observed variability in plasma levels for both species seems to be saturation of the solubility of the drug at high doses, as well as a high and saturable hepatic first-pass effect. The rate limited dissolution process is evidenced by a systematic shift in the t_{max} at high doses without any change in the total amount absorbed. The single dose absorption studies were performed on males only, thus a gender-related effect on single dose pharmacokinetics has not been performed. In the repeated dose studies both genders are represented. The high inter-individual variability combined with few animals per dose group makes assessment of gender-related effects difficult. However, in rats the exposure levels tend to be higher in females than in males, while in monkeys the exposure levels tend to be higher in males than in females.

Distribution studies were only performed on the rat. Because the toxicity studies were conducted in both rats and monkeys, a distribution study had preferably to be performed in both species. Agomelatine and/or its metabolites are rapidly and extensively distributed throughout the body, with a rather moderate volume of distribution, in accordance with the lipophilic properties of agomelatine. The levels in the CNS were relatively 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. At late sampling times (48-96 h), highest levels were seen in oesophagus, stomach, and intestinal wall, which may indicate an affinity for mucosa and epithelia. The high levels in the gastrointestinal system are by the applicant explained by gastric secretion. The binding to melanin is considered as weak (half life: 6-10h) and rapidly reversible in comparison to melanin turn-over which is measured in years. Further, no signs of ocular toxicity were observed in the toxicological evaluations.

Agomelatine was moderately bound to plasma proteins (75% to 95%) in all animal species and in humans. The protein binding profile of the four main metabolites (7DP, 3HP, DHDP and DAPACID) were similar in rats, monkeys and humans, and was high (95-98%) for DAPACID, moderate (71-78%) for 7DP and 3HP, and low (2-25%) for DHDP. The metabolite 3H7DP had low affinity for protein binding (bound fraction of 56-60%) in human heparinised plasma samples. 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 cross at a high grade, 3HP at an intermediate and DAPACID at a low grade.

The main routes of metabolism in rat, monkey and man have been identified as 3-hydroxylation, 7-desmethylation and oxidation of the naphthyl moiety at position 7, leading to the main metabolites 3HP, 7DP, and DHDP. The combination of 3-hydroxylation and 7-desmethylation leads to formation of the major metabolite 3H7DP in man, moderate in monkey and barely present in rat. DHDP is most likely formed after hydrolysis of a 3,4-epoxide-agomelatine intermediate. Neither the epoxide-intermediate nor glutathione, cystein conjugate or mercapturic acid derivatives were observed in monkey plasma, indicating that the potential intermediate has a low reactivity and/or a rapid detoxification. Both rat and monkey were found to be representative toxicological species, and the metabolites identified in humans have been found in at least one of these species. The monkey was a relevant species for almost all the human metabolic pathways, except the oxidative deamination, where the rat was complementary. Enzyme induction is observed to different degree in rodent and monkey at oral doses ≥ 125 mg/kg, with a subsequent decrease in exposure of unchanged agomelatine. Agomelatine causes 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 were slightly down-regulated. UGT was not investigated in monkey. Further, as an additional evidence of hepatic enzyme induction, a slight decrease in AUC_{24} occurred during the first month of dosing from 150 mg/kg. The enzyme induction is associated with a dose-dependent increase in liver weight. The relatively weak increase in liver weight observed in monkeys was not correlated with histological signs of hepatic injury. Even though the P450 cytochrome induction was minimal it remains the most likely explanation for the increased liver weight.

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 were readily excreted into rat milk, with mean milk/plasma ratio increasing from 0.348 (0.5 h) to 1.128 (2.5 h), consequently the drug should not be used during lactation. This was adequately reflected in the SPC.

The potential for pharmacokinetic interactions was not studied in animals. The evaluation of potential for drug interactions was based on assessment of human data.

Toxicology

Agomelatine was assessed in a variety of toxicity tests *in vitro* and *in vivo*. The studies included conventional single-dose toxicity studies in mice, rats and monkeys, repeated dose toxicity studies in mice, rats and monkeys, *in vitro* and *in vivo* genotoxicity, carcinogenicity studies in mice and rats, and reproduction toxicity studies in rats and rabbits. In addition, several mechanistic studies were performed in order to elucidate potentially drug-related carcinogenic findings.

- Single dose toxicity

All studies showed a dose-related sedatory effect of agomelatine on the CNS, with a rather low acute toxicity profile (LD50 ≥ 100 times the human dose).

- Repeat dose toxicity (with toxicokinetics)

Repeat dose toxicology was studied in rats (4-, 13-, 26-week studies) and monkeys (4-, 13-, 26- and 52-week studies) with both oral and intravenous administrations. The repeat dose toxicity studies indicated that liver is the target organ of toxicity in both rats and monkeys, with high safety margins in rats and low in monkeys. Agomelatine caused hepatic enzyme induction with subsequent increased metabolism and reduced drug exposure. The level of induction was more pronounced in rats than in monkeys. As a consequence of induction at doses > 125 mg/kg/po, the animals showed enlarged livers and/or hepatocellular hypertrophy. Increased excretion of porphyrins and porphobilinogen in the urine

was associated with discoloration of the urine. Additional studies did not show inhibition of rate-limiting enzymes in the heme cascade or a potential for hepatic porphyrin accumulation. Dark liver discoloration was observed in rats at low dose levels. According to the applicant, the discoloration is related to the enzyme induction. The applicant did not present any data confirming a direct correlation between liver discoloration and enzyme induction. However, similar discoloration was observed in the mechanistic studies with phenobarbital, supporting the suggested relation to enzyme induction.

- Genotoxicity and carcinogenicity

In a standard battery of *in vivo* genotoxicity studies, no genotoxic potential of agomelatine was found. Equivocal results were obtained in the first mouse lymphoma assay *in vitro*. A second study was conducted in order to clarify the results with metabolic activation. No reproducible or concentration-related trends in mutation frequency at the tk locus were observed. Clear positive results were seen in a chromosomal aberration assay with human lymphocytes when performed according to guideline ICH S7B. In the 3 hour assay, only a single concentration was used, thus a NOAEL for these findings could not be established. However, in view of the otherwise negative *in vitro* and *in vivo* genotoxicity studies, the positive results in the chromosome aberration test were considered of minor clinical relevance.

In the carcinogenicity studies agomelatine increased the incidences of hepatic adenomas and carcinomas in mice (both genders) and rats (males), and increased incidences of mammary fibroadenomas in rats (both sexes). Toxicokinetic studies showed that males (rats) are more exposed than females, especially at 104 weeks. The gender-related differences in occurrence of hepatic tumours could therefore be related to gender-related differences in exposure.

Mechanistic studies showed that agomelatine caused dose-related increased levels of modified DNA bases and potential agomelatine adducts in both males and females following 28 days *in vivo* exposure, and at levels higher than the positive control 2-AAF. Negative *in vitro* studies indicated that the modified bases *in vivo* is not due to agomelatine-adducts. A mechanistic study aimed at evaluating a potential relationship between DNA modifications and the presence of enzyme induction in the male rat liver was performed at early (6 and 24h) time-points following agomelatine exposure. Agomelatine was administered by gavage of a low, non-inductive, dose and a high, inductive dose. At 6h the plasma levels of agomelatine and its major metabolites were higher than those observed at 24h (3 to 189-fold). No DNA modifications or enzyme inductions were detected at 6h after administration. At 24h both DNA modifications and a 10-fold CYP 2B1/2 enzyme induction (not involved in the metabolism of agomelatine in rats) were detected in the high dose, but not in the low dose group. Additionally, in a 28 day study of continuous feeding of agomelatine, DNA modifications were detected after repeat administration of agomelatine when the typical pattern of enzyme induction was achieved (marked CYP 2B1/2 and mild CYP 1A1/2 inductions).

Taken together, the new data provided further supported the weight of evidence that agomelatine has no genotoxic potential. Rodent hepatic adenomas and carcinomas observed in the carcinogenicity studies most likely occur through non-genotoxic mechanisms and do not pose carcinogenic hazard to human at the non-enzyme inducing therapeutic dose. The safety margins based on plasma AUC in the carcinogenicity studies were in the mice 3-fold and in male rats 8-fold the mean human exposure at 50 mg, respectively. However, considering the high first pass hepatic metabolism of agomelatine and the fact that tumours were observed in liver, it is more appropriate to consider the safety margin based on the dose in mg/kg, i.e. about 150- and 50-fold for the mouse and the rat respectively.

In rats, there was a significant increase of mammary fibroadenomas in the high dose groups. Agomelatine reduced prolactin levels in males, and reduced prolactin surges in females. However, agomelatine had no major effects on normal hormonal functions following repeat administrations up to 28 days, at exposure levels in the range of those found in the carcinogenicity study. Statistical analysis where the results of the incidence of mammary tumours were compared to the in house

control values concluded on non-statistical difference for males and a statistical significance at 0.01 for females as compared to one of the control groups. No statistical significance was raised from pooled or pair wise comparisons for both males and females. Agomelatine is not mutagenic, does not induce a hyperprolactinemic state or hormonal imbalance, and does not accumulate in the mammary gland. The applicant therefore concluded that the increase in frequency of mammary fibroadenomas (the second most common spontaneous tumour in the female F344) can be regarded as belonging to the expected biological variations. Although it was agreed that the incidence of mammary tumour was marginal, probably occurred by a nongenotoxic mechanism with a clear threshold and was species-specific, the concomitant increased incidence in both males and females was difficult to be seen as incidental. On the other hand, a mechanistic explanation was not available and safety margins existed relative to the clinical use. A reference to the increased frequency of benign fibroadenomas was provided in section 5.3 of the SPC proposed by the applicant. The safety margin for liver tumours was calculated based on dose and this was considered acceptable due to high first pass metabolism while the safety margin for mammary fibroadenomas was calculated based on plasma AUC. The high first pass effect did not influence the mammary tumours in the same degree. This information was included in section 5.3 of the SPC.

- Reproduction Toxicity

Reproduction toxicity studies did not indicate any adverse effect of agomelatine on fertility or on embryonal or foetal development. Only minor effects were seen on T cells in female rats, without any effect on T cell-mediated immune responses.

- Local tolerance

Studies on local tolerance on rabbit skin and eye did not indicate any adverse effect. Only mild, early-onset, transient and reversible ocular changes occurred.

Ecotoxicity/environmental risk assessment

An environmental risk assessment was performed in the time course of the development of agomelatine (S 20098). At that time, the guidance document available was the "Note for guidance on environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 draft, 24 July 2003).

Since the $PEC_{SURFACE\ WATER}$ was above 0.01µg/L, a Phase II Tier A assessment was performed.

The ratios $PEC_{SURFACE\ WATER}$ / $PNEC_{WATER}$ and $PEC_{SURFACE\ WATER}$ / $PNEC_{MICROORGANISM}$ were below 1, and it was concluded that agomelatine is unlikely to present a risk for the aquatic environment and for sewage treatment plants. Further, the logKow was below 3 and the Koc was below 10 000 L/kg. It was therefore concluded that agomelatine has no potential to bioaccumulate and/or to contaminate the terrestrial environment. As a consequence, a Tier B assessment was not necessary.

In accordance with the updated guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, 01 June 2006), more studies are needed to identify environmental fate and effects of agomelatine:

- the substance being not biodegradable, a water-sediment study for determining the disappearance of the substance from sediment and water column according to OECD 308;
- a reproduction test with daphnids according to OECD 211;
- an early-life stage toxicity test on fish according to OECD 210.

These studies are to be performed in future and the time schedule proposed for the availability of the reports is Q1/2010. The Environmental Risk Assessment for agomelatine will be revised accordingly and an updated version will be submitted once the results of these experiments will be available.

2.4 Clinical aspects

Introduction

GCP

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

A total of 19 pharmacokinetic (or both PK and PD) studies were submitted, with a total of 409 adult persons enrolled (all Caucasian). Two analytical assays were developed for the analysis of agomelatine (S20098) in biological matrices. An LC-Fluorescence method was initially developed and validated in mouse, rat, rabbit, monkey and human plasma and was then used in all pivotal toxicology studies. At a later stage of development, a more sensitive LC-MS/MS method was developed and validated for the analysis of agomelatine in human plasma and saliva samples. In addition, a GC-MS method was developed and validated in human plasma at the CRO centre (BIOTEC) for further routine analysis of melatonin in clinical studies. In parallel to the GC-MS assays, a more rapid LC-MS/MS method was developed and validated in another analytical CRO centre (AAI) for the measurement of melatonin in human plasma samples.

The bioanalytical method validations showed an overall good performance. Pharmacokinetic parameters were calculated by using non-compartmental methods and population pharmacokinetic analysis. Standard statistical methods were applied.

- Absorption

Absorption of agomelatine given orally was rapid. Median t_{max} from single dose studies with doses relevant for the posology applied for (25-50 mg) was found to be 0.75-1.5 hours (ranging from 0.5-4 hours). Following administration of agomelatine in healthy volunteers at 200 mg, 400 mg, or 800 mg, the median t_{max} varied between 1.5 and 2.8h. The intestinal absorption was at least 80 %. The results of a Caco-2 cells study showed a complete absorption by passive diffusion and showed that agomelatine is not a p-gp substrate (efflux ratio near 1). The permeability was comparable to testosterone, having a high Papp-value of approximately 20×10^{-6} cm/s.

The absolute oral bioavailability of agomelatine was not calculated conventionally by comparing AUC values after oral and intravenous administration in the same population, but the mean bioavailability was estimated to about 3-4% in population pharmacokinetic analysis. Inter- and intra-individual variability in oral bioavailability was estimated to be 160% and 104%, respectively. In the therapeutic dose-range, agomelatine systemic exposure increases roughly proportional with dose. At higher doses a saturation of first pass effect occurs. Administration time, gender, oral contraceptives and smoking was shown to be a significant determinant of agomelatine bioavailability. The bioavailability estimate was 2-fold higher for women compared to men, 3-fold higher in non-smoker women under oestrogen treatment compared to non-smoking women without oestrogen treatment, and 3-fold higher at a.m. administration compared to p.m. administration. A lower bioavailability was observed among smokers, and higher bioavailability was observed in elderly versus younger in some analysis, but the data of different studies were conflicting. There was a tendency of a meal to slow down the absorption of agomelatine, but AUC was not significantly changed by a meal.

- Distribution

Agomelatine was mainly bound to two major plasma proteins, albumin and α1-acid glycoprotein, showing a non-saturable and saturable, respectively, binding of approximately 35 % each. The plasma to blood concentration ratio was equal to 1.45. Agomelatine is 90-94 % bound to human plasma proteins and protein binding is not concentration-dependent (5-1000 ng/ml).

The volume of distribution at steady-state (Vss) calculated after intravenous infusion was found to be 32-37 L while the volume of the central compartment (Vc) was 20-23 L. The apparent central volume

of distribution after oral administration (Vc/F) was estimated to be 1880 L. A linear correlation ($r^2 = 0.915$) was observed between the plasma and saliva concentrations and saliva concentrations of agomelatine were found to represent 2.8% of the plasma concentrations.

- Elimination and metabolism

The total plasma clearance was found to be dose independent (about 1100 ml/min) after i.v. doses of 1.5 mg, 7.5 mg, or 37.5 mg. The elimination was mainly metabolic, with a very low urinary excretion of unchanged drug (0.01% of the dose in the 37.5 mg group). The pharmacokinetics of agomelatine was characterised by a biphasic decrease with mean half-lives ($t_{1/2}$) of 0.2 and 1.4h, respectively. About 80 % of agomelatine was excreted in the urine, mostly as metabolites, and nearly 20% was excreted in the faeces over a 168 h collection period following a single dose of 50 mg.

In vitro incubations with pooled human liver microsomes and recombinant enzyme systems revealed that the main liver CYP1A isoform, CYP1A2, was responsible for the major metabolism of agomelatine. CYP2C9 and CYP2C19 were also capable of metabolizing agomelatine, but these enzymes were likely to be of potential relevance only at higher agomelatine concentrations. Many different metabolites of agomelatine were produced in human liver microsomes incubations and the most important pathways *in vitro* were 3-hydroxylation and 7-desmethylation. CYP1A2 was crucial in the 3-hydroxylation, whereas CYP2C9 and CYP2C19 were dominant in the O-demethylation pathway.

In *in vivo* studies, agomelatine was found to be mainly metabolised by reactions including 3-hydroxylation, 7-desmethylation, trans-3,4-dihydrodiol formation, 3-hydroxylation-7-desmethylation, and 3,4-dihydroxylation. An extensive amount of metabolites are formed *in vivo*. The metabolites were further metabolised principally by glucuronidation and eliminated into the urine. For most metabolites $t_{1/2}$ was found to be between 1 and 3 h, but a few had longer half-lives, up to 5.8 h.

A number of affinity studies were performed evaluating the affinity of agomelatine and some major metabolites to a large set of receptors. No summarised description of the contribution of the metabolites to the overall effect was found, and many metabolites were present in higher concentrations in plasma than agomelatine itself. During the procedure the applicant was requested to discuss the potential contribution of the stated effect of agomelatine versus the metabolites (considered significant) taking into account the potency studies performed, the protein binding of the respective metabolite and the plasma concentration levels in comparison to agomelatine. It was concluded and accepted that the majority of the effect reside with agomelatine.

- Dose proportionality and time dependencies

Agomelatine pharmacokinetics showed non-linearity across doses after oral administration (roughly proportional within the therapeutic range), but not after intravenous administration. This was explained by an extensive first pass metabolism, which becomes partly saturated with increasing dose. In a study where 200-800 mg agomelatine OD was given for 7 days, no time-dependent change in exposure was observed. Based on these data and the theophylline interaction data it was concluded that there is probably no significant time dependency.

- Variability

The variability in drug exposure (AUC) after oral administration varied between different studies, from approximately 100-150% CV due to the variability in first pass metabolism. Inter-individual differences is the main contributor to this variability, although the intra-individual variability is considerable: inter-and intra-individual variability for absolute bioavailability was estimated to 157% CV and 104% CV and corresponding figures for CL were 22%CV and 11% CV, respectively.

- Special populations

Target population: Pharmacokinetic differences between healthy subjects and patients were not observed and were considered to be unlikely.

Impaired renal function: The effects of renal function of agomelatine pharmacokinetics were investigated in Study PKH-015, which included healthy volunteers and patients with severe impaired

renal function (creatinine clearance (CLcr) <30 ml/min), receiving a single oral dose of 25 mg agomelatine. This study revealed that in patients with severe renal impairment the C_{max} and AUC increased approximately 40 and 25 % respectively, compared to healthy subjects. Even if it was agreed that there were no relevant modification of pharmacokinetic parameters observed in patients with severe renal impairment, only limited clinical data were available in these patients. As a result, a precaution for use of agomelatine in these patients has been introduced in the SPC. (The effects of agomelatine in renal impaired patients are further discussed in the Clinical Safety section – "Safety in special populations").

Impaired liver function: A specific study (PKH-014) investigated the influence of liver insufficiency in patients with hepatic cirrhosis on plasma levels of agomelatine. In patients with mild hepatic impairment the increase in AUC and C_{max} was on average 70 and 60 –fold, respectively, compared with healthy subjects. Corresponding figures for moderate hepatic impairment were 140- and 110-fold, respectively, compared with healthy subjects (see table below). The unbound fraction of agomelatine was increased in subjects with hepatic insufficiency, and approximately doubled in patients with moderate hepatic impairment.

Table 1: Mean pharmacokinetic parameters of agomelatine administered at 25 mg in healthy subjects and subjects with mild and moderate hepatic impairment.

	Healthy subjects n=8	Patients with mild hepatic impairment n=8	Patients with moderate hepatic impairment n=8
C_{max} (ng/mL) [1]	3.0 ± 2.8 (2.2)	191 ± 136 (214) *	283 ± 169 (240) *
t_{max} (h) [2]	1 (0.5 – 4)	1 (0.5 – 1.5)	0.5 (0.5 – 1.5)
t_{lag} (h) [2]	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)
AUC (ng.h/mL) [1]	4.9 ± 5.6 (2.89)	405 ± 352 (467) *	539 ± 307 (595) *
$t_{1/2,z}$ (h) [3]	0.9 ± 0.4	3.3 ± 2.1	2.4 ± 0.8
fu 1h30 (%) [3]	3.3 ± 1.1	5.8 ± 3.6	8.5± 2.9
fu 6h00 (%) [3]	4.2 ± 3.6	6.4 ± 2.4	7.2± 3.6

[1]: mean = SD (median)
[2]: median (min – max)
[3]: mean ± SD
**: p < 0.0001 mild or moderate versus healthy subjects*
n: number of healthy volunteers or patients in each group

A contraindication in <u>all</u> patients with liver disease resulting in hepatic impairment was initially proposed in the product information, and a strengthened amendment of this contraindication (i.e. in all patients with hepatic impairment – i.e. cirrhosis and active liver disease) was proposed. However this precautionary action alone was considered to be not sufficient to assure a safe use of this product, as there were no safety data at these exposures and it was considered that to avoid usage in patients with mild hepatic impairment was difficult. According to the applicant agomelatine is well tolerated in patients with mild and moderate hepatic impairment, however the overall safety in these patients could not be firmly concluded based on a total of 16 patients with a single dose administration and the very large exposure increase observed. A major objection was therefore raised during the procedure with respect to safety in this subpopulation. The actual exposures obtained were not sufficiently covered with phase II/III data . In addition, when relevant fractions unbound differences were taken into account, the exposure differences were even larger (see table above). However, the contraindication for use of agomelatine in <u>all</u> patients with hepatic impairment was considered to be sufficient provided that the applicant committed to monitor the LFT at initiation and regularly during the treatment period for both 25 mg and 50mg dosing, until more data were to become available on the timing and duration of liver function monitoring.

Gender: It was indicated that females have on average a 2-fold higher relative bioavailability compared with men. The population PK analysis also indicated that co-administration of oral estrogens results on average in a 3-fold increase in relative bioavailability, in non-smoking women only.

Weight: A lack of effect on weight could not be made formally, since the effect on weight was not assessed properly in the population analysis.

Race: No studies were performed to evaluate the possible influence of race on pharmacokinetics of agomelatine. During the procedure the applicant was requested to discuss this. A number of references were submitted. It was considered that genetic factors alone were unlikely to cause the high variability observed with CYP1A2 substrates. However, no specific study on this was performed.

Elderly: In study PKH-010, a single dose study evaluating the effect of smoking, age and gender, no effect of age on agomelatine pharmacokinetics was found. The influence of age was also evaluated in three population pharmacokinetic studies (NP06724, NP15939 and NP23957). In NP06724, a 3.8-fold higher exposure was observed in older (mean 78-y; n=80) compared to younger (30-y; n=37) subjects, but higher frequencies of smokers in latter group may have been a confounding factor. In NP15939 and NP23957, age was not shown to be a significant determinant of agomelatine bioavailability.

No effect of age was found in the final population analysis, but the data did not include subjects above the age of 78 years.

Children: No studies were performed to evaluate pharmacokinetics in children.

- Pharmacokinetic interaction studies

In vitro
No relevant protein binding interactions were observed with highly plasma protein bound drugs. The *in vitro* studies revealed that CYP1A2 is the major enzyme involved in the hepatic metabolism of agomelatine. Thus, CYP1A2 inhibitors and inducers were considered able to affect the clearance of agomelatine. It was shown that CYP2C9 and CYP2C19 are also involved in the metabolism of agomelatine, which was further investigated in the *in vivo* studies.

The K_i values for inhibition by agomelatine of CYP1A2 and CYP3A4 were 3.68 µM and 39.5 µM respectively. These values were approximately 10 and 100-fold higher than the plasma concentrations normally obtained with a 50 mg dose. Therefore, from the *in vitro* data on CYP1A2, it could not be excluded that agomelatine does not inhibit CYP1A2 *in vivo*.

In the *in vitro* study NP15748 with primary human hepatocytes, a potentially relevant induction of CYP1A2 activity by agomelatine was observed.

In vivo
Antipyrine was metabolised via several CYP enzymes and was not an optimal substrate to evaluate CYP1A2 induction. Antipyrine is an old probe substrate used mainly in the past for detecting effects of modulation of cytochrome P450 enzyme activity. During the procedure the applicant was requested to discuss the possibility to detect not only potent induction but also modest to moderate induction when using antipyrine as probe substrate. The theophylline interaction study evaluated the inhibition potential of agomelatine on CYP1A2 and showed an absence of an effect. However, a longer study was considered necessary to properly assess the potential CYP1A2 inducing capacity of agomelatine. There were limitations in the induction study, however given that a 5-fold dose of agomelatine was administered and that no induction on antipyrine was observed, it was concluded that agomelatine is likely not a relevant CYP1A2 inducer (even though a mild inducing effect on CYP1A2 could not be excluded). It was concluded that most likely agomelatine is not a CYP1A2 inhibitor.

Co-administration of fluvoxamine resulted in an approximately 50 and 60-fold increase for C_{max} and AUC respectively. The effect was also very variable, with a range of individual exposure ratios of 12-412. The concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated (Section 4.2 of the SPC).

The CYP1A2 inducing effect of smoking was variable as expected. The effect predicted in the population analysis was a 50 % reduction in the relative bioavailability. Exposure among smokers was 1/3-1/4 compared to non-smokers.

No significant pharmacokinetic interactions were observed between agomelatine and lithium, lorazepam, fluconazole, paroxetine and ethanol.

- Pharmacokinetics using human biomaterials

Pharmacokinetic studies using human biomaterials are described above in connection with *in vitro* plasma protein binding studies, binding interaction studies between agomelatine and selected drugs to

human plasma proteins and studies on agomelatine *ex vivo* binding to proteins in different groups (healthy young and elderly smoker/non smoker male and female volunteers, patients with impaired hepatic and renal function).

Pharmacodynamics

- Mechanism of action

In vitro, agomelatine showed to act selectively as an agonist at both melatonin MT_1 and MT_2 receptors and as an antagonist at 5-HT_{2C} receptors and at 5-HT_{2B} receptors. Agomelatine did not interact with adenosine, adrenergic, dopamine, GABA, muscarinic, nicotinic, histamine, excitatory amino acid, benzodiazepine and sigma receptors, or with sodium, potassium or calcium channels.

In vivo, agomelatine elicited a dose-dependent elevation in extracellular levels of both dopamine and noradrenaline in the frontal cortex of freely moving rats, which probably involves blockade of 5-HT_{2C} receptors. Agomelatine showed to have effect on resynchronization of circadian rhythms in different animal species, and this effect was thought to involve the melatoninergic action via MT_1 and MT_2 receptors.

- Primary and Secondary pharmacology

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 observed. 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. In healthy volunteers agomelatine preserved sexual function in comparison with paroxetine.

The minor biological effects shown raised the question whether the chosen dose of agomelatine was appropriate. Of the early phase I and II studies, only one study was actually performed with the 25 mg dose of agomelatine, which was the dose chosen for the phase III clinical trials.

Some observations perhaps indicated that the evening administration of agomelatine was to be preferred to the morning administration; sleep EEG showed an increase in stage 3 duration of sleep, after repeated administration of agomelatine in the evening. The morning administration of agomelatine was accompanied by mild sedation, as evaluated by objective sleep parameters.

The effects of agomelatine on QT interval were evaluated in two specific studies. In the first study only 13 subjects were exposed to agomelatine. Agomelatine did not seem to cause any clinically meaningful changes in cardiac depolarization. However, during the procedure the applicant was asked to justify the very low number of subjects in the agomelatine group. In response, the applicant referred to a newly performed study (CL1-054) including 56 subjects (28 males and 28 females) which showed that single doses of agomelatine 50 mg and 400 mg fulfilled the demands set out in the CHMP/ICH/2/04 "Note for guidance on the clinical evaluation of QT/QTc Interval prolongation and proarrhytmic potential for non-antiarrhytmic drugs".

No clear relationship between pharmacokinetic parameters and pharmacodynamic (antidepressant) effect was shown. However, in the only study designed for this evaluation, saliva samples and not plasma samples were used for the measurement of agomelatine concentration. This made the interpretation of the data rather complex. However, it was unlikely that a clear correlation between plasma levels and pharmacodynamic properties could be demonstrated.

No pharmacodynamic drug interactions were observed between agomelatine and ethanol and between agomelatine and lorazepam.

Clinical efficacy

The main clinical documentation for agomelatine consists of one short-term pilot study (CL2-007), one dose-finding study (CL2-014) and five other short-term studies (CL3-022, CL3-023, CL3-024, CL3-042 and CL3-043). In addition, two relapse prevention studies were performed for the evaluation of maintenance of effect (CL3-021 and CL3-041). Data from five supportive studies were also provided, as well as data from a placebo-controlled study in an elderly population (CL3-026). Long-term effect was also studied in double-blind extensions of the short-term studies CL3-022 and CL3-035. Studies in children were not performed.

The main clinical studies were all multicentre, double-blind and placebo controlled (Table 2). Some of the short-term studies included an active control as well.

Table 2: Summary of 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	Randomised double blind parallel groups	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	
CL3-042	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 mg Agomelatine50 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
CL3-041	Randomised double blind parallel groups	Agomelatine 25 mg and 50 mg vs. placebo	Relapse prevention	339	34 weeks	MDD	HAM-D	20 weeks
CL3-025	Randomised double blind parallel groups	Agomelatine 25, 25-50 mg o.d.	Efficacy and safety Dose escalation Partial	448	4 + 4 weeks	MDD with partial response to 4 weeks / 25 mg	HAM-D	16 weeks + optional 24 weeks open

			responders					
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 mg or 50 mg (from W2) Venlafaxine 75 mg or 150 mg (from W2)	Short-term: Sleep Long-term: Depression	334	6 weeks	MDD	Sleep: LSEQ Depression: Short-term: HAM-D Long-term: CGI	18 weeks

- **Dose response studies**

Study CL2-007

The pilot study CL2-007 compared the safety and efficacy of agomelatine administered orally at a dose of 5 or 100 mg once a day for one month after a 7 day placebo run-in period. Agomelatine was administered to 30 patients of both genders, aged between 18 and 65 years, with a single or recurrent major depressive episode without psychotic symptoms according to DSMIII-R criteria. A minimum score of 25 on MADRS (Montgomery Åsberg Depression Rating Scale) was required at inclusion.

The main objective of this study was to assess agomelatine's tolerability and antidepressant activity and its effect on sleep and wake cycle and a possible resynchronisation of circadian rhythms.

The main criteria were the MADRS total score; CGI (Clinical Global Impression) therapeutic index; actigraphy (duration of sleep, night activity index, daily average activity), and the Spiegel Sleep Questionnaire. No formal statistical assumptions were made.

30 patients were selected, 28 patients were randomised (14 in each treatment group), 19 completed the study, 9 discontinued treatment prematurely: 4 in the agomelatine 5 mg group due to adverse event (1), lack of efficacy (2), major protocol deviation (1), 5 in agomelatine 100 mg group due to adverse event (1), lack of efficacy (2), non medical reason (1), major protocol deviation (1).

No significant differences between the two doses of agomelatine were observed on any of the variables studied. Within group analyses revealed a similar decrease in the MADRS score after one month on both the 5 mg and the 100 mg agomelatine groups (15.8 and 13.0 points respectively) as compared with baseline values. This total score decrease was significant and was judged as clinically relevant since the score was decreased by at least 50% in 80% of patients in the agomelatine 5 mg group and in 78% of patients in the agomelatine 100 mg group.

The average score for the CGI therapeutic index was 2.6 in each treatment at the last evaluation, indicating an improvement of symptoms and few adverse events.

The actigraphy evaluation revealed no significant difference at D28 compared to baseline for any parameters.

The Spiegel Sleep Questionnaire revealed that there was a significant improvement of time to fall asleep, quality of sleep and condition in the morning at D28 compared to baseline with both doses: the scores were increased by one point from average to good.

Study CL2-014

Study CL2-014 was a multicentre, multinational, double-blind, randomised, controlled versus placebo with five parallel groups, one of which being a positive control group (paroxetine) to ensure the sensitivity of the study.

Patients were aged between 18 and 65 years inclusive, suffering from a single or recurrent episodes of major depressive or bipolar II disorders diagnosed according to the DSM-IV criteria, with a total HDRS score (17-item version) $\geq$4, were included in the trial. After the run-in period, patients with a total HDRS score (17-item version) $\geq$22 at W0 without a decrease of more than 20% between the selection and inclusion visits and CGI severity score $\geq$4 were randomised.

Overall, baseline characteristics were similar and no between-group differences of importance were present. Of the 711 patients that were randomised, approximately two thirds were female patients (66.5%) and one third were male patients (33.5%). Their age ranged from 19 to 65 years with a mean of 42.3 years. Most patients had major depressive disorders (98.2%) with recurrent episodes (67.0%), and 1.8% had bipolar II disorders. 39.8% of patients had an endogenous depressive disorder. The current episode had a mean duration of 5 ±10 months. The mean total HDRS score at baseline was 27.4.

Agomelatine was given in daily doses of 1 mg, 5 mg and 25 mg. Placebo was given twice daily, and paroxetine was given once daily (20 mg during treatment period and 10 mg during follow-up period).

The study included a 1-week run-in placebo period (W-1), 8-week double-blind treatment period (W0-W8), and a 2-week follow-up period (W10) (paroxetine 10 mg in the paroxetine group and placebo in the other groups, or optional antidepressant treatment in all treatment groups, or no treatment).

The main objective was to detect a difference between any of the 3 different doses of agomelatine and placebo using the Hamilton Depression Rating Scale (HDRS) in out- or in-patients with major depressive disorders or bipolar II disorders without seasonal pattern treated for 8 weeks.

Secondary objectives were to assess the effects on sleep by the mean of Spiegel sleep questionnaire and the safety of 3 different doses of agomelatine compared to placebo.

HDRS was assessed at each visit, and the primary endpoint was the total score of HDRS at the end of treatment. Response to treatment defined as an improvement of 50% in the HDRS score at the end and over treatment period was also assessed.

Secondary endpoints were MADRS and Hamilton Anxiety Rating Scale (HARS) assessed at W0, W4, and W8, CGI, response to treatment defined as a CGI item 2 (global improvement of illness) ≤3 at the end of treatment period, Hopkins Symptom Check-List (HSCL), and the Spiegel sleep questionnaire.

The total number of patients planned to be included was 650 (130 per group). The total number of patients actually included was 711 (147 in the paroxetine group, 139 in the placebo group, 141 in the agomelatine at 1 mg, 147 in the agomelatine at 5 mg and 137 in the agomelatine at 25 mg groups).

Assay sensitivity was demonstrated by the inclusion of a group of patients receiving paroxetine 20 mg. At the end of treatment the mean total HDRS score was significantly lower ($p = 0.030$) in the paroxetine (13.09) than in the placebo group (15.34) with an estimated difference of 2.25. The observed percentage of responders (defined as a decrease of at least 50% in total score) was higher with paroxetine (56.25%) than with placebo (46.32%), but not statistically significant ($p = 0.097$). The time to first response differed significantly between paroxetine and placebo ($p = 0.038$); the estimated first response rate was higher with paroxetine from 28 treatment days onwards.

Efficacy of agomelatine: Mean HAM-D total scores at baseline were in the range 27.3 to 27.9. At the end of treatment there was a significant difference in HDRS between the treatment groups ($p = 0.037$) in the FAS. Pairwise comparisons with placebo demonstrated that the mean total HDRS score was significantly lower in the agomelatine 25 mg group than in the placebo group with an estimated difference of 2.57. No statistically significant differences between agomelatine and placebo were observed in the PP set.

In addition to comparing mean changes in total score, efficacy was assessed by response at the end of treatment (decrease of 50% in total HDRS score). The percentage of responders was 46.3% in the placebo group, 62.5% in the agomelatine 1 mg group, 51.4% in the 5 mg group, and 61.5% in the 25 mg group. At the end of treatment there was a significant difference between the treatment groups ($p = 0.016$). The percentage of responders was significantly higher with agomelatine at 1 mg and 25 mg than with placebo, with estimated differences of 16.2% and 15.2% respectively. The response rate in the 5 mg group was not statistically significant from placebo (estimated difference 5.1%). There was no statistically significant difference between agomelatine and placebo in the PP set.

Time to first response was statistically significantly different between the treatment groups ($p = 0.017$). Pairwise comparisons showed a significant difference for both agomelatine 1 mg and 25 mg as compared to placebo, but not for the 5 mg group.

Secondary assessment criteria: At the end of treatment there was a statistically significant difference in total MADRS score between the treatment groups (p = 0.050): pair wise comparisons with placebo showed it to be significantly lower in the agomelatine 25 mg group than in the placebo group (estimated mean difference = 3.6).

- **Main studies**

Study CL3-042 and study CL3-043 (parallel groups, placebo-controlled short-term studies)

Methods

Study Participants

Studies CL3-042 and CL3-043 included in- or out-patients, male or female, aged between 18 and 65 years (inclusive), with a current moderate to severe episode of Major Depressive Disorder (DSM-IV), with a HAM-D total score at least equal to 22, and requiring an antidepressant treatment.

Treatments

Patients were randomised between agomelatine 25 mg and placebo with the option to increase the dose to 50 mg after 2 weeks if necessary (in case of insufficient improvement). The patients randomised to active treatment took 2 tablets (agomelatine 25 mg + placebo) once daily in the evening from the beginning of the study in order to maintain the blind after the potential adjustment of the dosage at week 2. Patients randomised to placebo took 2 placebo tablets throughout. During the extension period, patients from the placebo group and from the agomelatine 25 mg group were to receive 25 mg agomelatine and those on agomelatine 50 mg were to continue under agomelatine 50 mg in double blind conditions.

Total treatment duration was 52 weeks: a 1-week run-in period without treatment, a 6-week double-blind mandatory treatment period from W0 to W6 (with intermediary visits at W2 and W4), a 46-week optional extension treatment period until W52 under agomelatine, and a 1-week follow-up period after treatment discontinuation.

Objectives

The primary objective of these two studies was to assess the efficacy of agomelatine (25 mg with potential adjustment at 50 mg) compared to placebo.

Outcomes/endpoints

The primary efficacy variable was Hamilton Depression Rating Scale (HAM-D) 17 items total score at 6 weeks measured at each visit.

Sample size

In order to detect a mean difference of 4 on the HAM-D total score with 90% power at the 5% significance level, and assuming a standard deviation of 9, 107 patients had to be included in each group. This corresponds to 80% power to detect a difference of 3.5. For Study CL3-042 a total of 238 patients were included, 118 in the agomelatine group and 120 in the placebo group. For Study CL3-043 a total of 212 patients were included, 107 in the agomelatine group and 105 in the placebo group.

Randomisation

The randomisation of the two treatments was non-adaptive, balanced, stratified on the centre and was performed using permutation blocks of fixed size 4. At the end of W2 the allocation to "dose increase" was generated centrally, based on the HAM-D total score at W0 and W2 and CGI score at W2.

Blinding (masking)

Dose escalation was blind to investigator and patient.

Statistical methods

Agomelatine and placebo were compared over W0-W6 period HAM-D Total Score by the two sample t test and two-way analysis of covariance including the factors group and centre (random effect) with baseline as a covariate and without interaction. Missing values were imputed by last observation carried forward.

Results

Table 3: Patient disposition in study CL3-042

Status	Agomelatine	Placebo	All
Included and randomised	**118**	**120**	**238**
in compliance with the protocol	82	92	174
with a protocol deviation at inclusion	36	28	64
Withdrawn due to	**17 (14.4%)**	**18 (15.0%)**	**35 (14.7%)**
adverse event	4	5	9
lack of efficacy	7	9	16
non-medical reason	3	2	5
protocol deviation	3	2	5
Completed	**101 (85.6%)**	**102 (85.0%)**	**203 (85.3%)**
in compliance with the protocol	78	77	**155**
with a protocol deviation during the study	23	25	**48**

Table 4: Patient disposition in study CL3-043

Status	Agomelatine	Placebo	All
Included (randomised)	**107**	**105**	**212**
in compliance with the protocol	104	101	205
with a protocol deviation at inclusion	3	4	7
Withdrawn due to	**7 (6.5%)**	**12 (11.4%)**	**19 (9.0%)**
adverse event	3	3	6
lack of efficacy	2	7	9
non-medical reason	2	2	4
Completed	**100 (93.5%)**	**93 (88.6%)**	**193 (91.0%)**
in compliance with the protocol	84	72	156
with a protocol deviation during the study	16	21	37

For both studies there were no patients lost to follow-up. For Study CL3-042 there were approximately 15% of patients who discontinued treatment in both groups (17 out of 118 in the 25-50 mg agomelatine group and 18 out of 120 in the placebo group). For Study CL3-043 there were 6.5% (7 out of 107) of patients who discontinued treatment in the 25-50 mg agomelatine group, and 11.4% (12 out of 105) patients who discontinued treatment in the placebo group.

Recruitment

For study CL3-042 patients were recruited in the period August 2002 – April 2004. For study CL3-043 patients were recruited in the period October 2002 – June 2003.

Conduct of the studies

These were multicentre, multinational (according to Amendment No. 1), randomised, double-blind, two parallel groups, placebo controlled, 6-week studies with possible adjustment of the dosage after 2 weeks of study treatment. The criteria for dose increase were defined prior to study start and the dose increase and the treatment allocation were made centrally using IVRS in a double-blind procedure, so that both the patients and the investigators were blind to the dose increase. The mandatory period was followed by an optional extension period of 46 weeks on agomelatine. As there was no control group in the extention period (all patients were treated with agomelatine), only safety data are relevant for this period.

Baseline data

With the exception of almost twice as many patients with a previous suicide attempt in the agomelatine group (17.8% patients) compared to placebo (9.2% patients) Study CL3-042 was fairly well balanced. Of the 238 patients that were randomised, approximately 73.5% were female patients, and 26.5% were male patients. Their age ranged from 18 to 65 years, with a mean age of 45 years old. Single episode MDD patients were 26.3% in the agomelatine group and 20% in the placebo group. MDD patients with recurrent episodes were 73.7% in the agomelatine group and 80% in the placebo group.

For Study CL3-043 there were more men in the placebo group compared to the agomelatine group (45% and 35%, respectively). Otherwise the treatment groups were well balanced with respect to demographic and disease characteristics. The age of the 212 patients that were randomised ranged from 18 to 65 years, with a mean age of 42.5 years old. Single episode MDD patients were 19.6% in the agomelatine group and 26.7% in the placebo group. MDD patients with recurrent episodes were 80.4% in the agomelatine group and 73.3% in the placebo group.

Numbers analysed

In CL3-042 and CL3-043 studies the full analysis set (FAS) included respectively: 116 and 106 patients in the agomelatine group and 119 and 105 patients in the placebo group. The observed cases W6 set for CL3-042 and CL3-043 respectively included: 104 and 100 patients in the agomelatine group and 106 and 94 patients in the placebo group.

Outcomes and estimation

Response to treatment

For Study CL3-042 a statistically significant mean difference of 3.18 on the HAM-D total score was observed in the FAS. Similar estimates were obtained in the observed cases set and with adjustment for centre and baseline.

In the FAS, 54.3% of the patients in the agomelatine group versus 35.3% in the placebo group were responders (response defined as decrease of at least 50% in the HAM-D total score between the baseline and the concerned visit) at the last post-baseline evaluation ($p = 0.003$).

At the end of the second week of treatment (W2), the dose was adapted for 29 patients under agomelatine and for 54 patients under placebo in the FAS. In this group the percentage of responders reached 48.3% in the agomelatine 25-50 mg group versus 25.9% in the "placebo increased" group. The benefit of agomelatine over placebo was also shown in the Observed Cases W6 Set, where 57.7% of the patients in the agomelatine group versus 39.6% in the placebo group responded to the treatment ($p = 0.009$). The results were confirmed in subgroups of patients with higher scores of HAM-D and/or CGI at baseline.

In the FAS as well as in the other efficacy sets the percentage of patients in remission at last post-baseline evaluation was higher in the agomelatine group than in the placebo group (in the FAS: 17.2% *versus* 11.8%, respectively).

For Study CL3-043 the last post baseline value of the HAM-D total score in the FAS was statistically significantly lower in the agomelatine group than in the placebo group (14.1 vs 16.5) with a p-value of 0.022. Similar results were obtained after adjustment for centre and baseline.

The benefit of agomelatine versus placebo demonstrated in the FAS was more pronounced in subgroups of patients with higher scores of HAM-D and/or CGI at baseline. In the Observed Cases W6 Set, mean values of HAM-D total score at W6 were 13.7 in the agomelatine group versus 15.9 in the placebo group ($p = 0.042$), with an estimated difference of 2.10. A similar number of patients in both groups had a dose adaptation (increase to 50 mg): 36 patients on agomelatine and 38 patients on placebo.

In the FAS, 49.1% of the patients in the agomelatine group versus 34.3% in the placebo group were responders (response defined as decrease of at least 50% in the HAM-D total score between the baseline and the concerned visit) at last post-baseline evaluation. The estimated between-group difference was -14.8 ($p = 0.030$).

In the FAS as well as in the other efficacy sets, the percentage of patients in remission at last post baseline evaluation was numerically higher in the agomelatine group than in the placebo group (in the FAS: 20.8% versus 13.3%, respectively; not statistically significantly different).

Studies CL3-022, CL3-023 and CL3-024 (parallel groups, positive-controlled, short-term studies with extension phase)

Methods

Study Participants

Male or female out- or in-patients, aged between 18 and 59 years (inclusive), suffering from a single or recurrent episode of Major Depressive Disorder according to DSM-IV criteria, with or without melancholic features, without atypical features (with or without seasonal pattern for CL3-023 and -024), and without psychotic features were included in each of these 3 studies. Eligibility criteria were a HAM-D Total score ≥22 at inclusion. CL3-022 had additional criteria that the decrease in HAM-D Total score should not be more than 20% between start of run-in and inclusion visits, and a severity of illness ≥4 on the Clinical Global Impression scale (CGI).

Treatments

In Study CL3-022 agomelatine 25 mg was given once daily as an oral capsule (tablet masked in capsule), to be taken in the evening, in association with a placebo capsule taken in the morning. Placebo was given as an oral capsule twice a day. Fluoxetine (positive control product) 20 mg was given once daily as an oral capsule, in the morning, in association with a placebo capsule taken in the evening. The study comprised a single blind run-in placebo period with a duration ranging from 7 to 14 days, an active double-blind placebo-controlled treatment period of 6 weeks (W0 to W6), an optional double-blind placebo-controlled extension treatment period of 18 weeks (W6 to W24), and a follow-up period of one week without treatment (W7 or W25).

Study CL3-023 followed a protocol and duration treatment similar to CL3-022, however in this study Paroxetine (20mg), not Fluoxetine, was used as the positive control.

Study CL3-024 also followed a protocol and duration treatment similar to CL3-022, with the same active comparator (Fluoxetine 20 mg). The main difference was the addition of a separate treatment arm where patients received the 50 mg tablets.

Objectives

The primary objective of these studies was to confirm the efficacy of the target dose agomelatine compared to placebo.

The sensitivity of the studies was checked by comparing the effect of the active comparator (fluoxetine 20 mg or paroxetine 20 mg) to placebo. A secondary objective in Study CL3-024 was to study the efficacy of agomelatine 50 mg given orally.

Outcomes/endpoints

The primary efficacy variable was the last post-baseline value of HAM-D total score assessed by the investigator. Secondary endpoints were CGI, Montgomery and Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), and the Leeds Sleep Evaluation Questionnaire (LSEQ). All but the latter were assessed by the investigator.

Sample size

In order to detect a mean difference of 4 on the HAM-D total score with 90% power at the 5% significance level, and assuming a standard deviation of 9, 107 patients had to be included in each group. This corresponds to 80% power to detect a difference of 3.5.

A total of 420 patients from 74 centres were included and 419 randomised in Study CL3-022 (133 in the agomelatine group, 149 in the placebo group and 137 in the fluoxetine group).

A total of 418 patients were included from a total of 45 centres in 10 countries in Study CL3-023 (142 in the agomelatine group, 137 in the placebo group and 138 in the paroxetine group).

For Study CL3-024 the total number of patients planned to be included was 520 (130 per group), calculated on the basis of a relevant difference of 3.5 points at the final HAM-D scores between treatment groups, with α = 5%, β=10%, and a standard deviation of 9. A total of 607 patients were actually included in this study and were recruited from 75 centres in 7 countries (150 in the 25 mg agomelatine group, 151 in the 50 mg agomelatine group, 158 in the placebo group and 148 in the fluoxetine group).

Randomisation

The randomisation of treatments (agomelatine, placebo, fluoxetine or paroxetine) was non-adaptive, non-centralised, and balanced with a 1:1:1 ratio. There was no stratification and permutation blocks were of fixed size = 6.

Blinding (masking)

Agomelatine, placebo and fluoxetine (or paroxetine) were disguised in tablets or capsules (or tablets) of identical appearance and taste.

Statistical methods

Short term (W0-W6 period) efficacy analyses

For each HAM-D analytical approach, fluoxetine or paroxetine was compared to the placebo with the same methodology as for the agomelatine-placebo comparison, in order to demonstrate assay sensitivity.

The main analysis compared the last post-baseline value between groups. Student's t test (without adjustment) and a two-way analysis of covariance with adjustment on centre and baseline were used to compare agomelatine and placebo. Subgroup analyses were performed in all FAS subsets using the t-test. Response to treatment (decrease in HAM-D total score of at least 50% according to baseline) and remission (HAM-D total score $\leq$ 6) was compared between groups using a Chi-Square test. Time to first response to treatment and time to first remission were compared between groups by Kaplan-Meier method and log-rank test.

The response was also studied in the Sub-FAS with HAM-D $\geq$ 25 at W0 and the Sub-FAS without benzodiazepines, remission in the Sub-FAS with HAM-D $\geq$ 25 at W0 and time to first response in the Sub-FAS without benzodiazepines. The estimate of the difference agomelatine *versus* fluoxetine means was done using a 95% Confidence Interval (CI) for all HAM-D expressions except time to first response and time to first remission and for all secondary criteria.

Secondary efficacy criteria, i.e. MADRS, HAM-A, CGI scale, LSEQ were compared between groups using a Student's t test in the FAS. For the last 2 criteria, a Mann-Whitney test was performed as a robustness analysis in the FAS. HAM-A and LSEQ were studied also in the Sub-FAS without benzodiazepines. For each criterion, the agomelatine group and the fluoxetine group were compared to the placebo group with the same methodology.

Long term (W0-W24 period) efficacy analyses

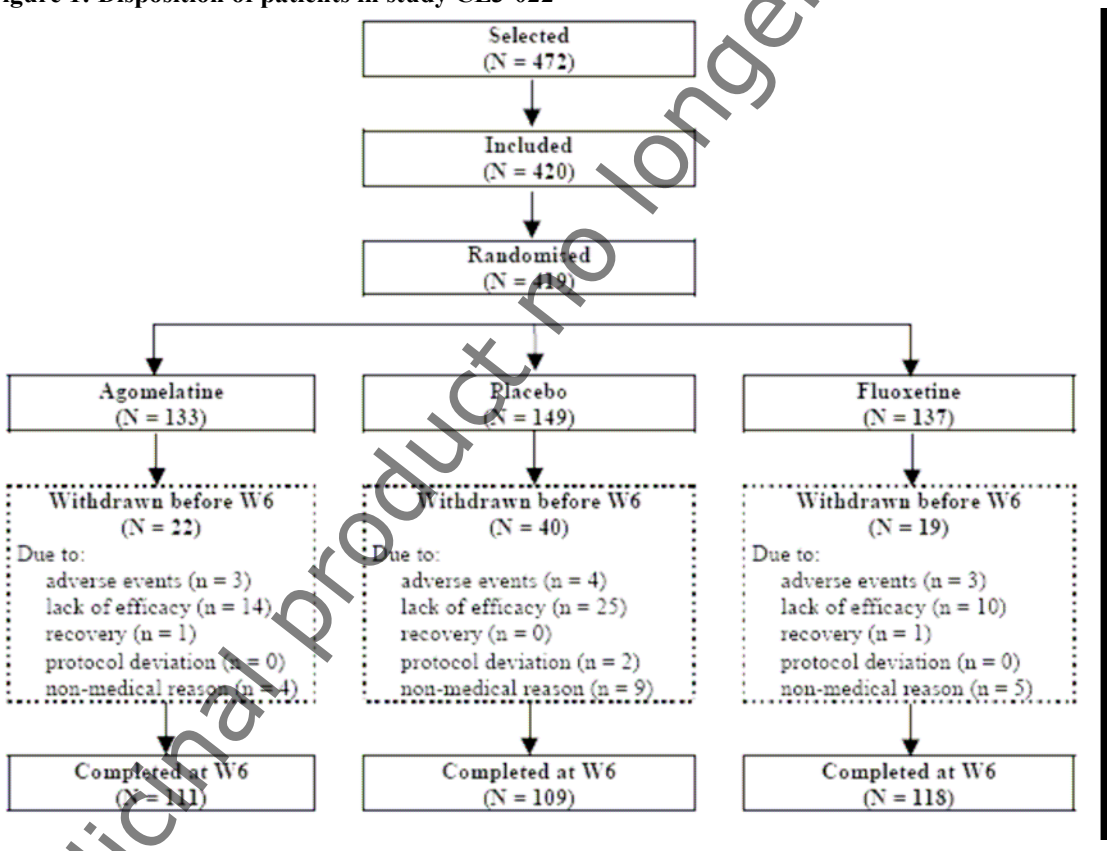
In the Sub-FAS of responders to treatment at W6 who entered the optional extension period, agomelatine and placebo on the one hand, and fluoxetine and placebo on the other hand, were compared using t test on the last post-baseline value (HAM-D) and log-rank test for the time to first relapse (HAM-D total score returned to 16 or more or suicide or suicide attempt) and time to first loss of response.

Results

Participant flow

Study CL3-022

Figure 1: Disposition of patients in study CL3-022

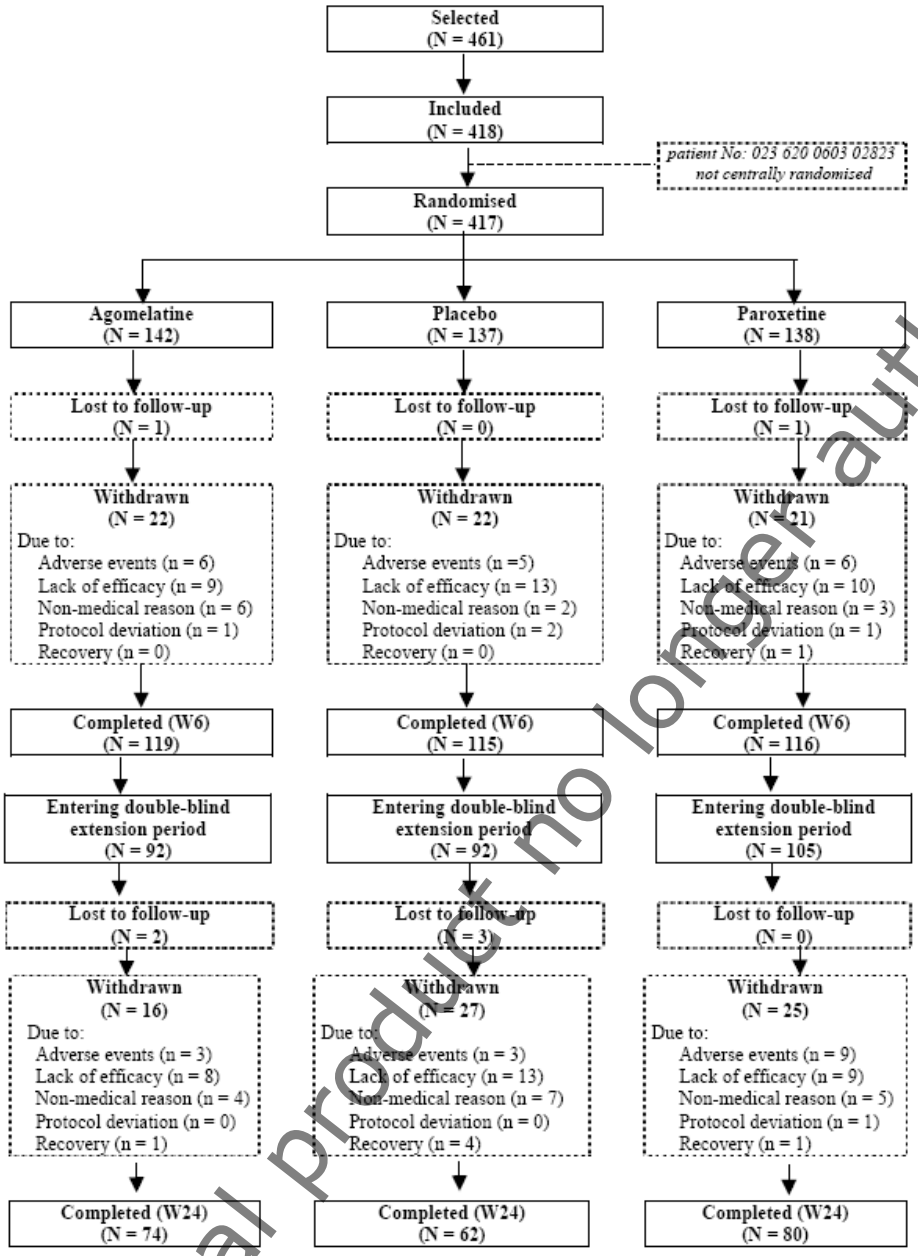


Approximately 85% completed six weeks of double-blind treatment in the agomelatine and fluoxetine groups compared with 73% in the placebo group where more patients withdraw due to lack of effect (Figure III-2).

The overall morning and evening compliances were satisfactory (between 70% and 130%) in 91% of randomised patients during the W0-W6 period. There were no relevant between-group differences for treatment duration or compliance.

Study CL3-023

Figure 2: participant flow from selection, through double-blind treatment period and to completion for Study CL3-023.

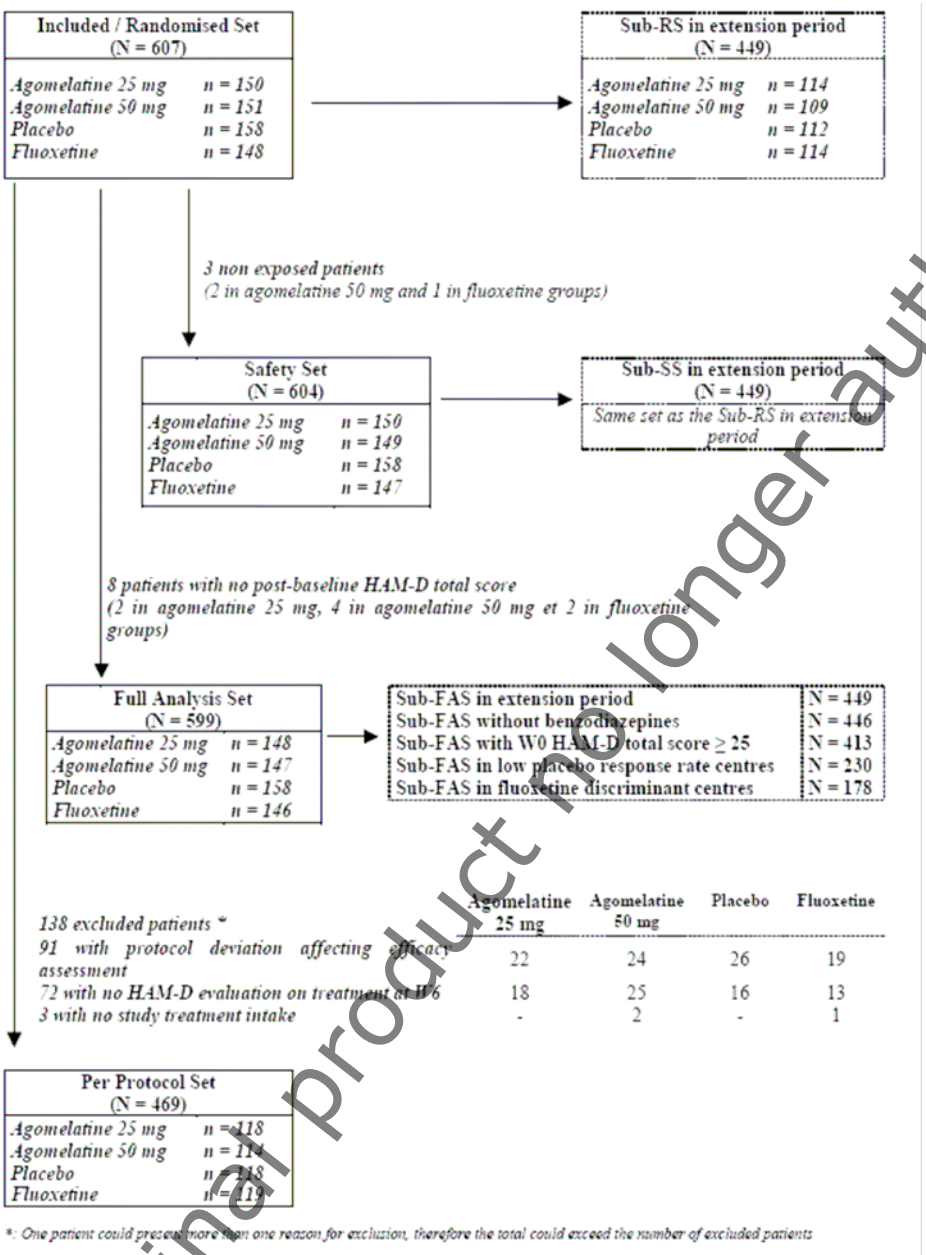


84% percent of the patients completed six weeks of double-blind treatment with no major differences between the treatment groups with respect to amount, cause and timing of withdrawal (Figure III-3).

As shown in the table above, more patients were withdrawn (due to lack of efficacy) in the placebo group than in the active treatment groups. In the paroxetine group more patients were withdrawn due to adverse events.

Study CL3-024

Figure 3: participant flow and the number of patients included in the different analysis sets for Study CL3-024.



The completion rate was fairly high (85%). There were no major differences in withdrawals between the treatment groups with respect to amount and cause with the exception of more withdrawals due to non-medical reasons (mostly withdrawal of consent) in the agomelatine 25 mg group (Figure 3). The discontinuations tended to occur earlier in the agomelatine groups.

Recruitment

Patients were recruited during the period September 1999 to August 2001 for Study CL3-022, from December 1999 to September 2001 for Study CL3-023 and from June 2000 to May 2002 for Study CL3-024.

Conduct of the studies

Studies CL3-022 and CL3-023 were multicentre, randomised, double-blind placebo-controlled study in three parallel groups, one assigned to agomelatine (25 mg/day), one to placebo and the third group to a positive control (fluoxetine 20 mg/day or paroxetine 20 mg/day respectively) to ensure assay sensitivity. Study CL3-022 was national (France), whereas Study CL3-023 was international.

Study CL3-024 was a multicentre, multinational, randomised, double-blind, placebo-controlled study in 4 parallel groups (agomelatine 25 mg group, agomelatine 50 mg group, placebo group and fluoxetine group used to assay the sensitivity of the study).

Baseline data

Study CL3-022: Of the 409 patients that were included in the FAS, 31% were male patients and 69% were female patients. Their age ranged from 19 to 60 years, with a mean age of 42.5 years old. In general the groups were comparable at baseline, but the agomelatine patients were somewhat younger than the placebo and fluoxetine patients. There were also more single episode patients in this group.

Study CL3-023: Of the 417 patients that were randomised, 25.4% were male patients and 74.6% were female patients. Their age ranged from 18 to 60 years, with a mean age of 40.9 years old. Overall baseline characteristics were similar in the three treatment groups.

Study CL3-024: Of the 607 patients in the randomised set, 27.5% were male patients and 72.5% were female patients. Their age ranged from 18 to 65 years, with a mean age of 40.9 years old. Single episode MDD patients were 32.7% in the 25mg agomelatine group, 33.1% in the 50mg agomelatine group, 27.8% in the placebo group, and 29.1% in the fluoxetine group. MDD patients with recurrent episodes were 67.3% in the 25mg agomelatine group, 66.9% in the 50mg agomelatine group, 72.2% in the placebo group and 70.9% in the fluoxetine group. No relevant between-group differences were observed for the main demographic data and baseline characteristics. All the patients met DSM-IV criteria for episodes of Major Depressive Disorder. About two thirds of the patients (69.4%) had recurrent episodes.

Numbers analysed

Study CL3-022: The FAS (W0-W6) contained a total of 419 subjects including 129 patients in the agomelatine group, 147 patients in the placebo group and 133 patients in the fluoxetine group. The observed cases W6 set included 114 patients, 124 patients and 122 patients in the three groups respectively.

Study CL3-023: The randomised set contained a total of 417 subjects (142 in the agomelatine group, 137 on placebo and 138 on paroxetine). The sub-RS in the double blind extension period contained 289 subjects (92 on agomelatine, 92 on placebo and 105 on paroxetine). For week 0-6 the FAS contained 415 subjects (141 on agomelatine, 137 on placebo and 137 on paroxetine).

Study CL3-024: of the 607 patients that were randomised, 599 were included in the FAS (W0-W6) (148 in the 25mg agomelatine group, 147 in the 50mg agomelatine group, 158 in the placebo group and 146 in the fluoxetine group). Fewer patients in the fluoxetine group were withdrawn due to lack of efficacy than in the other groups. In the W0 – W6 period withdrawals due to adverse events were slightly more frequent in the fluoxetine group.

Outcomes and estimation

Study CL3-022: In the FAS, the mean last post-baseline value of the HAM-D total score over the W0-W6 period was lower in the agomelatine group than in the placebo group, without statistically significant difference (27.6±2.9 and 14.5±8.2 versus 28±3.6 and 15.9± 8.6 respectively). Similar results were observed at W6 for the Observed Cases (12.8±6.8 versus 14.2±7.7). There was no statistically significant difference between the agomelatine and placebo groups in the percentage of responders (defined as a patient having a decrease from baseline of at least 50% in the HAM-D total score) to treatment (53% in the agomelatine group and 47% in the placebo group) and in the percentage of patients in remission.

Assay sensitivity was demonstrated. In the FAS, the mean last post-baseline HAM-D total score was significantly lower (p = 0.008) in the fluoxetine group than in the placebo group. The mean difference was 2.59.

Long term (W0-W24 period): In the Sub-FAS in the double-blind extension period, the mean last post-baseline HAM-D total score was 10.0 in the agomelatine group, 10.7 in the placebo group and 8.4 in the fluoxetine group. Among the responders to treatment (according to the HAM-D) at W6 who entered the optional extension period (Sub-FAS of W6 responders – complementary analyses), the mean last post-baseline HAM-D total score was lower in the agomelatine group (7.4) than in the placebo group (10.2), but not statistically significant. Among the patients with a HAM-D total score < 16 in this Sub-FAS of W6 responders, 9 (14.3%) in the agomelatine group, 20 (33.3%) in the placebo group and 13 (17.8%) in the fluoxetine group relapsed over the W6-W24 period. The survival curve analysis of the time to relapse showed a statistically significant difference in favour of agomelatine (15.8%, log rank test p = 0.017) and fluoxetine (19.9%, log rank test p = 0.045) compared to placebo (35.0%).

Study CL3-023: In the FAS, the mean last post-baseline HAM-D total score was slightly lower in the agomelatine group than in the placebo group (13.0±8.0 versus 13.8±8.0) without statistically significant difference with or without adjustment for centre and baseline. Similar results were observed in the PPS and for the response to treatment, remission, and the time to first response and to first remission.

Assay-sensitivity: In the FAS, the mean last post-baseline HAM-D total score was lower in the paroxetine group than in the placebo group (12.2±8.1 versus 13.8±8.0) without statistically significant difference with or without adjustment for centre and baseline. Similar results were observed in the PPS.

Long term efficacy: In the Sub-FAS in double-blind extension period, results on the primary criterion (HAM-D) and on CGI were similar to those observed in the FAS (*i.e.* no relevant differences between the treatment groups). In the Sub-FAS of W6 responders, neither statistically significant nor clinically relevant difference were observed in the incidences over time of the first relapse and first loss of response when comparing agomelatine group or paroxetine group with the placebo group (complementary analyses).

Study CL3-024: In the FAS, the estimated difference of the last post-baseline HAM-D total score over the W0-W6 period between the agomelatine 25 mg group and the placebo group was not statistically significantly different (12.0±8.2 versus 13.4±8.4). The estimated difference was 1.31 (p=0.29).

Assay sensitivity: The estimated difference of the last post-baseline HAM-D total score over the W0-W6 period between the fluoxetine and placebo groups was 0.53 in favour of fluoxetine but did not reach statistical significance (p=0.54).

No statistically significant differences between the agomelatine 50 mg and placebo were observed for the last post-baseline HAM-D total score over the W0-W6 period.

Long-term efficacy analyses over the W6-W24 period: Among patients of the Sub-FAS in the double-blind extension period responders to treatment at W6 (decrease from baseline in HAM-D total score ≥50%) no statistically significant differences were observed between both agomelatine or fluoxetine groups and the placebo group for the time to first loss of response. The unusually low relapse rate in the placebo group made it difficult to conclude about the maintenance of efficacy in active treatment groups.

Studies CL3-021 and CL3-041 (Relapse prevention Studies)

Methods

Study Participants

Both studies 021 and 041 were multi-centre studies.

In Study CL3-021, 92 centres included patients: France (61 centres, 332 included patients), Spain (22 centres, 186 included patients) and Germany (9 centres, 33 included patients). Patients had to fulfil the

DSM-IV criteria for recurrent MDD, otherwise the inclusion and exclusion criteria were similar to those in the short-term studies.

In Study CL3-041, 56 centres included at least one patient: Australia (7 centres, 39 included patients), Finland (11 centres, 174 included patients), France (20 centres, 125 included patients), South Africa (6 centres, 75 included patients) and United Kingdom (12 centres, 79 included patients). Patients had to fulfil the DSM-IV-TR criteria for recurrent MDD, have a HAM-D total score of at least 22 with the sum of items 1+2+5+6+7+8+10+13 constituting at least 55% of the total score, a CGI-S score of at least 4, and a Hospital Anxiety Depression-Depression sub-score of at at least 11. Otherwise the inclusion and exclusion criteria were similar to those in the short-term studies.

Treatments

Study CL3-021: The study used one active treatment - agomelatine at 25 mg - and a placebo, administered once daily in the evening, as tablets of identical appearance. The dosage schedule was as follows: agomelatine 25 mg, during the open period (W0-W8); either agomelatine 25 mg or placebo, during the mandatory double-blind period (W8-W34); either agomelatine 25 mg or placebo, during the optional double-blind extension period (the same treatment as during the mandatory double-blind period).

No treatment was prescribed during the follow-up period, and no dose adjustments were allowed during the study. As far as possible, anxiolytic or hypnotic treatment was not to be taken during the study; however, as anxiolytic treatment a maximum dose equivalent to 20 mg of diazepam was allowed. If, following the W4 visit, a concomitant treatment by benzodiazepine was inferior, or equivalent, to 10 mg of diazepam, then it was authorised beyond W8.

Study CL3-041: All patients were treated with agomelatine (administered in the evening) during the open treatment period. From inclusion (W0) to W2, all patients received a dose of 25 mg of agomelatine daily + 1 placebo tablet. At W2, the 25 mg dose of agomelatine was either maintained or increased to 50 mg daily, depending on the clinical improvement of the patient, under double-blind conditions. This treatment was maintained until W8 /W10.

Patients fulfilling the randomisation criteria at W8 or W10 entered the double-blind treatment period. Patients randomised in the agomelatine group continued on the same dose as that taken from W2 to W8/W10. Patients entering the optional double-blind treatment period (BW24-BW44) continued on the same treatment. During the follow-up period patients did not receive any study treatment.

Objectives

The primary objective of study CL3-021 was to assess that agomelatine prevents the occurrence of depressive relapse compared to placebo in out-patients and hospitalised patients suffering from recurrent MDD during a mandatory double-blind period (W8 to W34). The secondary objective was to provide additional safety data on long term use of agomelatine (W8 to W52).

The primary objective of study CL3-041 was to assess the efficacy of agomelatine (25 mg / 50 mg) in the prevention of depressive relapse in ambulatory patients suffering from recurrent MDD, during 24 weeks of treatment after an initial response to agomelatine (25 mg or 50 mg). The secondary objective was to provide additional safety data on long-term use of agomelatine.

Outcomes/endpoints

Study CL3-021: The primary efficacy criterion was the HAM-D total score, mainly expressed as time to relapse. The time to relapse was defined as the time in days from the date of first intake of the randomised treatment to the date of the first event (or date of censoring), where relapse was defined as a total score ≥ 16 on HAM-D or suicide or attempted suicide.

The secondary analytical approaches were:

- Time to first loss of remission (days):
    - Loss of remission was defined as a HAM-D total score ≥ 7
    - The censoring was defined as the time of the measurement of the last HAM-D total score available on the analysed period

- Last post-W8 value
- Response to treatment, taking into account last post-W8 value, response being defined as follows:

$$100 \times \frac{\text{HAM-D}_{W0} - \text{HAM-D}_{(\text{post W8})}}{\text{HAM-D}_{W0}} = \% \text{ Response}$$

The response was considered as positive, if % Response ≥ 50.0%.

Secondary efficacy criteria:

- Severity of illness score, Global improvement score and Efficacy index issued from CGI scale
- Getting off to sleep score, Quality of sleep score, Sleep awakening score and Integrity of behaviour score issued from LSEQ

These criteria were expressed as last post-W8 value.

Study CL3-041: The primary efficacy criterion was the relapse which corresponds to the re-appearance of the index episode that occurs within 6 months after either a response, or a remission of the previous episode. Relapse was defined as one of the following: HAM-D 17-item total score ≥ 16, withdrawal for lack of efficacy, suicide, or suicide attempt.

The main analytical approach was the time to relapse during the double-blind treatment period defined as the time between the date of the first randomised treatment administration and the date of the relapse (or date of censoring).

A global assessment of the patient's general condition was determined by the item 2 of Clinical Global Impression scale (CGI) as a secondary endpoint.

Sample size

Sample size was estimated in relationship with the time until relapse, in order to have a statistically significant difference between placebo and agomelatine, using a two-sided log-rank test at 5% type I error. For 90% power, 71 events and so 158 patients per group were proven to be necessary in order to show a difference between placebo and agomelatine survival distributions, according to the respective appearance rate of 30% and 15%, 6 months after randomisation (Geddes, 2003).

In order to obtain 316-320 randomised patients in the double-blind period, and assuming that about 35% of included patients were expected to withdraw from the study before W8/W10, the number of patients included was therefore fixed at 500.

Randomisation

Study CL3-021: Treatments (agomelatine, placebo) were allocated by balanced randomisation, without stratification at W8. The treatments were allocated to patients according to a randomisation list. The randomisation was done using permutation blocks of fixed size (block size = 4). Each centre was given entire permutation blocks (implicit stratification factor). In each centre, the treatments were assigned to patients according to the chronological order of inclusion in the double-blind treatment period.

Study CL3-041: Allocation and randomisation of treatments was managed by an International Voice Response System (IVRS), according to specifications established before the beginning of the study. At W2, the 25 mg dose of agomelatine was either maintained or increased to 50 mg daily under double-blind conditions in the open period. For patients fulfilling the randomisation criteria at W8 or W10, agomelatine or placebo treatment was allocated to the patient by a balanced (non-adaptive) randomisation with stratification on the centre and on the randomisation visit (W8 or W10) in double-blind randomised treatment period. If the patient entered the optional double-blind treatment period, the same therapeutic number was conserved in the optional double-blind treatment period.

Blinding (masking)

Study CL3-021: Tablets of agomelatine and placebo were of identical appearance and taste and were packaged in identical blister packs of 18 tablets with identical labelling. Investigators (and/or pharmacists) were provided with sealed envelopes containing identity of the treatment administered to each patient. These envelopes were to be returned to the sponsor at the end of the study. The blind for any study patient could be broken by the investigator or an authorised person if it was absolutely necessary i.e., in case of life threatening emergencies, for which the treatment received by the patient could have an influence on the emergency therapy. If the blind was broken, the investigator was to complete, date and sign a form stating the number of the involved persons and reasons for breaking the blind.

Study CL3-041: Dosage schedule, study treatment appearance and organoleptic features (taste) were the same from inclusion to the end of the treatment period. Tablets were packaged in identical blisters of 12 tablets with identical labelling. The criteria for adjusting the dose, and whether or not the dose was adjusted at W2, were not disclosed to the investigator or to the patient, in order to eliminate subjective effects on the evolution of the patient's condition. The dose adjustment at W2 was centrally performed using an IVRS procedure. Therapeutic units were centrally and blindly allocated to patients at inclusion (W0), at W2, and at randomisation (W8/W10 = BW0) using an IVRS procedure. The decoding system used was a centralised decoding by IVRS. The code for any patient could be broken by the investigator or an authorised person if it was absolutely necessary to ascertain the type of treatment given.

Statistical methods

Study CL3-021

Main analysis: Incidence of relapses over time was estimated by the Kaplan-Meier method. The difference between agomelatine and placebo on the time to relapse was tested using a (non-stratified) Log-rank test (non-parametric procedure).

Supportive analyses: A Cox model associated with the Likelihood ratio test was performed involving only treatment effect, in order to compare groups and estimate the relative risk of agomelatine versus placebo and its 95% confidence interval on the time to relapse. An adjusted Cox model associated with the Likelihood ratio test was performed, which included the treatment effect and four covariates, in order to compare groups and estimate the relative risk of agomelatine versus placebo and its 95% confidence interval on the time to relapse. The following covariates were taken into account: Age (< 50 years and ≥ 50 years), Number of major depressive episodes (≤ 3 and > 3), Current major depressive episode duration (≤ 2 months and > 2 months) and HAM-D total score at W8 (< 7 and ≥ 7).

- Analyses defined above were also carried out on PPS over the W8-W34 period.

As secondary analyses, same strategy was carried out on FAS post-W10 and PPS post-W10 during the period W10-W34.

To study maintenance of efficacy on the long-term, the same analyses were performed on the FAS over the period W8-W52.

Secondary analytical approaches of primary criterion:

- Incidence of loss of remission over time was estimated by the Kaplan-Meier method.
- The difference between agomelatine and placebo was studied on the time to first loss of remission using a (non-stratified) Log-rank test (non-parametric procedure) on the Sub-FAS with W8 HAM-D total score < 7 over W8-W34 and W8-W52.
- Moreover, a Cox model associated with the Likelihood ratio test was performed involving only the treatment effect, in order to compare groups and estimate the relative risk of agomelatine versus placebo and its 95% confidence interval over W8-W34 and W8-W52.
- The difference between agomelatine and placebo was studied for the last post-W8 value using a 95% confidence interval on the FAS and PPS over W8-W34.
- The difference between agomelatine and placebo was studied for response to treatment taking into account the last post-W8 value using a 95% confidence interval on the FAS and PPS over W8-W34.

Study CL3-041
Primary criterion

- Main analysis:

The incidence of relapse over BW0-BW24 was compared between agomelatine and placebo groups using a log-rank test stratified for centre type (centres managed by psychiatrists or by GPs) and randomisation visit (W8 or W10) in the FAS.

In order to estimate the hazard ratio of relapse on agomelatine as compared to placebo, a Cox model associated with the likelihood ratio test was performed in the FAS, with adjustment for centre type and randomisation visit.

In addition, descriptive statistics by treatment group were provided.

- Sensitivity analyses:

The hazard ratio of relapse on agomelatine as compared to placebo was also estimated using a Cox model with adjustment for HAM-D 17-item total score at inclusion in addition to centre type and randomisation visit. Furthermore, a non-stratified log-rank test and an unadjusted Cox model were carried out.

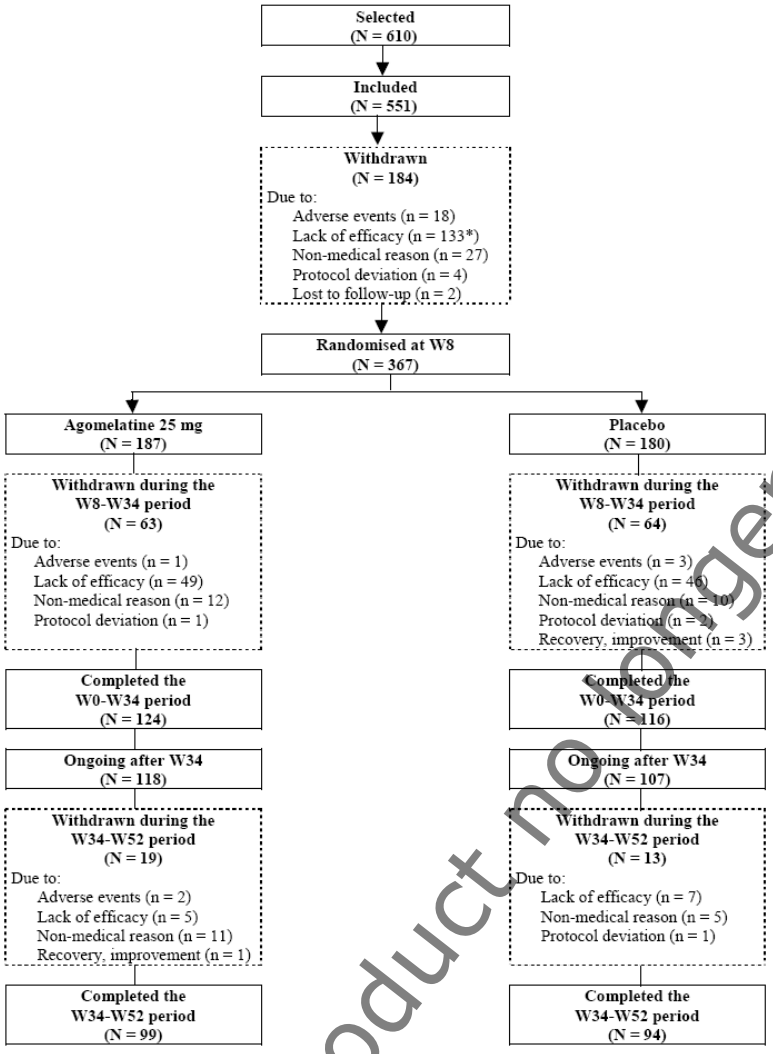
- Secondary analyses:

The same analysis strategy was applied to the two subsets of clinical interest of the FAS, with obviously no stratification on the centre type in the Sub-FAS Psychiatrists.

Results

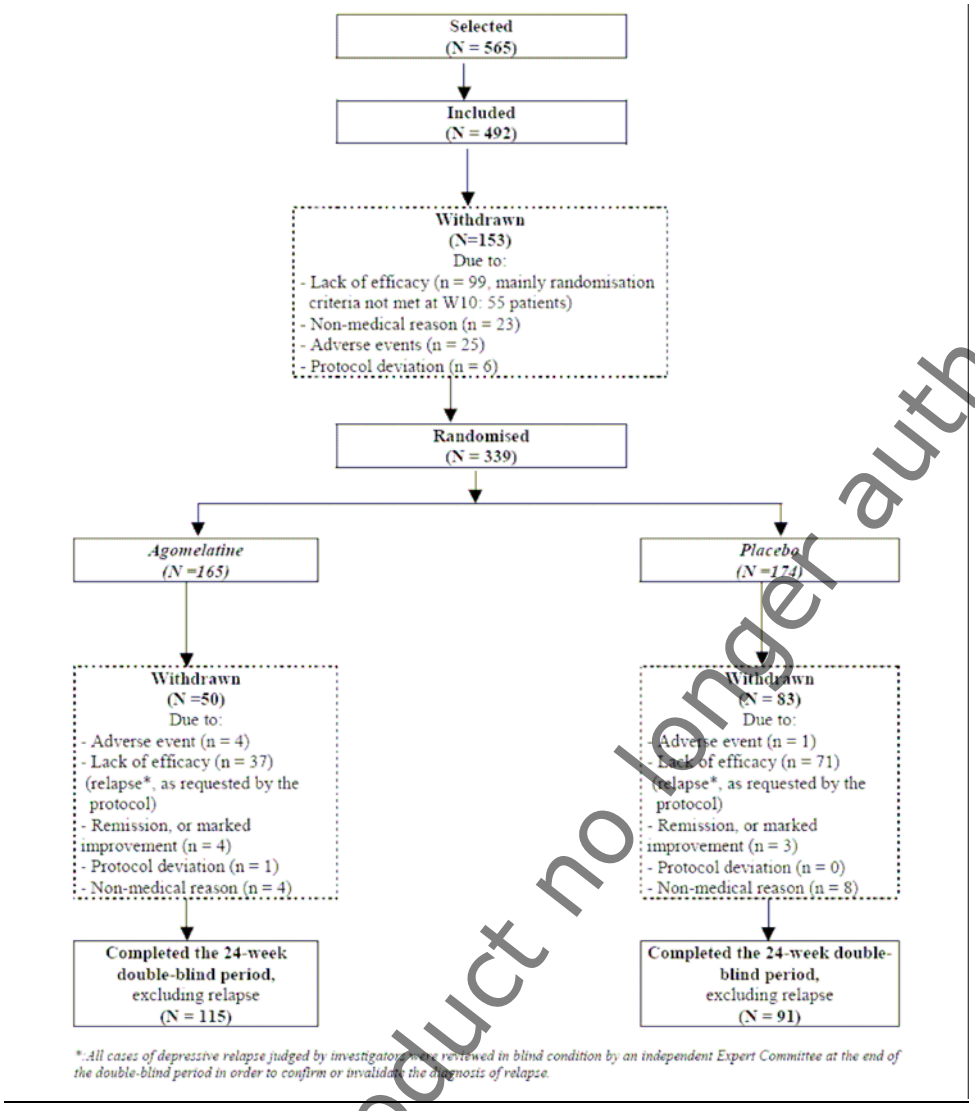
Participant flow

Figure 4: Disposition of patients included and randomised in Study CL3-021.



** Including one patient, who had no HAM-D assessment after visit W6, continued on the study until W10 with a non-randomised treatment, before being withdrawn due to lack of efficacy.*

Figure 5: Disposition of patients included and randomised in Study CL3-041.



As regards to the agomelatine dose, 109 patients of the 471 continuing at W2 (23.1%) had a dose increase to 50 mg. Among them, 60 were randomised (23 to agomelatine and 37 to placebo).

Recruitment

For study CL3-041 the first patient was enrolled on 03 February 2005; study completion was 07 February 2007.

For study CL3-021 the first patient was enrolled on 30 September 1999; study completion was 26 June 2002.

Conduct of the studies

For study CL3-021 the original protocol was dated 1st July 1999; there were six amendments, two of them mentioned below:

- Amendment No.1, dated 5 October 1999, concerned, among other things, ongoing criteria for the mandatory double-blind period: a concomitant treatment by benzodiazepine was permitted only in patients who were already taken a benzodiazepine for at least 1 month before inclusion at a stable dosage (at a dose equivalent of < 10 mg of diazepam at W4).

Amendment No. 3, dated 14 June 2000, concerned selection criteria: hospitalised patients could be selected.

For study CL3-041 the original protocol was dated 12th October 2004; there were 3 amendments.

Amendment No. 1, dated 17 March 2005, added Servier Research and Development Limited as local sponsor for UK.

Amendment No. 2, dated 5 April 2005, added a new country, Australia, to make the recruitment easier.

Amendment No. 3, dated 30 December 2005, added a HAD sub-score of depression of at least 11 to selection criteria in order to characterise the depression as regards patients' point of view. This amendment was applied in all centres for patients further selected.

Baseline data

Study CL3-021: Of the 367 patients included in the randomised set, 22.1% were male patients and 77.9% were female patients. Their age ranges from 19 to 67 years, with a mean age of 45.7 years old.

Study CL3-041: Of the 339 patients included in the randomised set, 25.7% were male patients and 74.3% were female patients. Their age ranges from 19 to 65 years, with a mean age of 43.3 years old.

Numbers analysed

For study CL3-021 most analysis sets were defined before study unblinding. The Randomised Set comprised a total of 367 patients; 187 in the agomelatine group and 180 in the placebo group. The Full Analysis Set (FAS) consisted of 364 patients (99.2% of the Randomised Set). In all, 3 patients of the Randomised Set were excluded from the FAS due to a HAM-D total score > 10 at W8: 2 in the agomelatine group and 1 in the placebo group.

FAS post-W10, defined as all patients of the FAS having at least one HAM-D evaluation on the [W10-W34] period. This was to distinguish relapse from rebound and withdrawal phenomena after W8, when some patients experienced a change of treatment.

In addition, subsets of the FAS were defined:

Sub-FAS with HAM-D total score ≤ 6 at W8, defined as all patients of the FAS with a HAM-D total score ≤ 6 at W8. A total of 182 patients (49.5% of the RS) were considered as being in remission.

Sub-FAS in extension period, defined as all patients of the FAS having decided to continue in the optional double-blind placebo-controlled extension period (W34-W52).

Sub-FAS not in extension period, defined as the complementary set of the Sub-FAS in extension period.

In study CL3-041 the Randomised Set comprised a total of 339 patients; 165 in the agomelatine group and 174 in the placebo group. The Full Analysis Set (FAS) included the same patients as the Randomised Set and thus consisted of 339 patients.

Two subsets of the FAS were defined:

- The **Sub-FAS psychiatrists**, defined as patients of the FAS followed by a psychiatrist, consisted of 227 patients (67.0% of the FAS)
- The **Sub-FAS with W0 HAM-D total score ≥ 25**, defined as all patients of the FAS with HAM-D 17-item total score at inclusion ≥ 25, consisted of 270 patients (79.6% of the FAS).

Outcomes and estimation

For study CL3-021:

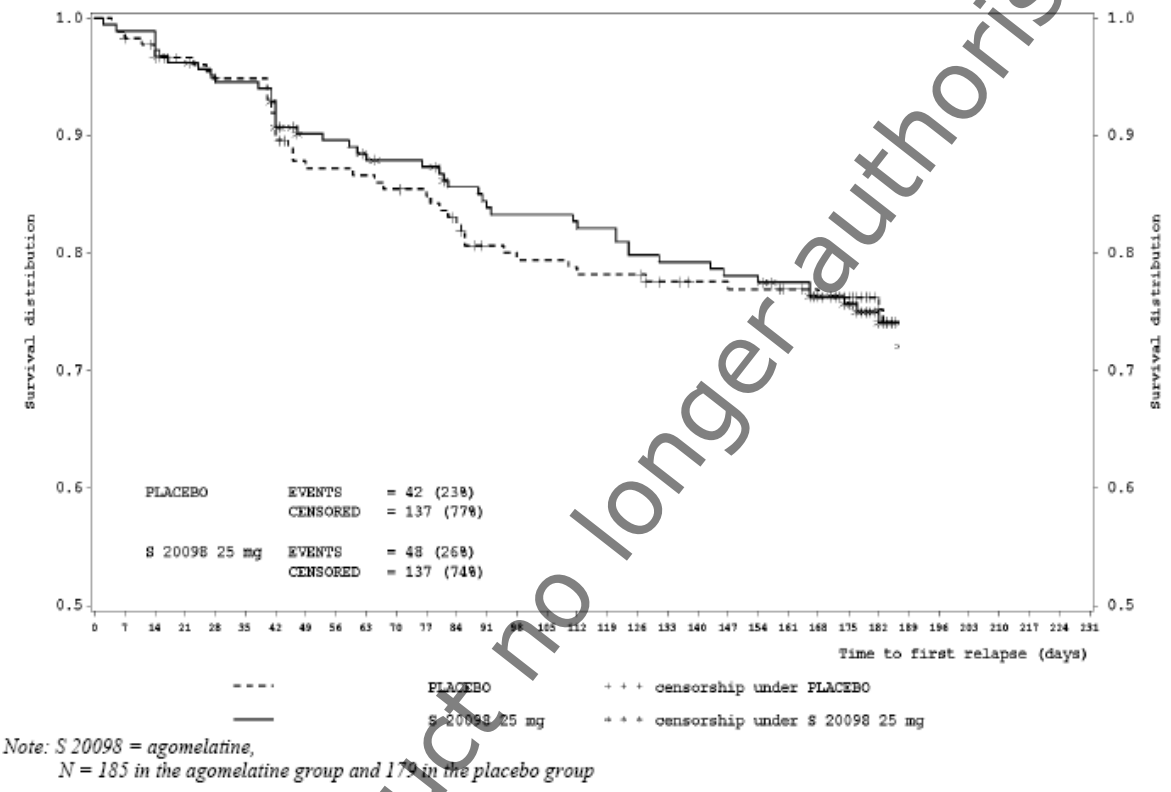
The primary criterion was HAM-D total score. The main analytical approach was time to relapse after W8. The time to relapse was defined as the time interval in days between the first randomised treatment administration and relapse.

In the FAS, the incidence of patients with relapse was 25.9% (48/185) in the agomelatine group *versus* 23.5% (42/179) in the placebo group over W8-W34.

In a *post-hoc* analysis, in the group of more severe patients (with HAM-D > 25 and CGI-S ≥ 5 at W0), agomelatine reduced the percentage of relapse (21.3%) compared to placebo (31.3%) over W8-W34.

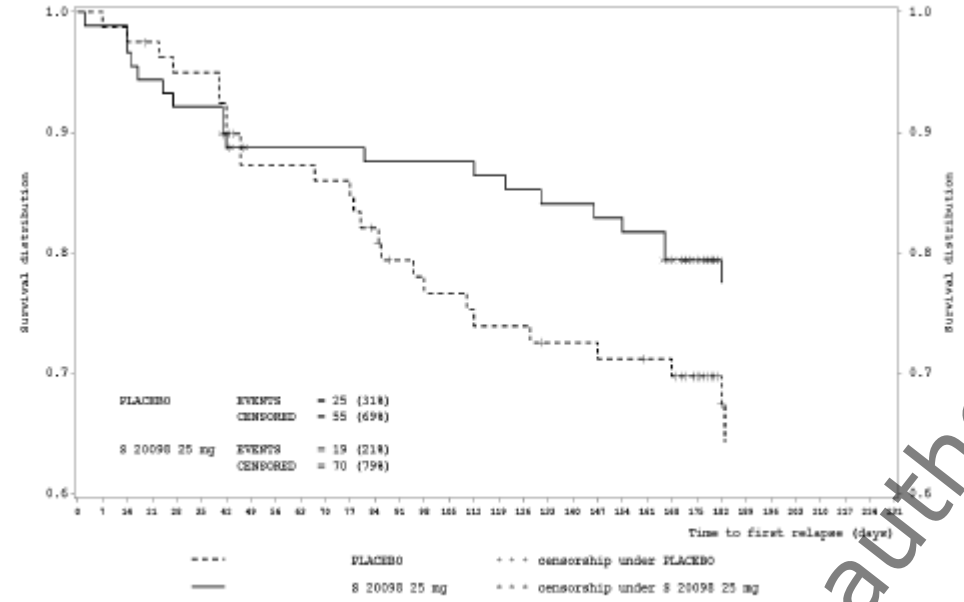
This difference became statistically significant (HR= 0.57, p = 0.046) over the period W8-W52. In the population of more severe patients who were in remission at W8, the RR value of 3.020 corresponds to a reduction of about 67% in the relative risk of relapse in the agomelatine group *versus* the placebo group. Statistically significant differences were also observed over the period W10-W34 in the subgroup of severe patients in the Sub-FAS post-W10 HAM-D > 25 and CGI-S ≥ 5 at W0, and Sub-FAS post-W10 HAM-D > 25 and CGI-S ≥ 5 at W0 who were in remission at W8.

Figure 6 : Time to relapse in the FAS over the period W8-W34 in CL3-021



Note: S 20098 = agomelatine,
N = 185 in the agomelatine group and 179 in the placebo group

Figure 7 : Time to relapse in the sub-FAS with HAM-D greater than 25 and CGI-S greater than or equal to 5 at W0 over the period W8-W34 in CL3-021



Note: S 20098 = agomelatine,
N = 89 in the agomelatine group and 80 in the placebo group

Secondary analytical approach
During the open agomelatine treatment period W0-W8, the mean HAM-D total score in the FAS was reduced from 26.1 ± 2.8 (range 21-37; n=364) to 6.1 ± 2.7 (range 0-10; n=364) at W8. After randomisation, the HAM-D total scores in the two groups were similar throughout, and no statistically significant difference between agomelatine and placebo was observed. At W34 both groups had a mean score of 6.3, and the last observation in the agomelatine group was 9.3 *versus* 9.6 in the placebo group.

Secondary efficacy criteria:

CGI scores: **The severity of illness score**, which had shown improvement during the open period of the study, was maintained during the randomised period. The severity of illness score increased from 1.8 ± 0.8 at W8 to 2.3 ± 1.5 at the last post-W8 visit in the agomelatine group. The same result was obtained in the placebo group. **The global improvement score** which had shown lowered (improved) scores at the end of the open period of the study (from 3.0 ± 1.0 at baseline to 2.2 ± 1.4) increased, in both groups, over the randomised period. In the FAS, the mean score in the agomelatine group increased from 2.8 ± 1.5 at W10 to 3.5 ± 1.9 at the last visit. Similar results were observed in the placebo group. **The efficacy index score** showed slight fluctuations in both groups during the randomised period, but overall little change. **LSEQ scores**: LSEQ scores improved during the open period, but these improvements were gradually reduced during the randomised period, in both treatment groups. Although the between-group differences were not significant at the last post-W8 value over W8-W34 period, the four mean scores in the agomelatine group were lower, which may indicate a persistent positive effect on sleep in this group. Similar results were observed over the period W8-W52.

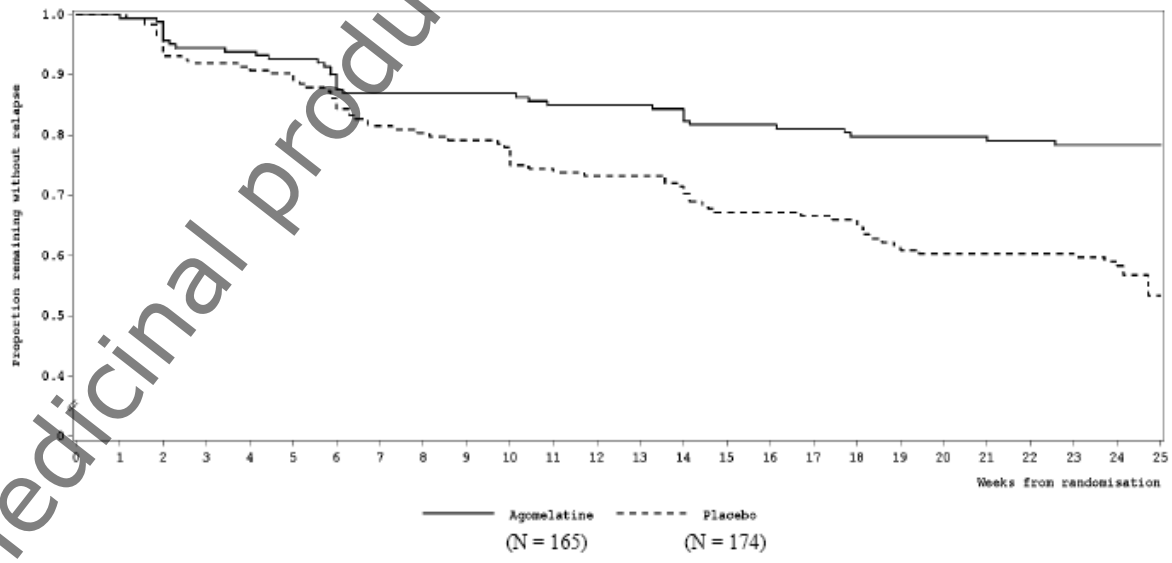
For study CL3-041
The primary efficacy criterion was the relapse. The time to relapse during the double-blind treatment period was the main analytical approach. It was defined as the time interval in days between the date of the first administration of randomised study treatment and the date of relapse (or date of censoring). Number of patients with a depressive relapse during the 24-week double-blind period, incidence over time, and risk of relapse in the FAS and Sub-FAS are presented in Table 5.

Table 5: Number of patients with a depressive relapse during the 24-week double-blind period, incidence over time, and risk of relapse in the FAS and Sub-FAS

		Agomelatine		Placebo
FAS		N=165		N=174
Total events*	**N (%)**	**34 (20.6%)**		**72 (41.4%)**
Main analysis				
Incidence after 175 days	E (SE)[1]	21.7% (3.3%)		46.6% (5.0%)
Stratified log-rank test[(a)]	p value		0.0001	
Adjusted Cox-model[(a)]	E (SE)[2]		0.458 (0.095)	
	95% CI[3]		[0.305 ; 0.690]	
Sub-FAS psychiatrists		N = 110		N = 117
Total events*	N (%)	**22 (20.0%)**		**56 (47.9%)**
Incidence after 175 days	E (SE)[1]	21.3% (4.0%)		56.1% (6.9%)
Stratified log-rank test[(b)]	p value		< 0.0001	
Adjusted Cox-model[(a)]	E (SE)[2]		0.376 (0.095)	
	95% CI[3]		[0.230 ; 0.617]	
Sub-FAS with W0 HAM-D total score ≥ 25		N = 128		N = 142
Total events*	N (%)	**28 (21.9%)**		**64 (45.1%)**
Incidence after 175 days	E (SE)[1]	22.7% (3.8%)		50.4% (5.3%)
Stratified log-rank test[(b)]	p value		0.0001	
Adjusted Cox-model[(a)]	E (SE)[2]		0.432 (0.098)	
	95% CI[3]		[0.277 ; 0.673]	

*: Total number of patients having a relapse during the double-blind period.
[1]: Estimate (Standard Error) of the percentage of patients with a relapse after 175 days of treatment (Kaplan-Meier's method)
[2:] Estimate (Standard Error) of the adjusted Hazard Ratio of relapse between treatment groups: agomelatine versus placebo
[3]: 95% confidence interval of the estimate
[(a)]: Stratified or adjusted for centre type (psychiatrists or GP), and randomisation visit (W8 or W10).
[(b)]: Stratified or adjusted for randomisation visit (W8 or W10)

Figure 8:Time to relapse over the double-blind period in the FAS (Kaplan-Meier estimation) in CL3-041



Secondary efficacy criteria

HAM-D total score

In the Open Set, the mean HAM-D total score progressively decreased during the open period, from W0 (27.0 ± 2.7) up to last post-baseline assessment (9.9 ± 7.3). At the same time, the percentage of responders (defined as patients with a decrease from baseline of at least 50%) progressively increased from 10.4% at W2 to 78.6% at the last assessment.

During the double-blind period, in the FAS, the therapeutic benefit, acquired during the open period was maintained in the agomelatine group (mean change in HAM-D total score of 1.4 ± 6.9 between BW0 and the last post-randomisation assessment). In the placebo group, the mean score increased (mean change of 4.7 ± 8.4). Similar results were observed in both FAS subsets.

CGI

In the Open Set, the mean severity of illness score (4.9 ± 0.7 at W0), and the mean global improvement score (3.0 ± 0.8 at W2) decreased up to the last post-baseline assessment during the open period (2.4 ± 1.3, and 1.8 ± 1.1, respectively). At the same time, the percentage of responders according to the global improvement score (score of 1 or 2) increased from 25.7% at W2 up to 80.3% at the last assessment.

During the double-blind period, in the FAS, both mean scores were smaller in the agomelatine group than in the placebo group at the last post-randomisation assessment (2.1 ± 1.2 for severity, and 3.8 ± 1.6 for global improvement according to randomisation in the agomelatine group *versus* 2.6 ± 1.5, and 4.4 ± 1.7, respectively for the placebo group). In the agomelatine group, the therapeutic benefit, acquired during the open period was maintained during the double-blind period as regards the severity of illness whereas severity of illness worsened in the placebo group. Similar results were observed in both FAS subsets.

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

In a meta analysis including six of the pivotal studies (i.e. all the placebo-controlled short-term studies) whether positive (CL2-014, CL3-042, CL3-043) or not (CL3-022, CL3-023, CL3-024), with 1210 patients receiving agomelatine 25 and 50 mg but also sub-therapeutic doses, 1 and 5 mg, and 805 patients receiving placebo, an overall treatment effect of about 1.5 on the HAM-D in favour of agomelatine over placebo was observed. Using a model with study included as a fixed effect, the estimated difference was 1.51 with a 95% confidence interval of [0.80, 2.22]. When the study was modelled as a random effect, the estimated difference was 1.55 [0.61, 2.48].

- **Clinical studies in special populations**

Study CL3-026: efficacy in elderly patients with Major Depression

Efficacy and safety in elderly patients with Major Depressive Disorder was studied in Study CL3-026, comparing agomelatine (25 mg) given orally once a day for 6 weeks to placebo. This was a randomised double-blind, placebo-controlled, parallel group study with a 18-week extension period.

218 male or female out- or in-patients, aged ≥60 years, suffering from a single or recurrent episode of major depressive disorder according to DSM-IV criteria, with a MADRS score of at least 24, were included in this study. The duration of the current episode was to be ≤ 6 months. 109 patients were randomised to agomelatine 25 mg, 109 patients to placebo.

The age distribution of the participants for the agomelatine group in the study was the following: 60-65 years: 46 (42.2%) patients, 65-75 years: 51 (46.8%) patients and ≥ 75 years: 12 (11%) patients. In the placebo group the distribution was: 60-65 years: 36 (33%) patients, 65-75 years: 59 (54.1%) patients and ≥ 75 years: 14 (12.8%) patients.

The primary objective was to assess the efficacy of agomelatine 25 mg compared to placebo, using the Montgomery and Åsberg Depression Rating Scale (MADRS), after a 6-week treatment in elderly patients suffering from Major Depressive Disorder.

Short term efficacy (W0-W6): In the FAS no statistically significant between-group difference was observed in MADRS total score at the last post-baseline evaluation. The estimated difference was 0.19 (p=0.89). Similar results were obtained with adjustment for demographic variables, in the SUB-FAS without benzodiazepines, and in the PPS including completers only.

The percentage of patients responding to treatment according to the MADRS was 46% in the agomelatine group and 52% in the placebo group (p=0.41).

In an unplanned subgroup analysis of patients with more severe depression at baseline, agomelatine was found to be more effective than placebo. The estimated difference in the subgroup with MADRS ≥ 30 and CGI-S ≥ 5 was 5.58 (p=0.018) (see Table below).

Table 6: Difference in MADRS score at the end of short-term treatment between agomelatine 25 mg and placebo in the overall population and subgroups of more severely depressed patients in study CL3-026 (FAS-Last assessment)

Population	N	Difference	P-value
Overall (primary analysis)	212	0.19	0.894
MADRS≤30	102	3.97	0.066
MADRS≤30 and CGI-S≥5	86	5.58	0.018

In a pooled analysis of the positive short-term studies (CL2-014, CL3-042 and CL3-043 : only studies allowing patients over 60 years of age to be included) a more pronounced effect was observed in patents between 60 and 66 years of age (Table 7).

Table 7: Difference in HAM-D score between agomelatine and placebo in subgroups based on age in the positive short-term studies (FAS-Last assessment)

Age	N	Difference	P-value
60-66 years	53	4.50	0.033
<60 years	668	2.73	<0.001

Long term efficacy (W0-W24 period): In the SUB-FAS in double-blind extension period, the mean MADRS total score decreased between baseline and W24 visit. Regarding the last post-baseline value over the (W0-W24) period, the mean MADRS total score was 10.6 in the agomelatine group and 9.6 in the placebo group.

The percentage of responders according to MADRS increased over the (W0-W24) period to reach 70% in the agomelatine group *versus* 78% in the placebo group at last post-baseline evaluation. The percentage of remitters at last post-baseline evaluation was 65% *versus* 72%, respectively. No difference was observed between the two groups in the percentage of responders at the last post-baseline evaluation during the W0-W24 period in the sub-group of responders at W6 (83% and 87% in the agomelatine and placebo groups, respectively).

The mean severity of illness score and global improvement score of the CGI scale decreased over the (W0-W24) period in both groups. The mean efficacy index increased at each visit in both groups without between-group difference.

Overall, no statistically significant difference between placebo and agomelatine 25 mg was observed. The estimated difference on the MADRS between agomelatine and placebo was 0.19, which was considered to be negligible. Still, the applicant argued that in subgroup analyses of more severely depressed patients a positive effect was observed. However, with the almost total lack of treatment difference in the overall population in the elderly study, the validity of positive results in the subgroups with more severely depressed patients was questioned. The more pronounced effect seen in patients aged 60-66 years in the non-elderly studies could not be indisputably extrapolated to older patients. The lack of convincing data on efficacy in elderly was considered and raised as a major objection during the procedure. In response, the applicant proposed to conduct a post-marketing study of the efficacy and safety of agomelatine in patients older than 65 years with a special focus on patients aged 75 years and above. The applicant provided an early draft synopsis and recruitment plan for this study which was considered acceptable.

- **Supportive studies**

The following were presented as supportive studies: Study CL3-025, on the efficacy and safety of agomelatine 50 mg in depressed patients who failed to respond to agomelatine 25 mg after 4 weeks; Study CL3-036, to assess sexual function after 3 months of treatment with agomelatine (50mg/day) versus venlafaxine (150mg/day); a randomised double-blind study comparing agomelatine 25-50mg to venlafaxine 75-150 mg (Study CL3-035); Study CL3-030, aimed to assess the safety of agomelatine 25 mg after an abrupt discontinuation after 12 weeks. Study CL3-035 is presented below.

Study CL3-035: Effects on sleep The agomelatine impact on sleep in depressed patients was the primary objective in one venlafaxine-controlled study (CL3-035) and a secondary objective in some of

the placebo controlled studies. Study CL3-035 was a randomised, double-blind study with a short-term phase and an extension phase in which agomelatine 25-50 mg was compared to venlafaxine 75-150 mg. A modest effect in favour of agomelatine was demonstrated, primarily on the LSEQ Getting off to sleep sub-score (5 mm versus venlafaxine on a 100 mm VAS).

- **Discussion on clinical efficacy**

The main dose finding study, CL2-014, compared the efficacy of 1, 5 and 25 mg agomelatine vs. placebo with paroxetine 20 mg as an active control to ensure the assay sensitivity. Agomelatine 25 mg and paroxetine 20 mg were statistically significantly superior to placebo with absolute difference in HAM-D 17 items (Hamilton Depression Rating Scale) score of 2.57 and 2.25, respectively, in the FAS. Agomelatine 1 mg showed a non significant, absolute effect of 2.17 compared to placebo, whereas agomelatine 5 mg consistently performed worse than the two other groups (the advantage over placebo was only 0.64). The statistically significant advantage of agomelatine 25 mg was not reproduced when comparing completers only, which made the results from the FAS less convincing. The lack of efficacy in the agomelatine group also made the dose-response relationship questionable.

Studies CL2-007 and CL2-014 did not provide clear-cut dose responses and the drug showed highly variable PK implying that exposures vary a lot from patient to patient. Later efficacy studies compared agomelatine 25 mg and 50 mg without clearly showing better efficacy of the higher dose, e.g. in one study (CL3-024) 25 and 50 mg were compared to placebo but both doses as well as the active comparator fluoxetine failed to show a positive effect versus placebo.

During the procedure the applicant was requested to commit to perform a proper dose-finding study. However the applicant claimed to have shown sufficient efficacy for the two chosen doses of 25 mg and 50 mg per day and no new data were submitted. Agomelatine had an intrinsic unpredictable and highly variable pharmacokinetic profile. Given that the dose-response relation remained unclear, the applicant committed to perform a post approval study of the dose-response relationship of agomelatine, including also a randomised dose adjustment in non-responders to 25 mg agomelatine after 2 weeks.

In the overall clinical program it was difficult to distinguish a greater efficacy with the dose of 50 mg in comparison to 25 mg, although a fraction of the patients seemed to improve from this dose increase.

In most of the studies showing an effect, (short-term studies CL3-042 and CL3-043 and long-term studies CL3-041, and CL3-035 extension), the 25 mg starting dose was increased to 50 mg after two weeks in case of insufficient response. Thus the recommended dosage proposed in the SPC "*25 mg QD with a dose increase to 50 mg if there is no improvement of symptoms after two weeks of treatment"* seemed reasonable. However, in study CL3-025 where patients with insufficient response to 25 mg at week 4 were randomised between 25 and 50 mg, no benefit of a dose increase could be demonstrated, and the applicant was later requested to justify the recommended posology. In response, the applicant concluded that while the objective of the supportive study CL3-025 was to obtain the full response in patients partially responders to a 4-week treatment with agomelatine 25mg, the objective of studies CL3-042 and CL3-043 was to reverse the course of the outcome of patients with early poor improvement, and that the conclusion in CL3-025 was not valid for the posology in question. However**,** the CHMP did not agree that the clinical benefit of increasing the dose from 25 mg to 50 mg after two weeks had been convincingly documented. The applicant was requested to perform a new study randomising between 25 and 50 mg in patients not responding to the initial dose of 25 mg after two weeks of treatment in accordance with the proposed posology. The applicant committed to perform a study with an acceptable design as a FUM.

Short-term efficacy results

Agomelatine showed statistically significant superiority to placebo in the pivotal trials CL3-042 and CL3-043, as measured on the HAM-D. In total, these two studies included 631 patients, who were treated with agomelatine 25 mg with a possible dose increase to 50 mg after 2 weeks. No active comparator was included in the study design. The absolute advantage of agomelatine over placebo at the end of week 6 was 3.18 points on the HAM-D in the FAS in study CL3-042 and 2.41 in study CL3-043. These absolute differences were in line with results in other studies comparing antidepressants to placebo, but could not be interpreted directly since an active comparator was not included.

The pivotal studies CL3-022, -023 and -024 included a total of 1444 patients. CL3-022 and -023 compared the efficacy of agomelatine 25 mg vs. placebo with fluoxetine 20 mg and paroxetine 20 mg, respectively, as active comparators to check assay sensitivity. No direct comparison between agomelatine and fluoxetine or paroxetine was thus planned or performed. In CL3-024 a four-armed design was used comparing both agomelatine 25 mg and 50 mg to placebo, again including fluoxetine to ensure assay sensitivity. None of these studies showed any statistically significant difference between agomelatine treatment and placebo. Only in CL3-022 the active comparator (fluoxetine 20 mg) proved to be superior to placebo. The lack of efficacy of the active comparator drugs was believed mainly to be due to an insufficient dose and possibly to unusually high placebo responder rates.

Although the results for agomelatine on the average seemed similar to the results for the SSRI comparators, the overall impression was that the proportion of non-significant results is probably larger for agomelatine compared to SSRIs in general. Three of the six studies indicated a possible treatment effect of agomelatine compared to placebo. Trial failure did not seem to be due to lack of power since the number of patients included was larger than in the studies showing a positive treatment effect; it was the efficacy estimate that was very small. A meta-analysis of these six studies resulted in an overall estimate of the difference between agomelatine (also including sub-therapeutic doses 1 and 5 mg) and placebo of 1.5 on the HAM-D with a 95% confidence interval [0.80, 2.22]. The CHMP considered this difference to be of doubtful clinical relevance and one of the major objections against the approval of agomelatine. In their response the applicant referred to a newly finished short-term (6 weeks) study, CL3-046, where agomelatine (flexible dose 25 to 50 mg) and sertraline (50 to 100 mg) were compared. Although the primary objective was to assess the efficacy on the rest-activity cycle, the short-term antidepressant efficacy was evaluated using the HAM-D and CGI scales. The head-to-head comparison (LOCF, FAS) showed a statistically significant superiority of agomelatine over sertraline on HAM-D total score (pre-specified efficacy analysis: difference = 1.68, p=0.031). Although the magnitude of effect was still considered to be of marginal clinical relevance, it was acknowledged that agomelatine had documented some short-term efficacy.

Long-term efficacy results

Study CL3-021 was designed as a relapse prevention study comparing agomelatine 25 mg to placebo following 8 weeks open treatment with agomelatine. During the open treatment period mean HAM-D score was reduced from 26.1 to 6.1. During the 26 weeks of double blind treatment the incidence of relapse was 25.9% in the agomelatine group vs. 23.5% in the placebo group, HR= 1.046, logrank *p*= 0.833. The relapse rates observed *during* treatment both in the agomelatine group and in the placebo group actually corresponded to reports on relapse in patients successfully treated with other antidepressants who are no longer receiving pharmacological treatment and importantly, there was no difference between agomelatine and placebo. No relapse preventing effect was thus demonstrated in the pre-specified analyses. In *post hoc* defined subgroup analyses in patients with baseline HAM-D>25 and CGI-S≥5 the estimated hazard ratio was 0.63 (*p*=0.125). The proportion of patients in this subgroup was 46%. Only when these patients were followed until W52, the difference between agomelatine and placebo became statistically significant (HR=0.57, *p*=0.046).

After the negative CHMP opinion in 2006 an additional relapse prevention study was finalised. This study, CL3-041, included 492 patients with Major Depressive Disorder. A statistically significant difference in time to relapse in the total population was demonstrated, HR=0.458, logrank *p*=0.0001. 20.6% relapsed in the agomelatine group *vs* 41.4% in the placebo group. In a subgroup of patients with HAM-D≥25 (79.6% of the total population) a slightly larger effect was shown, 21.9% *vs* 45.1% in the agomelatine and placebo group, respectively (HR=0.432, logrank *p*<0.0001).

There were striking differences (perhaps related to patient selection) in the results of the two relapse prevention studies. Even if the main criterion of a HAM-D score of at least 22 was used in both studies, there was a different proportion of patients with more severe depression (HAM-D≥25) in study CL3-041 (approximately 80% in CL3-041 *vs* 46%in CL3-021). Even though the reasons for the inconsistency between the results of the two studies remained unknown, the results of study CL3-041 were accepted as a demonstration of maintenance of efficacy. No difference in efficacy between severely depressed patients and patients with moderate/mild depression was found.

Recently submitted data after extension to 10 months in study CL3-041 seemed to sustain and confirm the results achieved after 6 months, as the percentage of patients with relapse over 44 weeks was still more than two-fold lower in the agomelatine group compared to the placebo group.

In addition, there was long-term data from two double-blind extensions of short-term studies (CL3-022 and CL3-035); the applicant claimed these were supportive of long-term efficacy. However, in study CL3-022, at 6 months there was no difference between the placebo and agomelatine arms in terms of withdrawals / patients staying on treatment, while more patients remained in the fluoxetine arm. This was not reassuring and questioned the effect of agomelatine. In the long-term phase of CL3-035, global assessment by the CGI-I was the primary outcome measure. Although the results showed that agomelatine 25-50 mg was superior to venlafaxine 75-150 mg and the results were supported by trends in favour of agomelatine in the long-term analysis on the remitters (60.0% versus 50.3% respectively, p=0.076), bias from the initial focus on subjective sleep parameters in favour of agomelatine versus venlafaxine could not be excluded. The venlafaxine dose (75-150 mg/d) might be viewed as sub-optimal. It was also considered a weakness that only the CGI scale was used as a rating scale and not a more specific depression rating scale

In addition, as mentioned earlier under Clinical studies in special populations, there was also a lack of convincing data on efficacy in the elderly.

In summary, some positive treatment effect of agomelatine in Major Depressive Episodes was demonstrated although the magnitude of effect was still considered to be of marginal clinical relevance. Results on long-term efficacy differed between the two relapse prevention studies – only the more recent study including a larger proportion of patients with more severe depression succeeded in demonstrating a significant difference in time to relapse.

Clinical safety

The safety of agomelatine was investigated in all clinical studies of the overall agomelatine clinical development programme, 57 completed studies and 8 ongoing studies at the cut-off date of 31st March 2007 (4 Phase III studies in MDD patients, 1 Phase III study in bipolar I depressed patients, 1 Phase II study in children with Smith-Magenis syndrome and 2 studies in healthy volunteers).

The 57 completed studies comprised:

- 27 PKH/phase I studies: 25 conducted in healthy volunteers, 1 in subjects with renal impairment and 1 in subjects with liver impairment
- 30 phase II/III studies conducted in patients: 13 in MDD patients, 2 specific safety studies in MDD (or bipolar or Seasonal Affective Disorder (SAD)) and 15 in other indications.

The ongoing studies were assessed only for serious adverse events using the cut-off date of 31st March 2007.

- **Patient exposure**

The number of exposed individuals (healthy volunteers, MDD patients including bipolar patients, patients with Seasonal Affective Disorder (SAD), severely ill hospitalised depressed patients, and patients in other indications) who received at least one dose of agomelatine, in either controlled or open studies, by oral or i.v. route, is presented in Table 8.

Table 8: Number of individuals who received at least one dose of agomelatine.

No. of individuals	Volunteers in phase I studies	MDD patients[1]	Patients in other indications	Total exposed
Completed studies	522	3956	782	5260[2]
Ongoing studies[3,4]	10	528	-	538
Total	532	4484	782	5798

[1] including 21 bipolar patients and 355 patients with Seasonal Affective Disorder

2 not taken into account were 9 children with Smith-Magenis Syndrome exposed to agomelatine and 33 patients of cross-over studies who received the comparator or placebo in the first treatment period

3 cut-off: 31 March 2007

4 estimated number of patients on agomelatine in ongoing studies = number of included patients x ½ (2-arm studies) or 2/3 (3-arm studies including 2 agomelatine arms)

The strategy of the overall safety evaluation was:

- An analysis of safety data collected from pharmacological studies in healthy volunteers (or subjects with renal or liver impairment). Special attention was paid to the emergence of adverse events in the drug-drug interaction studies, since concomitant treatments are prevalent in the MDD populations.

- An analysis of the pooled safety data from all completed Phase II/III studies in patients (whatever the indication) (Overall Safety Set, N = 6931). This dataset was used to identify potential non-specific safety concerns and rare events. These patients received either agomelatine, placebo, fluoxetine, paroxetine or venlafaxine treatment. Analyses were performed by treatment group (and by agomelatine dose group for some analyses).

- Analyses of several study groupings were made in order to provide a greater coherence in population, study design and patient exposure. A particular focus was made on double-blind placebo-controlled studies in MDD patients; the descriptive analyses are presented first for short-term and then long-term double-blind placebo-controlled studies, before other groupings. Analyses were performed by treatment group and by agomelatine dose. Patients who received the therapeutic agomelatine doses, 25mg or 50mg, were also pooled to provide a clearer clinical picture.

The main analysis sets were:

- *Short-term double-blind (DB) placebo-controlled (PC) MDD Set* (N = 2973): an analysis of the first 6 to 8 weeks of treatment in studies with similar designs.

- *Long-term DB PC MDD Set* (N = 1244): studies that were extended after the short-term observation period, up to 6 months. Only patients who entered the extension period were considered. These patients received either agomelatine, placebo, fluoxetine or paroxetine. Analyses were performed mainly over the period from 6 to 24 treatment weeks.

- *DB PC MDD Set* (N = 2973): an analysis of double-blind placebo-controlled MDD studies irrespective of study duration. This set was used to limited extent in the analysis of adverse events of special interest to avoid unnecessary repetition.

- *All MDD Set* (N = 5822): an analysis of the pool of all MDD studies to describe the overall exposure in the depressed population and to globally assess the consistency of the agomelatine safety profile, whatever the conditions of evaluation (placebo-controlled, active-controlled, or open). Patients received either agomelatine, placebo, fluoxetine, paroxetine or venlafaxine.

In total, 4738 patients irrespective of the studied disorder (Overall Safety Set) received agomelatine. The mean treatment duration under agomelatine (all doses) was 4.2 ± 3.6 months (i.e. about 16 weeks), ranging from 1 day to 19 months.

When considering the target population of depressed patients (All MDD Set), a total of 3956 patients were exposed to agomelatine. Among these patients, 1030 had 6-month of exposure to agomelatine. 368 patients received agomelatine 25 mg and 32 patients received agomelatine 50 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. 319 patients in the MDD population were 60 years or older, while 109 patients were 65 years or older.

Of the patients ≥ 75 years receiving agomelatine, 13 were MDD patients. All of these were treated with 25 mg agomelatine. Due to the limited number of patients included in the studies, agomelatine should be prescribed with caution in this age group (≥ 65 years of age).

Table 9: Number of exposed patients by safety set, treatment and duration

	All exposed individuals[1]	All exposed patients (Overall safety set)	All exposed depressed[2] patients (all MDD set)			
	agomelatine	agomelatine		agomelatine	placebo	active control[4]
All periods	5260	4738[3]	all periods	3956	826	1040
			for 5 months	1704	293	565
			for 6 months[5]	1030	68	164
			for 1 year[6]	400	-	-

[1] *including healthy and patient volunteers*
[2] *patients with MDE in the framework of Unipolar disorder except, 13 patients with Bipolar II (CL2-014), 21 patients with Bipolar I (CL3-029) depressive disorders and 355 patients with Seasonal affective disorder (CL3-037).*
[3] *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*
[4] *fluoxetine, paroxetine or venlafaxine*
[5] *exposed for at least 175 days*
[6] *exposed for at least 350 days*

Demographics

In the *Overall Safety Set (OSS),* the mean (± SD) patient age was 46.4 ± 15.5 years with a range of 16 - 102 years. The patients in the *All MDD Set* were slightly younger at 43.4 ± 12.0 years, while the patients in the *DB PC MDD Set* averaged 44.0 ± 12.5 years.

As was expected in this disorder, most patients were female: 69.3% in the OSS, 71.0% in the All MDD Set and 69.8% in the DB PC MDD Set.

Just over 60% of patients had previously received psychotropic treatments. Taking the *DB PC MDD Set* as an example, these treatments were mainly antidepressants (47.2%), in particular Selective Serotonin Reuptake Inhibitors (SSRIs; 29.2%), anxiolytics (33.5%, mainly benzodiazepine derivatives: 33.1%) and hypnotics/sedatives (19.2%, mainly benzodiazepine-related drugs: 13.7%). There were no relevant differences between groups.

Demographic data from the Short-term Double-blind Placebo-controlled MDD Set, showed that age ranged from 18 to 80 years with a mean (± SD) of 43.9 ± 13.0 years in the agomelatine 25/50mg group and 45.5 ± 12.9 years in the placebo group. The vast majority of the patients (about 87%) were less than 60 years old. The mean age of patients in the agomelatine and placebo groups was slightly higher than for fluoxetine and paroxetine, because only the former groups included patients in a study conducted in elderly (≥ 60 years) patients (study CL3-026).

Most of the patients were female: about 70% in all treatment groups.

About 60% of patients were taking at least one concomitant treatment at inclusion (mainly anxiolytic benzodiazepine derivatives), with no relevant differences between groups.

The main demographic data and other baseline characteristics of patients of the *Long-term Double-blind Placebo-controlled MDD Set* and of the other analysis sets did not differ notably from those in the Short-term Double-blind Placebo-controlled MDD Set.

- **Adverse events**

Agomelatine at the 50 mg dose appeared to cause a slightly higher incidence rate of AEs than at the 25 mg dose. However this did not appear to be a serious problem, and an increase in SEAEs was not reported. Most AEs seemed to be rather mild to moderate.

In the *Short-term Double-blind Placebo-controlled MDD Set* (up to 6/8 weeks), 53.6% of patients reported at least one adverse event emergent under treatment, with an incidence in the agomelatine 25/50mg group (52.8%) similar to that in the placebo group (51.7%).

Emergent adverse events by system organ class and preferred term reported by at least 1% of patients exposed to agomelatine 25/50mg in the Short-term Double-blind Placebo-controlled MDD Set are detailed in Table 38.

The most frequently affected system organ classes in the agomelatine 25/50mg group, and at a higher rate than in the placebo group (difference of at least 1%), were Nervous system disorders (24.7% versus 21.5%), Psychiatric disorders (10.5% versus 8.8%) and Skin and subcutaneous tissue disorders (5.1% versus 3.6%).

Table 10 Common emergent adverse events by SOC and PT (≥ 1% in the agomelatine 25/50 mg group) – Short-term double-blind placebo-controlled MDD Set (W0-W6/W8) – analysis by treatment group

System Organ Class Preferred term	agomelatine 25/50mg N=1120 PM=1486.1			placebo N=998 PM=1337.6			fluoxetine 20mg N=284 PM=377			paroxetine 20mg N=283 PM=422.6		
	n	%	pm	n	%	pm	n	%	pm	n	%	pm
All	**591**	**52.8**	**39.77**	**516**	**51.7**	**38.58**	**140**	**49.3**	**37.14**	**191**	**67.5**	**45.20**
Nervous system disorders	**277**	**24.7**	**18.64**	**215**	**21.5**	**16.07**	**58**	**20.4**	**15.38**	**77**	**27.2**	**18.22**
Headache	158	14.1	10.63	141	14.1	10.54	34	12.0	9.02	38	13.4	8.99
Dizziness	61	5.5	4.10	31	3.1	2.32	8	2.8	2.12	10	3.5	2.37
Somnolence	32	2.9	2.15	23	2.3	1.72	10	3.5	2.65	21	7.4	4.97
Migraine	13	1.2	0.87	4	0.4	0.30	2	0.7	0.53	1	0.4	0.24
Tremor	11	1.0	0.74	8	0.8	0.60	3	1.1	0.80	10	3.5	2.37
Gastrointestinal disorders	**217**	**19.4**	**14.60**	**186**	**18.6**	**13.91**	**67**	**23.6**	**17.77**	**88**	**31.1**	**20.82**
Nausea	86	7.7	5.79	71	7.1	5.31	20	7.0	5.31	45	15.9	10.65
Dry mouth	39	3.5	2.62	33	3.3	2.47	18	6.3	4.77	16	5.7	3.79
Diarrhoea	35	3.1	2.36	26	2.6	1.94	13	4.6	3.45	14	5.0	3.31
Abdominal pain upper	27	2.4	1.82	13	1.3	0.97	3	1.1	0.80	1	0.4	0.24
Constipation	20	1.8	1.35	21	2.1	1.57	4	1.4	1.06	5	1.8	1.18
Dyspepsia	14	1.3	0.94	11	1.1	0.82	4	1.4	1.06	2	0.7	0.47
Infections and infestations	**118**	**10.5**	**7.94**	**97**	**9.7**	**7.25**	**26**	**9.2**	**6.90**	**33**	**11.7**	**7.81**
Influenza	26	2.3	1.75	22	2.2	1.64	7	2.5	1.86	5	1.8	1.18
Nasopharyngitis	24	2.1	1.61	23	2.3	1.72	2	0.7	0.53	5	1.8	1.18
Psychiatric disorders	**117**	**10.5**	**7.87**	**88**	**8.8**	**6.58**	**27**	**9.5**	**7.16**	**44**	**15.6**	**10.41**
Insomnia	27	2.4	1.82	26	2.6	1.94	10	3.5	2.65	12	4.2	2.84
Anxiety	22	2.0	1.48	12	1.2	0.90	6	2.1	1.59	6	2.1	1.42
Depression	15	1.3	1.01	12	1.2	0.90	1	0.4	0.27	3	1.1	0.71
General disorders and administration site conditions	**64**	**5.7**	**4.31**	**56**	**5.6**	**4.19**	**10**	**3.5**	**2.65**	**24**	**8.5**	**5.68**
Fatigue	29	2.6	1.95	20	2.0	1.50	4	1.4	1.06	12	4.2	2.84
Skin and subcutaneous tissue disorders	**57**	**5.1**	**3.84**	**36**	**3.6**	**2.69**	**16**	**5.6**	**4.24**	**17**	**6.0**	**4.02**
Hyperhidrosis	15	1.3	1.01	7	0.7	0.52	8	2.8	2.12	8	2.8	1.89
Musculoskeletal and connective tissue disorders	**56**	**5.0**	**3.77**	**56**	**5.6**	**4.19**	**15**	**5.3**	**3.98**	**10**	**3.5**	**2.37**
Back pain	17	1.5	1.14	13	1.3	0.97	3	1.1	0.80	2	0.7	0.47
Investigations	**33**	**3.0**	**2.22**	**44**	**4.4**	**3.29**	**3**	**1.1**	**0.80**	**12**	**4.2**	**2.84**
Reproductive system and breast disorders	**26**	**2.3**	**1.75**	**17**	**1.7**	**1.27**	**6**	**2.1**	**1.59**	**13**	**4.6**	**3.08**
Metabolism and nutrition disorders	**21**	**1.9**	**1.41**	**23**	**2.3**	**1.72**	**6**	**2.1**	**1.59**	**6**	**2.1**	**1.42**
Eye disorders	**19**	**1.7**	**1.28**	**10**	**1.0**	**0.75**	**6**	**2.1**	**1.59**	**4**	**1.4**	**0.95**
Ear and labyrinth disorders	**17**	**1.5**	**1.14**	**17**	**1.7**	**1.27**	**11**	**3.9**	**2.92**	**4**	**1.4**	**0.95**
Vertigo	12	1.1	0.81	12	1.2	0.90	6	2.1	1.59	3	1.1	0.71
Respiratory, thoracic and mediastinal disorders	**16**	**1.4**	**1.08**	**21**	**2.1**	**1.57**	**7**	**2.5**	**1.86**	**6**	**2.1**	**1.42**
Renal and urinary disorders	**15**	**1.3**	**1.01**	**12**	**1.2**	**0.90**	**6**	**2.1**	**1.59**	**1**	**0.4**	**0.24**
Surgical and medical procedures	**14**	**1.3**	**0.94**	**10**	**1.0**	**0.75**	**3**	**1.1**	**0.80**	**1**	**0.4**	**0.24**
Vascular disorders	**13**	**1.2**	**0.87**	**17**	**1.7**	**1.27**	**-**	**-**	**-**	**10**	**3.5**	**2.37**
Cardiac disorders	**12**	**1.1**	**0.81**	**15**	**1.5**	**1.12**	**2**	**0.7**	**0.53**	**3**	**1.1**	**0.71**
Injury, poisoning and procedural complications	**11**	**1.0**	**0.74**	**16**	**1.6**	**1.20**	**3**	**1.1**	**0.8**	**2**	**0.7**	**0.47**

SOC: System Organ Class PT: Preferred Term
N: number of patients by treatment group
n: number of patients with at least one emergent AE in a given PT or in a given SOC and a given treatment group
%: (n/N) x 100
PM: total number of patient-months in a given treatment group

pm: number of patients with at least one adverse event in a given level and a given treatment group per 100 patient-months = (n/PM) x 100

Of the most commonly reported adverse events in the short-term safety set, observed in the agomelatine 25/50 mg group (in ≥ 2% of patients) and with an incidence ≥ to that on placebo, were: headache (14.1% *versus* 14.1%), nausea (7.7% *versus* 7.1%), dizziness (5.5% *versus* 3.1%), dry mouth (3. 5% *versus* 3.3%), diarrhoea (3.1% *versus* 2.6%), somnolence (2.9% *versus* 2.3%) fatigue (2.6% *versus* 2.0%), abdominal pain upper (2.4% *versus* 1.3%), influenza (2.3% *versus* 2.2%), anxiety (2.0% *versus* 1.2%).

In this set, 3 EAEs (Emergent Adverse Events) were observed with a statistically significantly higher frequency in the agomelatine 25/50 mg group than in the placebo group: dizziness (described above), paraesthesia: 0.9% *versus* 0.1%, and vision blurred: 0.6% *versus* none.

The nature and the incidence of the most common EAEs (Emergent Adverse Events) on agomelatine were close to those on placebo, except for dizziness.

In the *Long-term Double-blind Placebo-controlled MDD Set* (from 6 to 24 weeks), 37.9% of patients reported at least one adverse event emergent under treatment, respectively 38.8% in the agomelatine 25/50mg group and 38.4% in the placebo group.

Emergent adverse events reported by at least 1% of patients exposed to agomelatine in the Long-term Double-blind Placebo-controlled MDD Set are listed in Table 39.

In this set, the most frequently affected system organ classes in the agomelatine group were roughly the same as those in the short-term, with a lower frequency.

Table 11 Common emergent adverse events by SOC and PT (≥ 1% in the agomelatine 25/50 mg group) – Long-term double-blind placebo-controlled MDD set (W6-W24) – Analysis by treatment group

System Organ Class Preferred term	agomelatine 25/50mg N=511 PM=1762.6			placebo N=406 PM=1370.1			fluoxetine 20mg N=222 PM=818.3			paroxetine 20mg N=105 PM=364.7		
	n	%	pm	n	%	pm	n	%	pm	n	%	pm
All	**198**	**38.8**	**11.23**	**156**	**38.4**	**11.39**	**71**	**32.0**	**8.68**	**47**	**44.8**	**12.89**
Nervous system disorders	**61**	**11.9**	**3.46**	**47**	**11.6**	**3.43**	**24**	**10.8**	**2.93**	**12**	**11.4**	**3.29**
Headache	42	8.2	2.38	27	6.7	1.97	18	8.1	2.20	3	2.9	0.82
Dizziness	6	1.2	0.34	4	1.0	0.29	-	-	-	1	1.0	0.27
Infections and infestations	**50**	**9.8**	**2.84**	**55**	**13.6**	**4.01**	**23**	**10.4**	**2.81**	**10**	**9.5**	**2.74**
Influenza	14	2.7	0.79	15	3.7	1.09	6	2.7	0.73	4	3.8	1.10
Nasopharyngitis	11	2.2	0.62	11	2.7	0.80	4	1.8	0.49	1	1.0	0.27
Sinusitis	7	1.4	0.40	-	-	-	-	-	-	1	1.0	0.27
Gastrointestinal disorders	**41**	**8.0**	**2.33**	**31**	**7.6**	**2.26**	**15**	**6.8**	**1.83**	**10**	**9.5**	**2.74**
Diarrhoea	8	1.6	0.45	4	1.0	0.29	2	0.9	0.24	3	2.9	0.82
Nausea	8	1.6	0.45	3	0.7	0.22	4	1.8	0.49	-	-	-
Dyspepsia	6	1.2	0.34	4	1.0	0.29	2	0.9	0.24	2	1.9	0.55
Abdominal pain upper	6	1.2	0.34	2	0.5	0.15	-	-	-	1	1.0	0.27
Constipation	6	1.2	0.34	2	0.5	0.15	-	-	-	-	-	-
Psychiatric disorders	**41**	**8.0**	**2.33**	**22**	**5.4**	**1.61**	**16**	**7.2**	**1.96**	**11**	**10.5**	**3.02**
Insomnia	13	2.5	0.74	3	0.7	0.22	4	1.8	0.49	3	2.9	0.82
Anxiety	9	1.8	0.51	4	1.0	0.29	5	2.3	0.61	2	1.9	0.55
Depression	7	1.4	0.40	4	1.0	0.29	5	2.3	0.61	1	1.0	0.27
Musculoskeletal and connective tissue disorders	**25**	**4.9**	**1.42**	**23**	**5.7**	**1.68**	**10**	**4.5**	**1.22**	**3**	**2.9**	**0.82**
Back pain	14	2.7	0.79	9	2.2	0.66	3	1.4	0.37	1	1.0	0.27
Arthralgia	5	1.0	0.28	4	1.0	0.29	-	-	-	-	-	-
Investigations	**14**	**2.7**	**0.79**	**11**	**2.7**	**0.80**	**2**	**0.9**	**0.24**	**5**	**4.8**	**1.37**
General disorders and administration site conditions	**10**	**2.0**	**0.57**	**15**	**3.7**	**1.09**	**4**	**1.8**	**0.49**	**1**	**1.0**	**0.27**
Injury, poisoning and procedural complications	**9**	**1.8**	**0.51**	**6**	**1.5**	**0.44**	**3**	**1.4**	**0.37**	**2**	**1.9**	**0.55**
Respiratory, thoracic and mediastinal disorders	**6**	**1.2**	**0.34**	**9**	**2.2**	**0.66**	**2**	**0.9**	**0.24**	**3**	**2.9**	**0.82**
Skin and subcutaneous tissue	**9**	**1.8**	**0.51**	**6**	**1.5**	**0.44**	**3**	**1.4**	**0.37**	**1**	**1.0**	**0.27**

disorders												
Reproductive system and breast disorders	**11**	**2.2**	**0.62**	**3**	**0.7**	**0.22**	**-**	**-**	**-**	**2**	**1.9**	**0.55**
Surgical and medical procedures	**5**	**1.0**	**0.28**	**3**	**0.7**	**0.22**	**1**	**0.5**	**0.12**	**3**	**2.9**	**0.82**

SOC: System Organ Class
N: number of patients by treatment group
n: number of patients with at least one emergent AE in a given preferred term or in a given SOC and a given treatment group
%: (n/N) x 100
PM: total number of patient-months in a given treatment group
pm: number of patients with at least one adverse event in a given level and a given treatment group per 100 patient-months = (n/PM) x 100

Of the most common emergent adverse events (in ≥ 2 % of the patients in the agomelatine group) reported over the long-term treatment period, with an incidence ≥ to that on placebo, were: headache (8.2% *versus* 6.7%), back pain (2.7% *versus* 2.2%) and insomnia (2.5% *versus* 0.7%).

The most common emergent adverse events reported in the agomelatine 25/50mg group over the short-term treatment period were generally observed with a substantially lower frequency over the long-term treatment period.

In this set, 2 EAEs were observed with a statistically significantly higher frequency in the agomelatine 25/50mg group than in the placebo group: insomnia (mentioned above) and sinusitis (1.4% versus none).

With regards to the results by dose of agomelatine in the Long-term Double-blind Placebo-controlled MDD Set, 35.8% of patients reported at least one emergent adverse event in the agomelatine 25mg group and 48.3% in the agomelatine 50mg group vs 38.4% in the placebo group.

In patients treated with agomelatine for one year, there were no unexpected EAEs (Emergent Adverse Events) that were not seen in short-term treatment. Out of the 400 patients of the "One-year" Agomelatine Exposure Set, 368 received the 25mg dose and 32 the 50mg dose. No data for placebo or active control are available over this observation period.

The analyses focused on adverse events that occurred after 6 months of agomelatine treatment (in accordance with the ICH guideline on patient exposure). Emergent adverse events with first occurrence after 6 treatment months in more than 1 patient are displayed in Table 40.

Few patients were concerned. Besides headache and back pain (which were also among the most frequent EAEs in the Short-term and/or Long-term Double-blind Placebo-controlled MDD Sets), most of the EAEs reported from 6 months onwards (in 8% of the patients of the set) were infectious diseases, events probably linked to intercurrent diseases, not caused by study treatment.

Table 12: Emergent adverse events under treatment in the «One-year» agomelatine exposure set (N=400) – number of patients having reported at least one EAE by PT from 6-months onward – (restricted to EAE, experienced by more than 1 patient).

Preferred Term	n (%)
Nasopharyngitis	12 (3.0)
Headache	11 (2.8)
Back pain	9 (2.3)
Gastroenteritis	6 (1.5)
Influenza	5 (1.3)
Bronchitis	4 (1.0)
Sinusitis	4 (1.0)
Urinary tract infection	4 (1.0)
Insomnia	4 (1.0)
Weight increased	4 (1.0)
Upper respiratory tract infection	3 (0.8)
Tonsillitis	3 (0.8)
Dizziness	3 (0.8)
Myalgia	3 (0.8)
Rheumatoid arthritis	3 (0.8)
Hypertension	3 (0.8)
Seasonal allergy	3 (0.8)

Respiratory tract infection viral	2 (0.5)
Bronchitis acute	2 (0.5)
Tooth abscess	2 (0.5)
Respiratory tract infection	2 (0.5)
Acute sinusitis	2 (0.5)
Laryngitis	2 (0.5)
Skin infection	2 (0.5)
Nausea	2 (0.5)
Abdominal pain upper	2 (0.5)
Musculoskeletal stiffness	2 (0.5)
Fatigue	2 (0.5)
Asthenia	2 (0.5)
Decreased appetite	2 (0.5)
Hypercholesterolaemia	2 (0.5)
Palpitations	2 (0.5)
Conjunctivitis	2 (0.5)

PT: preferred term %: (n/N) x 100
n: number of patients having had their first emergent adverse event from 6 months of treatment

The analysis by agomelatine dose revealed that after 6 months of treatment, only headache was experienced by more than 1 patient on 50mg (n= 2 patients). However, this finding should be considered taking into account the low number of patients on 50mg in this set (n = 32).

With regards to the serious emergent adverse events in the "One-Year" Agomelatine Exposure Set, those reported on agomelatine 25/50mg from 6 months onwards were: 1 hysterosalpingo-oophorectomy, 1 gastric bypass, 1 depression suicidal, 1 fibrocystic breast disease, 1 uterine disorder, and all considered not related to the study drug by the investigator.

Overall, the long-term exposure to agomelatine did not seem to raise any particular safety concerns.

- **Adverse events of special interest / Adverse events by organ system or syndrome**

The frequency of suicides in the agomelatine treated patients appeared similar to that of the comparator drugs in the short-term, double-blind, placebo-controlled MDD set. The rates were also similar between the placebo and the agomelatine groups. The small number of deaths made it difficult to assess rates, and suicides/suicidality is to be specially monitored in post-marketing surveillance.

With regard to manic episodes and seizures, there was no indication of an effect of agomelatine in the presented dataset. Body weight and sexual function appeared not to be affected in a significant way.

Regarding haemmorhages, there was no clear indication of an excess risk with agomelatine.

With regard to liver safety, there was a consistent trend throughout the dataset of more cases with potentially clinically important elevation of aminotransferases (> 3 x ULN) among those given agomelatine vs placebo, and the data suggested a dose-effect relationship.

As regards cutaneous reactions, agomelatine appeared to be associated with different kinds of rash; the incidence in the agomelatine group was 0.7% *vs* 0.4% for placebo. Also hyperhidrosis, pruritus, eczema and rash were reported. The incidence of severe skin and subcutaneous emergent adverse events was 0.5% in the agomelatine 25/50mg group and 0.2% in the placebo group. Analysis of severe emergent adverse events according to agomelatine dose showed a higher incidence in the agomelatine 50mg group (1.0%) than in the agomelatine 25mg group (0.4%).

There was no indication of adverse effects of agomelatine on the cardiovascular system (see also the Pharmacodynamics section).

- **Serious adverse event/deaths/other significant events**

Deaths

Deaths were analysed in the Overall Safety Set as a whole and subdivided into the All MDD Set and Other indications. Adverse events leading to death were considered up to one month after the last study drug intake.

No deaths occurred in healthy or patient volunteer studies. In the Overall Safety Set there were 26 deaths, of which 9 occurred in the All MDD set and 17 in studies in other indications. An overview of the incidence of deaths by treatment group and population is shown in Table 48.

Table 13: Incidence of deaths – Overall Safety Set and All MDD Set

	All n (%)	agomelatine all doses n (%)	placebo n (%)	fluoxetine 20mg n (%)	paroxetine 20mg n (%)	venlafaxine 75-150mg n (%)
Overall Safety Set	N=6931 26 (0.4)	N=4738 20 (0.4)	N=1153 2 (0.2)	N=284 1 (0.4)*	N=449 3 (0.7)	N=307 -
All MDD	N=5822 9 (0.2)	N=3956 4 (0.1)	N=826 1 (0.1)	N=284 1 (0.4)*	N=449 3 (0.7)	N=307 -
Other Indications	N=1109 17 (1.5)	N=782 16 (2.0)	N=327 1 (0.3)	NA	NA	NA

* *This patient died 18 months after the end of the study from a malignant melanoma diagnosed during study period*
N: number of exposed patients in the treatment group; n: number of deaths; NA: not applicable

Overall, treatment with agomelatine was not associated with an increase in mortality in MDD patients.

In the MDD studies, four deaths occurred in the agomelatine group (4/3956, 0.1%), an occurrence similar to that seen on placebo (1/826, 0.1%). The deaths in both groups were all due to suicide. In the paroxetine group, two deaths were due to suicide, whilst the third was due to a medical cause unrelated to study drug (cardiac arrest). In the fluoxetine group, the only death observed occurred 18 months after the end of the study further to a malignant melanoma diagnosed during study.

In indications other than MDD, however, all deaths on agomelatine except one occurred in a study involving 356 elderly patients who had Alzheimer's dementia (CL2-011). A higher percentage of deaths occurred in the agomelatine (16/782, 2.0%) than placebo group (1/327, 0.3%). All deaths in the agomelatine group except one occurred in the study of patients with Alzheimer's disease, bringing the death rate in this study to 15/356 (4.2%). It was considered that the difference in mortality between agomelatine and placebo groups in the Alzheimer study was probably related to an unbalance of risk factors of death between the agomelatine and placebo groups at baseline. A special warning regarding treatment of elderly patients with dementia has been included in section 4.4 of the SPC.

Table 14 - Overview of deaths - Other indications

Patient number	Sex	Age	Exposure duration (days)*	Time to onset** from drug discontinuation (days)	Dose	Cause of death (preferred term)	Causality[a]
Agomelatine all doses (N=782)							
011250000100172	F	77	28	18	1mg	Epilepsy NOS	Doubtful[1]
011250001500403	F	95	72	-	1mg	Accidental overdose (therapeutic agent)	NR
011250002200223	F	89	95	-	1mg	Pulmonary embolism	NR
011250006500253	F	96	154	-	1mg	Cardiopulmonary failure	NR
011250006600379	F	86	80	-	1mg	Sudden death unexplained	NR
011250000300335	F	87	140	10	10mg	Renal failure acute	NR
011250001200034	M	75	36	8	10mg	Sudden death unexplained	NR
011250001500161	F	96	17	-	10mg	Choking	NR
011250001500258	F	85	32	-	10mg	Myocardial infarction	Doubtful[1]
011250002200227	F	88	136	42	50mg	Cardiac arrest	NR
011250002400117	M	73	90	3	50mg	Haemorrhagic stroke	NR
011250006300024	F	87	134	-	50mg	Sudden death unexplained	NR
011250006300353	M	78	118	-	50mg	Pulmonary embolism	Doubtful[1]
011250000100171	M	72	139	-	50mg	Road traffic accident	NR
011250000300333	F	83	60	9	50mg	Peripheral ischemia NOS	NR
015250006100202	M	59	1	16	50mg	Haemorrhagic stroke	NR
Placebo (N=327)							
011250001500100	F	92	55	7	-	Malignant mediastinal	NR

neoplasm NOS

[*] *from first dose intake to death or treatment discontinuation*
[**] *onset of adverse event leading to death*
NR: not related
[1] *Doubtful adverse event was considered to be related to study drug in the Integrated Analysis of Safety*
[a] *Investigator's opinion*

Other serious adverse events
The incidence of serious emergent adverse events (SEAEs) was lower in the MDD studies (4.2% of patients) than in other indications (7.3%).

In the All MDD set, 151/3640 patients (4.2%) experienced at least one SEAE in the agomelatine 25/50mg group (125/3052, 4.1%, in the 25mg group and 26/588, 4.4%, in the 50mg group) versus 34/826 (4.1%) in the placebo group. Therefore overall no serious adverse events appeared to be significantly more frequently present on agomelatine than on placebo.

At the preferred term level, the most common SEAEs in the agomelatine group were suicide attempt (0.6% *versus* 0.4% in the placebo group), depression (0.5% *versus* 0.8% in the placebo group), fall (0.3% *versus* 0.3% in the placebo group).

A total of 7 serious emergent adverse events were reported in studies performed in healthy or patient volunteers, 2 on placebo and 5 on agomelatine.

These serious emergent adverse events were transaminases increased and salmonella infection (both on placebo). For agomelatine the following SEAEs were observed: increased ALAT, ASAT and GGT (50 mg agomelatine), alcohol intoxication [asthenia, disorientation] (25 mg agomelatine), convulsion crisis (25 mg agomelatine), general condition alteration [decompensated cirrhosis] (25 mg agomelatine) and ventricular premature beats [ECG artefact] (agomelatine 50 + lithium).

- **Laboratory findings**

Apart from elevation of liver function values, there was no safety signal regarding lab findings.

- **Safety in special populations**

Influence of age

- Children and adolescents
No clinical trials were conducted in the depressed paediatric population. Due to lack of clinical experience agomelatine is not recommended in depressed children and adolescents under the age of 18 years, and this is reflected in the SPC.

- Elderly patients
A specific pharmacokinetic study (PKH-010) was conducted in male and female volunteers aged 60 years old or more (n = 20). There was no influence of age on agomelatine pharmacokinetics and no safety concern was raised.

The numbers of MDD patients ≥ 65 years who reported emergent adverse events (EAEs), severe EAEs, EAEs leading to treatment discontinuation and serious EAEs are summarized in Table 14.

Table 15 – Incidence of patients ≥ 65 years who experienced EAEs – MDD safety set

	agomelatine (N = 109) %	placebo (N=76) %
EAE	63.3	59.2
Severe EAE	10.1	13.2
EAE leading to discontinuation	12.8	9.2
Serious EAE	4.6	5.3

N: total number of exposed patients in the considered treatment group
n: number of patients affected %: nx100/N

The percentage of patients who experienced at least one emergent adverse event (EAE) was similar in

older *versus* younger patients (Table (2.7.4) 5-1).

Table 16: Overall incidence of emergent adverse events in older *versus* younger MDD patients

	agomelatine 25/50mg			placebo		
Patient age group	**n/N**	**%**	**pm**	**n/N**	**%**	**pm**
≥ 60 years	176/299	58.9	13.3	73/121	60.3	17.8
< 60 years	2054/3341	61.5	12.8	401/705	56.9	19.4
≥ 65 years	68/107	63.6	15.7	45/76	59.2	17.3
< 65 years	2162/3533	61.2	12.8	429/750	57.2	19.3
≥ 75 years	8/14	57.1	nc	7/15	46.7	nc

N: number of patients by treatment group
n: number of patients with at least one emergent AE in a given age group and a given treatment group
%: (n/N) x 100
PM: total number of patient-months in a given treatment group
pm: number of patients with at least one adverse event in a given age group and a given treatment group per 100 patient-months = (n/PM) x 100
nc: not calculated

In MDD patients ≥ 65 years, no safety concern was seen in terms of adverse events, biochemical and haematological parameters, vital signs or ECG. The slightly higher proportion of patients who discontinued for EAE was due to headache, nausea and paraesthesia (2 patients corresponding 1.9% *versus* none for placebo).

With the age cut-off of ≥ 75 years in the *All MDD Set* and treated with agomelatine 25/50mg, were 14 patients (13 with MDD and 1 with bipolar disorder) all of whom received the 25mg dose.

Overall, the benign tolerability profile of Thymanax was confirmed in this population, however limited clinical data on the use of Thymanax in elderly patients with Major Depression Episodes ≥ 65 years old with major depressive episodes was available, and this is reflected in the SPC.

Renal impairment

A specially designed study (PKH-015) was performed to assess the influence of severe renal impairment on agomelatine pharmacokinetic plasma parameters after the administration of a single 25mg oral dose of agomelatine. Study PKH-015 revealed that in patients with severe renal impairment the C_{max} and AUC increased approximately 40 and 25 % respectively, compared to healthy subjects

(see the Clinical Pharmacokinetic section).

In the agomelatine clinical development program, the non-inclusion criteria in phase II and phase III study protocols prohibited patients with known renal disorders. However, some patients with moderate renal impairment, defined as a calculated creatinine clearance (corrected for body surface) < 50 mL/min/1.73 m², were included and therefore the safety of agomelatine was assessed separately in these patients. Only 39 patients fulfilled this criterion: 20 in the agomelatine group (18 on 25/50mg), 14 in the placebo group, 4 in the paroxetine group and 1 in the venlafaxine group (none in the fluoxetine group). Therefore, only a brief description of EAEs and potentially clinically significant abnormal biochemical and haematological values was given. The mean treatment duration was 4.0 ± 4.2 months for the agomelatine 25/50mg-treated patients and 2.8 ± 2.2 months for the placebo-treated patients. For agomelatine 25/50mg-treated patients, 50.0% (9/18) experienced at least one EAE, versus 35.7% (5/14) patients under placebo.

1,300 patients with mild renal impairment 50 < ClCr < 80 mL/min were treated by agomelatine 25/50 mg in Phase II and III studies. The available safety data did not raise any concern when compared to placebo.

Overall, it was agreed that no relevant modification in agomelatine pharmacokinetic parameters is observed in patients with severe renal impairment. However, only limited clinical data on the use of Thymanax in depressed patients with severe or moderate renal impairment with major depressive episodes was available. As a result, caution is to be exercised when prescribing Thymanax to these patients, and this is information is reflected in the SPC.

Hepatic impairment and hepatotoxicity

No data in patients with liver failure are available in phase II / III studies since this clinical condition was a non-inclusion criterion. However, a specific open study (PKH-014) was performed to evaluate the pharmacokinetics of agomelatine 25mg after a single oral dose in subjects with mild (Child-Pugh grade A) or moderate (Child-Pugh grade B) liver failure due to alcohol cirrhosis.

As discussed in the Clinical Pharmacokinetic section, patients with cirrhosis, Child Pugh grade A and B, reported significantly higher plasma levels of agomelatine compared to matched healthy volunteers.

Liver insufficiency was shown to increase AUC by up to 140 times and the safety of such large doses of agomelatine remained largely unknown. Thus, agomelatine is contraindicated in patients with hepatic insufficiency (i.e. cirrhosis and active liver disease) (SPC section 4.3). In addition, it was considered necessary to undertake appropriate risk minimisation steps, as outlined in section 4.4 of the SPC and in the RMP.

Increases in liver function parameters (> 3 ULN) were reported commonly in the clinical documentation (on 50 mg agomelatine) and in general more often in agomelatine treated subjects than in the placebo group. Crude incidences were 1,04% on agomelatine 25 mg and 1,39% on agomelatine 50 mg as compared to 0,72% on placebo. The data suggested a dose-effect relationship, and these liver reactions were not predictible. The Applicant argued that none of the patients in the clinical trials could be considered to be a Hy's law case, and that the data provided an indication that agomelatine does not have the potential to cause severe liver injury. Hy's law is considered useful and is applied widely in the evaluation of risk for liver injuries, but its sensitivity and specificity may need validation. Since only less than 800 patients were exposed to the 50 mg dose, the risk of severe liver injury was uncertain. The liver reactions observed were hepatocellular in nature and were usually reversible in a few weeks. Some reactions recovered during continued treatment and some upon treatment discontinuation. Even if most of the liver reactions seemed to occur at the 50 mg dosage and appeared early during treatment, hepatic reactions were also noted with 25mg dosing and in some cases the reaction occured late after 3 or 6 months agomelatine treatment. Serious hepatic reactions including hepatitis (cytolytic) and transaminase elevation > 10 x ULN were reported less frequently. One case of hepatitis that did not recover at follow-up (2.5 years after the end of the study) after discontinuation of agomelatine, was of concern. The mechanism of agomelatine related liver injury is unknown. Prolonged agomelatine treatment following development of transaminase elevation may be an important safety concern, particularly in patients with risk factors for liver injuries.

It was considered necessary to perform liver function tests at initiation and then periodically after around 6 weeks (end of acute phase), 12 weeks and 24 weeks (end of maintenance phase) and thereafter when clinically indicated for both 25 and 50 mg dosing, until more data on the appropriate timing and duration of liver function monitoring become available.

- **Safety related to drug-drug interactions and other interactions**

As already indicated (see paragraph "Pharmacokinetic interaction studies" in "Clinical aspects" section 3.4) co-administration of agomelatine and fluvoxamine increased AUC of agomelatine (AUC was increased 61 times). As a result, the concomitant use with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated in section 4.3, and potent and moderate CYP1A2 inhibitors are also included in section 4.4 and section 4.5 of the SPC.

- **Discontinuation due to adverse events**

No discontinuation symptoms were apparent after termination of agomelatine treatment. However, for paroxetine there was a statistically significantly higher incidence of discontinuation symptoms after one week. After two weeks no difference was reported. This seems to indicate that discontinuation-emergent symptoms are not a problem associated with agomelatine treatment abrupt cessation.

- **Post marketing experience**

At the cut-off date, i.e. 31 March 2007, agomelatine was only marketed in Ukraine (launch date: 19 February 2007). From 19 February to 31 March 2007, 1820 packs of 28 tablets of agomelatine 25 mg were marketed in Ukraine. These data did not allow an estimation of reliable exposure figures (packs or person – years). No data by age group, gender or dose were available and no spontaneous cases were reported over this period.

- **Discussion on clinical safety**

Agomelatine is an antidepressant with a claimed new mechanism of action and a different safety profile (lack of clinically relevant weight gain, low risk of sexual dysfunction, low incidence of gastro-intestinal reaction, absence of discontinuation symptoms and overall incidence rates of adverse events that are not different from placebo).

The analysis of the pool safety data from all completed Phase II/III studies in patients, irrespective of the indication (*Overall Safety Set*) included a total of 6931 subjects. Overall, the safety profile appeared favourable.

However, the CHMP had the following safety concerns:

- Efficacy in elderly patients was not demonstrated. The applicant committed to perform a post-marketing study of efficacy and safety of agomelatine in patients older than 65 years with a special focus on patients aged 75 years and above. The applicant adequately described the measures to deal with the difficulties related to recruitment of elderly, depressed patients, and the design of the study seems to be acceptable. The increased mortality in the agomelatine group relative to the placebo group observed in the study in Alzheimer patients was probably related to an unbalance of risk factors of death between groups at baseline. A warning against the use of agomelatine in Alzheimer patients is included in the SPC.
- The issue of interaction with CYP1A2 inhibitors was re-solved (after the oral explanation given to the CHMP by the applicant on 21 October 2008) by contraindicating concomitant use with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) in section 4.3 and including corresponding information in 4.5 of the SPC.
- Hepatic reactions: Among patients treated with agomelatine 25/50 mg (N= 4068), the incidence of emergent elevations of ALAT and/or ASAT > 3 x ULN in patients with normal transaminases at baseline was originally 0.8% as compared to 0.3% in the placebo group. Significantly higher incidences were observed in the agomelatine 50mg group (1.3%). The higher incidence of transaminases increase with higher dose was an important concern. The new data provided (whatever the transaminase values before intake) gave incidences of 1.04% on agomelatine 25 mg and 1.39% on agomelatine 50 mg as compared to 0.72% on placebo.

  Serious hepatic reactions including hepatitis (cytolytic) and transaminase elevation > 10 x ULN were reported .

  Liver function tests (LFT) were performed at baseline and during agomelatine treatment as planned in the clinical studies. The transaminase elevations were usually detected in patients without any symptoms and were reversible after treatment discontinuation. However, one documented-case with no recovery at follow-up after discontinuation of agomelatine was reported. It was concluded that continued agomelatine treatment following development of transaminase elevation may be an important safety concern, particularly in patients with risk factors for liver injuries.

  The incidence of abnormal LFT including all transaminase levels showed a clear dose-effect relationship when 25mg dosing is compared to other doses of agomelatine or placebo. However, the relative risk analysis, which takes into account the probability to detect elevated serum transaminases increases with the duration of observation, show no effect of agomelatine at doses inferior or equal to 25 mg. No correlation between the systemic exposure to agomelatine and the occurrence of liver injuries was found, suggesting that the hepatic reactions may not be predictable and may occur in susceptible patients. Although no predictable risk factors could be identified, alcohol consumption, concomitant medication or previous liver disorders were seen in some cases. The liver reactions with agomelatine seemed to be hepatocellular reactions and were usually reversible, and even if in most cases they occur at the 50 mg dosage and to appear early in treatment, hepatic reactions were also noted with 25mg dosing and late after 3 or 6 months agomelatine treatment.

  The mechanism of agomelatine-related liver injury remained unknown, and there were no sufficient data supporting different mechanisms for the hepatic reactions with different severities.

The major concern was the high frequency of elevated transaminases associated with agomelatine treatment (in particular with the 50mg dose), and how in the clinical setting the liver-related adverse event can be discovered and prevented before a more serious outcome occurs. Since agomelatine is proposed for long-term use, and considering the cases with late occurrence of elevated transaminases, LFT monitoring is to be performed at initiation, then periodically after around 6 weeks (end of acute phase), 12 weeks and 24 weeks (end of maintenance phase) and thereafter when clinically indicated, for both 25 mg and 50mg dosing, until more data become available. The applicant agreed with this proposal and suggested in the RMP to perform studies investigating the incidence and risk factors for the liver injuries. Studies investigating the effect of monitoring liver function are also agreed to be performed.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

During the procedure the applicant provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country was provided. The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The MAA submitted a Risk Management plan (version 4.0) based on the EMEA RMP-template and in line with the requirements in Volume 9A.
The MAA submitted a risk management plan, which included a risk minimisation plan.

Identified risks
The only identified risk was elevated liver transaminases. To further explore the potential liver injury and potential associated risk factors, specific investigations will be implemented for patients who exhibit abnormal liver enzymes in further clinical trials. A retrospective safety survey using the General Practice Research Database and a prospective epidemiologic study will be performed to study these hepatic events further in clinical practice. In addition, the Applicant was requested to perform studies on the effect of liver function test monitoring, and such studies are described in the RMP. Besides routine risk minimisation activities, the applicant proposed to provide prescribers with educational material and to perform a prescription survey to study the efficiency of this as an additional risk minimisation activity.

Potential risks
Skin reactions and suicidality are listed as potential risks and will be further studied in a prospective epidemiologic study. Regarding suicidality, the European standard text for antidepressants is stated in the SPC. The applicant will have special focus on suicidality in young adults aged between 18-30 years.

The applicant argued that agomelatine has a mechanism of action that is not expected to cause akathisia. In addition, akathisia has not been reported so far. Therefore, it was considered acceptable not to list akathisia as a potential risk at this point of time.

New mechanistic studies provided evidence that the DNA adducts observed in preclinical studies did not seem to be of clinical relevance. Thus, it was considered acceptable not to list DNA adducts as a potential risk.

During the procedure a concern over bleeding event events was noted. The applicant claimed that agomelatine did not have any effect on platelet functions and therefore bleedings was not included as a

potential risk in the RMP. This was considered acceptable, however data from post-marketing surveillance are to be collected and possible signals are to be analysed in PSURs regarding bleeding events.

Missing or limited information
No data were available regarding efficacy and safety in the paediatric age group.

The Applicant was asked to perform a post-marketing study on the efficacy and safety of agomelatine in patients > 75 years. A post-marketing study in elderly > 65 years with 1/3 of patients aged > 75 will be performed. Additionally, the elderly population will be studied in a prospective epidemiological study. Increased mortality relative to placebo was observed in a study in Alzheimer patients. This could be due to an imbalance in risk factors for death between agomelatine and placebo groups at baseline. A precaution against use of agomelatine in elderly patients with dementia has been included in the SPC (Section 4.4). The Applicant was requested to specify in the RMP their further plans for following up safety in Alzheimer patients.

More information on renally impaired patients will be provided with the proposed epidemiologic study to be performed. In the meantime, the RMP and the SPC have been updated to reflect that only limited data exist for patients with severe or moderate renal impairment. Overall, caution should be exercised when prescribing the drug to these patients.

Agomelatine is contraindicated in patients with hepatic impairment.

Interactions
It was agreed that oral contraceptives need not be listed as an interacting agent in the RMP. In addition, contraindication of concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacine) was agreed upon. The SPC and RMP have been updated to reflect this.

The applicant proposed to provide prescribers with educational material and to perform a prescription survey to study the efficiency of this program as a risk minimisation activity.

The potential for pharmacodynamic reactions is adequately discussed in the RMP.

Other aspects
Supratherapeutic drug levels may be a consequence of coadministration with potent CYP 1A2 inhibitors and/or impaired liver function. The applicant was asked to discuss in the RMP how routine therapeutic monitoring may address some of these concerns. It was agreed that routine therapeutic monitoring are not feasible for agomelatine because of its short half-time. Consequently, this aspect is not discussed in the RMP.

The Applicant suggested in the RMP to perform studies on the incidence and risk factors for the liver injuries. The Applicant was also requested to perform studies on the effect of monitoring liver function.

Table 17 - Summary of the EU risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed routine and additional risk minimisation activities
Identified risks		

Safety concern	Proposed pharmacovigilance activities	Proposed routine and additional risk minimisation activities
Elevated transaminases	- Submission of cumulative re-estimated data (see on-going studies, § 2.4) on ALAT, ASAT or ALP value >3 ULN or total bilirubin > 2 ULN from the updated overall safety data base in the framework of the PSURs. - Liver adverse reactions including abnormal liver function tests with documentation on influence of potential concomitant hepatotoxic drugs from all sources will be collected and specifically reviewed in the framework of PSURs. Specific questionnaires will be filled in for patients experiencing such events. - Retrospective safety survey using the General Practice Research Database to document the incidence of hepatobiliary disorders in clinical practice, in comparison with other antidepressants and in non-depressed patients. Submission of data in the framework of the PSURs. - Prospective epidemiological study (see Annex 4) to provide information on agomelatine in current medical practice in MDD patients. The follow-up of the participating patients will be done according to the approved SmPC and the physician's current medical practice. Analysis of adverse reactions in the framework of the PSURs. - To further explore the potential liver injury and potential associated risk factors, specific investigations will be implemented for patients who exhibit abnormal liver enzymes (ALAT, ASAT or ALP value > 3 x ULN or total bilirubin > 2 ULN) in the further clinical trials with agomelatine, with close follow-up of abnormalities until resolution, and also determination of key variables in liver function assessment and appropriate etiological investigations. DNA should be taken allowing for search of the influence of different genetic polymorphisms. Submission of corresponding data with documentation on influence of potential concomitant hepatotoxic drugs in the framework of the PSURs.	[SmPC § 4.2] After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets, taken together at bedtime. In patients in whom the dose is increased to 50 mg per day, liver function tests should be measured at the time of the dose increase and 6 and 12 weeks later. [SmPC § 4.3] Agomelatine is contra-indicated in patients with hepatic impairment (i.e. cirrhosis or active liver disease). Patients will be also informed through the Package Leaflet (Section 2 Before you take Thymanax). [SmPC § 4.4] *Increased serum transaminases:* In clinical studies, elevations of serum transaminases (>3 times the upper limit of the normal range) have been observed in patients with Thymanax/particularly at 50 mg (see section 4.8). When Thymanax was discontinued in these patients, the serum transaminases usually fell to normal levels. When the dose is increased to 50 mg, liver function tests should be performed at this time and at 6 weeks and 12 weeks after the dose increase. Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours. Therapy should be discontinued if the increase in serum transaminases exceed 3X upper limit of normal and liver function tests should be performed regularly until serum transaminases return to normal.

Safety concern	Proposed pharmacovigilance activities	Proposed routine and additional risk minimisation activities
		If any patient develops symptoms suggesting hepatic dysfunction liver function tests should be performed. The decision whether to continue the patient on therapy with Thymanax should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed therapy should be discontinued. Caution should be exercised when Thymanax is administered to patients who consume substantial quantities of alcohol or who are treated with medicinal products associated with risk of hepatic injury. [SmPC § 4.8] Hepato-biliary disorders: Increases (>3 times the upper limit of the normal range) in ALAT and ASAT were reported in 0.6% for ALAT and in 0.4% for ASAT of patients treated with Thymanax 25 mg. For Thymanax 50 mg the figures were 1.1% for ALAT and 0.9% for ASAT. Educational material to be provided to prescribers, with a prescription survey to follow this program.
Potential risks		
Skin reactions	- Safety information on skin reactions whatever the source of information (clinical studies, spontaneous report…) will be routinely collected and specifically reviewed in the framework of the PSURs. - Prospective epidemiological study (see Annex 4) to provide information on agomelatine in current medical practice in MDD patients. The follow-up of the participating patients will be done according to the approved SmPC and the physician's current medical practice. Analysis of adverse reactions in the framework of the PSURs	[SmPC § 4.8] Skin and subcutaneous tissue disorders: Common : hyperhidrosis Uncommon : eczema Rare : erythematous rash
Suicide	- Safety information on suicides with a specific focus on young adults aged between 18-30 years whatever the source of information (clinical studies, spontaneous report…) will be routinely collected and specifically reviewed in the framework of the PSURs. - Prospective epidemiological study (see Annex 4) to provide information on agomelatine in current medical practice in MDD patients. The follow-up of the participating patients will be done according to the approved SmPC and the physician's current medical practice. Analysis of adverse reactions in the framework of the PSURs.	[SmPC § 4.4] European standard text for antidepressants.
Missing or limited information		

Safety concern	Proposed pharmacovigilance activities	Proposed routine and additional risk minimisation activities
Paediatric age group (< 18 years)	Safety information in paediatric age group whatever the source of information (spontaneous cases,…) will be routinely collected.	[SmPC § 4.4] Thymanax is not recommended in the treatment of depression in patients under 18 years of age since safety and efficacy of Thymanax have not been established in this age group.
Elderly (≥ 75 years)	- Safety information in the elderly (≥ 75 years) whatever the source of information (clinical studies, spontaneous report…) will be routinely collected and specifically reviewed in the framework of the PSURs. - Specific post-marketing study in the elderly > 65 years with 1/3 of patients aged > 75 years (See Annex 5). - Prospective epidemiological study (see Annex 4) to provide information on agomelatine in current medical practice in MDD patients. The follow-up of the participating patients will be done according to the approved SmPC and the physician's current medical practice. Analysis of adverse reactions in the framework of the PSURs.	[SmPC § 4.2] Efficacy has not been clearly demonstrated in the elderly (≥ 65 years). Only limited clinical data is available on the use of Thymanax in elderly patients ≥ 65 years old with major depressive episodes. Therefore, caution should be exercised when prescribing Thymanax to these patients.
Pregnancy	No additional pharmacovigilance measures planned except routine pharmacovigilance.	[SmPC § 4.6] For agomelatine, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal / foetal development, parturition or postnatal development (see Section 5.3). Caution should be exercised when prescribing to pregnant women.
Lactation	No additional pharmacovigilance measures planned except routine pharmacovigilance.	[SmPC § 4.6] It is not known whether agomelatine is excreted into human milk. Agomelatine or its metabolites are excreted in the milk of lactating rats. Potential effects of agomelatine on the breast-feeding infant have not been established. If treatment with Thymanax is considered necessary, breastfeeding should be discontinued.
Hepatic impairment	Safety information in patients with liver impairment whatever the source of information (clinical studies, spontaneous report…) will be routinely collected and specifically reviewed in the framework of the PSURs.	[SmPC § 4.3] Agomelatine is contra-indicated in patients with hepatic impairment (i.e. cirrhosis or active liver disease).
Severe or moderate renal impairment	- Safety information in patients with severe or moderate renal impairment whatever the source of information (clinical studies, spontaneous report…) will be routinely collected and specifically reviewed in the framework of the PSURs. - Prospective epidemiological study (see Annex 4) to provide information on agomelatine in current medical practice in MDD patients. The follow-up of the participating patients will be done according to the approved SmPC and the physician's current medical practice. Analysis of adverse reactions in the framework of the PSURs	[SmPC § 4.2] There is no relevant modification in agomelatine pharmacokinetic parameters in patients with severe renal impairment. However, only limited clinical data on the use of Thymanax in depressed patients with severe or moderate renal impairment is available. Therefore, caution should be exercised when prescribing Thymanax to these patients.

Safety concern	Proposed pharmacovigilance activities	Proposed routine and additional risk minimisation activities
Drug interactions		
Interactions with potent CYP 1A2 inhibitors (*e.g.* fluvoxamine, ciprofloxacin)	Safety information in patients taking agomelatine and potent CYP1A2 inhibitors whatever the source of information (clinical studies, spontaneous report…) will be routinely collected and specifically reviewed in the framework of the PSURs.	[SmPC § 4.3] Concomitant use of potent CYP1A2 inhibitors (*e.g.* fluvoxamine, ciprofloxacin). Patients will be also informed through the Package Leaflet (Section 2 Before you take Thymanax). [SmPC § 4.5] Co-administration of Thymanax with potent CYP1A2 inhibitors (*e.g.* fluvoxamine, ciprofloxacin) is contra-indicated. Educational material to be provided to prescribers, with a prescription survey to follow this program.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

In vitro and *in vivo*, agomelatine acts as a melatonin agonist and a 5-HT_{2C} antagonist, whereas its metabolites have no pharmacological activity.

Agomelatine revealed antidepressant activity in the dose range 10-50mg/kg, i.p. or p.o., and anxiolytic-like effects at non sedative doses. No tolerance developed following chronic treatment and no withdrawal relapse was noted one week after cessation of treatment.

Agomelatine did not produce any unexpected or toxic effects in the safety pharmacology studies. The main CNS-related effects of agomelatine were slight CNS depressant action evident as sedation in both mice and rats (dose-related, with a rather low acute toxicity profile as LD50 ≥ 100 times the human dose).

The repeated dose toxicity studies indicated that liver is the target organ of toxicity in both rats and monkeys, with high safety margins in rats and low in monkeys. In rats and monkeys agomelatine caused hepatic enzyme induction associated with enlarged livers and/or hepatocellular hypertrophy with subsequent increased metabolism and reduced drug exposure.

Agomelatine induced no cardiovascular effects in monkeys (up to 32 mg/kg i.v.). No effect was noted on ECG, arterial blood pressure, heart rate, mean femoral and arterial blood flow, cardiac output, respiration rate, arterial blood gases and pH. Agomelatine had no effect on hERG current, on renal, gastro-intestinal and endocrinal functions.

No genotoxic potential of agomelatine was found *in vivo*. However agomelatine increased the incidences of hepatic adenomas and carcinomas (mice and rats) and mammary fibroadenomas (rats). There were gender-related differences in occurrence of hepatic tumours, whereby males appeared to be exposed higher than females.

Agomelatine had no adverse effect on fertility, or on embryonal or foetal development, and local tolerance studies in the rabbit showed no adverse effect on the skin and the eye.

No concerns were raised by the environmental risk assessment. However, the environmental fate and effects of agomelatine will be investigated in further, and the ERA for agomelatine will be revised and updated accordingly to include the new results.

Efficacy

Oral bioavailability of agomelatine was low and increased non-proportionally with the dose, in addition there was a substantial inter-individual variability; this implies an unpredictable therapeutic response. Overall, bioavailability appeared to be dependent on gender (female > male), intake of oral contraceptives (with oral oestrogens > without oral oestrogens), smoking habits (non-smokers > smokers), administration time (a.m. > p.m.) and possibly on age.

Although clear-cut, linear dose responses are rare for CNS effects, the dose-finding studies for agomelatine were far from ideal and considered to be unsatisfactory. The 25 mg dose was chosen based on a study where 5 mg and 100 mg seemed to be equally effective and where 1 mg also fulfilled the criteria of efficacy. In the overall clinical program greater efficacy with a dose of 50 mg in comparison to 25 mg was not demonstrated. The applicant has therefore committed to perform a post-approval dose –response study including a randomised dose adjustment to 50 mg in non-responders to 25 mg agomelatine.

Short-term efficacy (at 6 weeks) was demonstrated in three of six short-term pivotal trials (including the dose finding one) which 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 three trials only the dose finding trial (CL2-014) included an active comparator arm (paroxetine 20 mg). In this trial, the effect of agomelatine and paroxetine was in the same range. Four other trials, including a trial in the elderly, failed to discriminate between agomelatine and placebo. One of them demonstrated to have assay sensitivity since fluoxetine, used as a comparator, did discriminate from placebo. This suggested that the effect of agomelatine was smaller than fluoxetine 20 mg. Two of the studies failed to demonstrate assay sensitivity. In all trials fairly severe depressed patients were enrolled, and this excludes the explanation that the failure was due to a flooring effect. The effect size measured from baseline to endpoint was large in both treated and placebo groups. This may point to a large placebo effect as one cause of trial failure. All together the data available from the short-term studies showed that agomelatine 25 mg is probably less efficacious than other antidepressants. A meta-analysis of the six pivotal short-term studies resulted in an overall estimate of the difference between agomelatine (including sub-therapeutic doses 1 and 5 mg) and placebo of 1.5 on the HAM-D with a 95% confidence interval [0.80, 2.22].

In a recently submitted short-term study comparing agomelatine (25-50 mg) and sertraline (50-100 mg) where the primary objective was to assess the efficacy on the rest-activity cycle, the head-to-head comparison (LOCF, FAS) showed a statistically significant superiority of agomelatine over sertraline on HAM-D total score (pre-specified efficacy analysis: difference = 1.68, p=0.031).

Two relapse prevention studies were performed, whereby responders to agomelatine after 8-10 weeks of open label treatment were randomised between agomelatine and placebo. The first study failed to demonstrate a difference in time to relapse. The second study demonstrated a statistically significant difference in time to relapse between agomelatine and placebo. Additional submitted data after extension to 10 months in this study "seems to sustain and confirm the results achieved after 6 months, as the percentage of patients with relapse over 44 weeks was still more than two-fold lower in the agomelatine group compared to the placebo group. No difference in efficacy between severely depressed patients and patients with moderate/mild depression was found.

Efficacy in elderly patients was not demonstrated. The applicant has committed to perform a post-marketing study of efficacy and safety of agomelatine in patients older than 65 years with a special focus on patients aged 75 years and above. The applicant has adequately described the measures to deal with the difficulties related to recruitment of elderly, depressed patients, and the design of the study seems to be acceptable.

No tolerance developed following chronic treatment and no withdrawal relapse was noted one week after cessation of treatment. Among benefits on the safety side are the lack of clinically relevant weight gain, no effect on the cardiovascular system, low risk of sexual dysfunction, low incidence of gastro-intestinal reaction, and absence of discontinuation symptoms.

Safety

The increased mortality in the agomelatine group relative to the placebo group observed in the study in Alzheimer patients was probably related to an unbalance of risk factors of death between groups at baseline. A warning against the use of agomelatine in Alzheimer patients is included in the SPC.

Overall, the safety profile appeared favourable. However, a few important issues were identified. The lack of safety data in patients with hepatic impairment was re-solved by including appropriate information in the SPC (see "Hepatic reactions" paragraph below) and the issue of interaction with CYP1A2 inhibitors were re-solved by contraindicating concomitant use with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) in section 4.3 and including corresponding information in 4.5 of the SPC.

In addition, with regard to the identified risks of hepatic reactions (see "Hepatic reactions" paragraph below), appropriate risk minimisation steps have been agreed upon and have been included in the RMP.

Hepatic reactions

Among patients treated with agomelatine 25/50 mg (N= 4068), the incidence of emergent elevations of ALAT and/or ASAT > 3 x ULN in patients with normal transaminases at baseline was originally 0.8% as compared to 0.3% in the placebo group. Significantly higher incidences were observed in the agomelatine 50mg group (1.3%). The higher incidence of transaminases increase with higher dose was an important concern. The new data provided (whatever the transaminases values before intake) gave incidences of 1.04% on agomelatine 25 mg and 1,39% on agomelatine 50 mg as compared to 0,72% on placebo.

Serious hepatic reactions including hepatitis (cytolytic) and transaminase elevation > 10 x ULN were reported.

Liver function tests (LFT) were performed at baseline and during agomelatine treatment as planned in the clinical studies. The transaminase elevations were usually detected in patients without any symptoms and were reversible after treatment discontinuation. However, one documented-case with no recovery at follow-up after discontinuation of agomelatine was reported. It was concluded that continued agomelatine treatment following development of transaminase elevation may be an important safety concern, particularly in patients with risk factors for liver injuries.

The incidence of abnormal LFT including all transaminase levels showed a clear dose-effect relationship when 25mg dosing is compared to other doses of agomelatine or placebo. No correlation between the systemic exposure to agomelatine and the occurrence of liver injuries was found, suggesting that the hepatic reactions may not be predictable and may occur in susceptible patients. Although no predictable risk factors could be identified, alcohol consumption, concomitant medication or previous liver disorders were seen in some cases. The liver reactions with agomelatine seemed to be hepatocellular reactions and were usually reversible, and even if in most cases they occur at the 50 mg dosage and to appear early in treatment, hepatic reactions were also noted with 25mg dosing and late after 3 or 6 months agomelatine treatment.

The mechanism of agomelatine-related liver injury remained unknown, and there were no sufficient data supporting different mechanisms for the hepatic reactions with different severities.

The major concern was the high frequency of elevated transaminases associated with agomelatine treatment (in particular with the 50mg dose), and how in the clinical setting the liver-related adverse event can be discovered and prevented before a more serious outcome occurs. Since agomelatine is proposed for long-term use, and considering the cases with late occurrence of elevated transaminases, LFT monitoring is to be performed at initiation and then periodically after around 6 weeks (end of acute phase), 12 weeks and 24 weeks (end of maintenance phase) and thereafter when clinically

indicated during the whole treatment period for both 25 mg and 50mg dosing, until more data become available. The applicant agreed with this proposal and suggested in the RMP to perform studies investigating the incidence and risk factors for the liver injuries. Studies investigating the effect of monitoring liver function are also to be performed.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The user test has been well organised and performed in accordance with the Guidance on user testing. Possible weaknesses have been identified and this has resulted in changes to the PL. The aim of the user test is to find such weaknesses, and help improving the PL. Most of the answers to the specific questions in the Questionnaire were found 'easily' or 'very easily', something that indicates a well written and presented PL. The comments made by the participants on the open questions were also rather positive, and few negative comments were made.

The Guideline on the Readability states that out of 20 patients, 16 or more (80%) should be able to understand and answer each question correctly. In this user test the success criteria are met, and the user test has proven that the readability of the PL is acceptable.

Risk-benefit assessment

Agomelatine is an antidepressant with a new mechanism of action with a different safety profile compared to the SSRI/SNRIs group (lack of clinically relevant weight gain, low risk of sexual dysfunction, low incidence of gastro-intestinal reaction, absence of discontinuation symptoms and overall incidence rates of adverse events that are not different from placebo). Such a drug, despite an effect that might be lower than the effect of SSRIs, can be considered useful in the antidepressant treatment armamentarium. In the clinical studies several cases of abnormal liver function test and a few cases of hepatitis, indicating liver toxicity, were observed. Although some confounding factors existed in the hepatitis cases there is a non-negligible risk of potentially irreversible liver injuries if agomelatine is used outside controlled clinical trials (i.e. in clinical practice in more heterogeneous patient groups, in patients with more concomitant medication, in patients with unidentified mild hepatic impairment and without liver function tests at initiation and periodically during treatment). Since these hepatic reactions may not be predictable and in order to detect the liver-related adverse events and to prevent a more serious outcome to occur, monitoring of liver test function of all patients at all agomelatine doses is stated as a risk minimisation measure in the SPC.

The CHMP considered that the magnitude of the short-term efficacy was not similar to the effect generally shown for the SSRIs. However, the effect demonstrated in the second relapse prevention study was in line with what has been shown for the SSRIs. The CHMP concluded that with the proposed liver monitoring program, and considering the otherwise favourable safety profile compared to other antidepressants, the effect magnitude demonstrated was sufficient to provide a clinically valuable alternative in the antidepressant treatment armamentarium for some patients.

The B/R ratio for Thymanax in the therapeutic indication "treatment of Major Depressive Episodes in adults" is considered positive provided that the applicant commits to perform a number of post authorisation follow-up measures to be reported back to the CHMP within predefined timeframes.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. The following additional risk minimisation activities were required: see as detailed in section 2.3.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision (two divergent positions were based on robustness of efficacy and dose range study) that the

risk-benefit balance of Thymanax in the treatment of Major Depressive Episodes in adults was favourable and therefore recommended the granting of the marketing authorisation.

Divergent opinions were based on the following considerations:

Efficacy has not been consistently demonstrated and the magnitude appears less than the active comparators combined with the unquantified safety risk makes the risk/benefit assessment negative for first time line use. There is no data available on second line use. Thus licensing this product would not provide an evidence based addition to the currently available treatments for Major Depressive Episodes. The divergent CHMP members believed that the licensing should not be granted until robust efficacy has been demonstrated and the effective dosage range is known.