

2. SYNOPSIS

Name of Company: I.R.I.S. 50 rue Carnot 92150 Suresnes - FRANCE	Individual Referring of the Dossier	Study to	Table Part	<i>(For National Authority Use only)</i>
Name of Finished Product: Valdoxan®	Volume:			
Name of Active Ingredient: Agomelatine (S 20098)	Page:			
Title of study: Evaluation of the effects of agomelatine (25 mg and 50 mg) and escitalopram 20 mg during 9 weeks on emotional blunting, emotional processing and motivation in healthy male and female volunteers. A phase I, national, multicentric, randomised, double-blind, placebo-controlled study with 4 parallel groups. Protocol No.: CL1-20098-081 – EudraCT number: 2010-024570-19 The description of the study protocol given hereafter includes the modifications of the four substantial amendments to the protocol.				
Coordinator: [REDACTED] - [REDACTED] - United Kingdom				
Study centres: Two centres in United Kingdom: - [REDACTED] 66 participants included. - [REDACTED] 67 participants included.				
Publication (reference): Not applicable.				
Studied period: Initiation date: 29 December 2011. Completion date: 25 July 2013.			Phase of development of the study: Phase I	
Objectives: The objective of this exploratory study was to assess the effects of two doses of agomelatine (25 mg or 50 mg) and escitalopram (20 mg) on emotional blunting, emotional processing and motivation during 9 weeks treatment (as modified by Amendment No. 2 from “8 weeks treatment”) in healthy male and female volunteers.				
Methodology: This was a phase I, multicentric (2 centres), national (United Kingdom), randomised, double-blind, placebo-controlled, without therapeutic benefit, in healthy volunteers, with 4 parallel groups (<i>i.e.</i> agomelatine 25 mg, agomelatine 50 mg, escitalopram 20 mg, and placebo). Randomisation was balanced (non-adaptive), with stratification on gender and on centre. This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.				
Number of participants: Planned: In all 128 participants (64 males and 64 females), 32 per group (16 males and 16 females). Included: 133 participants (67 males and 66 females), 33 in the agomelatine 25 mg group, 32 in the agomelatine 50 mg group, 36 in the escitalopram 20 mg group and 32 in the placebo group.				
Main criteria for inclusion: Healthy male and female volunteers, aged between 18 and 45 years (both inclusive), non-smokers or moderate smokers (≤ 10 cigarettes per day) with ability and willingness to undergo neuropsychological and motivation tests batteries and self-rating or clinician-rated questionnaires. All participants had to sign an informed consent.				
Study drug: Agomelatine 25 mg and 50 mg – oral route – 1 capsule in the evening at around 8.00 p.m. from D0 (W0) to D63 (W9). Batch No.: Agomelatine 25 mg: L0037212, L0046514; Agomelatine 50 mg: L0037213, L0046516				

Reference product:

- Escitalopram – 10 mg or 20 mg – oral route – 1 capsule in the evening at around 8.00 p.m.
Participants received 10 mg/day from D0 (W0) to D7 (W1), 20 mg/day from D7 (W1) to D56 (W8), and 10 mg/day from D56 (W8) to D63 (W9) (tapering period).
- Placebo – oral route – 1 capsule in the evening at around 8.00 p.m. from D0 (W0) to D63 (W9).

Duration of treatment:

- Selection period: 1-6 weeks without treatment (according to Amendment No. 3) between selection visit (ASSE) and inclusion visit D0 (W0).
- 9 weeks of double-blind treatment period (according to Amendment No. 2) from D0 (W0) to D63 (W9):
 - Agomelatine 25 mg for 9 weeks.
 - Agomelatine 50 mg for 9 weeks.
 - Escitalopram 10 or 20 mg: 10 mg for the first week, 20 mg for the following 7 weeks and 10 mg for the tapering period.
 - Placebo for 9 weeks.
- Follow-up period without study treatment: 5-7 days after the end of the tapering period or in case of study withdrawal.

Criteria for evaluation:

PHARMACODYNAMIC ANALYSES

No primary criterion had been defined for this exploratory study

Criteria assessing the emotional blunting:

Emotional blunting was assessed by using the Oxford Depression Questionnaire (ODQ) at inclusion D0 (W0) (baseline, before drug intake, only section 1 of the ODQ) and at different time points after drug intake (sections 1 and 2 of the ODQ): visits D14 (W2), D55 (W8), follow-up visit (DEND) and in case of withdrawal if the participant withdrew on or after D35 (W5).

The following criteria were considered: ODQ total score, individual ODQ sections score, individual ODQ items (sections 1 and 2) scores, and individual ODQ dimension score (General reduction (GR), Emotional detachment (ED), Positive reduction (PR) and not caring (NC), and GR +ED and PR + NC ODQ dimension scores.

Moreover, an ODQ-Visual analogue scale (ODQ-VAS) including 8 items and the Gold Standard question on the level of blunting were evaluated at the same visits, except for items 1, 2 and 3 of the ODQ-VAS, also evaluated at D0 (W0).

Criteria assessing the emotional processing (perception and memory for positive and negative emotional information):

Five neuropsychological tests were performed at different time points following drug intake: visits D7 (W1), D55 (W8) or in case of withdrawal if the participant withdrew on or after D35 (W5). The tests were performed in the following order:

- Facial expression recognition task (FERT).
- Emotional categorisation task (ECAT).
- Faces dot-probe task (FDOT).
- Emotional memory free recall task (EREC).
- Emotional memory forced recognition task (EMEM).

Criteria assessing motivation:

A gait task (with and without a cognitive task) and a motivation score (from 0 to 10) to evaluate the volunteers motivation state, were assessed at inclusion D0 (baseline, before drug intake) and at different time points after drug intake: D3 (W0), D7 (W1), D14 (W2), D35 (W5) and D56 (W8) or in case of withdrawal if the participant withdrew on or after D35 (W5).

Criteria for evaluation: (Cont'd)

PHARMACODYNAMIC ANALYSES (Cont'd)

Moreover, three motivation tasks were performed at different time points following drug intake: visit D3 (W0), D14 (W2) and D56 (W8) or in case of withdrawal if the participant withdrew on or after D35 (W5).

The following criteria were assessed:

- Sensitivity to reward and punishment in a basic probabilistic learning task (Task 1).
- Sensitivity to reward and punishment in a complex probabilistic learning task (Task 2).
- Motivation and effort duration task.

Criteria assessing sexual acceptability:

Sexual acceptability was assessed by using the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) at inclusion D0 (W0) (baseline, before drug intake) and at different time points after drug intake: visits D14 (W2), D35 (W5), D55 (W8), at the follow-up visit (DEND) and in case of withdrawal if the participant withdrew on or after D35 (W5). PRSexDQ total score and individual PRSexDQ item scores were considered.

A VAS on sexual functioning satisfaction (SFS-VAS) was also completed at the same visits.

Criteria for volunteers' subjective assessments:

Hospital Anxiety Depression (HAD) sub-scores, State-Trait Anxiety Inventory (STAI)-State total score, mood VAS (6-item VAS) scores and Social Adaptation Self Evaluation Scale (SASS) total score were assessed at inclusion visit D0 (W0), D7 (W1), D55 (W8) or in case of withdrawal if the participant withdrew on or after D35 (W5).

Criteria assessing cognitive and physical functioning:

The Massachusetts General and Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) total score and sub-scores were assessed at inclusion visit D0 (W0), D14 (W2), D35 (W5) and D56 (W8) or in case of withdrawal if the participant withdrew on or after D35 (W5).

SAFETY ANALYSES

Adverse events and vital signs (systolic and diastolic blood pressure, heart rate) during the whole study, body weight and Body Mass Index (BMI) at ASSE, D0 (W0) and follow-up visit, laboratory parameters (blood and urine biochemistry and haematology) at ASSE, D14 (W2), D35 (W5) and follow-up (DEND) were evaluated.

OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO PHARMACODYNAMICS OR SAFETY MEASUREMENTS

Serum and plasma Brain Derived Neurotrophic Factor (BDNF) and Vascular Endothelial Growth Factor (VEGF) were measured at selection (ASSE), D14 (W2) and D35 (W5).

DRUG CONCENTRATIONS

Saliva samples were collected during the treatment period in order to measure concentrations of agomelatine and escitalopram for compliance determination. Moreover saliva samples were collected at D34 (W5) for pharmacokinetic analysis.

Agomelatine and escitalopram concentration in saliva were analysed by a central laboratory by using previously validated methods.

Statistical methods:**PHARMACODYNAMIC ANALYSES**

In addition to descriptive statistics by treatment group (and some by gender) for each analytical approach of criteria on D0-D56 in the PPS, the following analyses were performed:

- Emotional blunting: initially, scores obtained from the ODQ-VAS and ODQ total score were compared between some treatment groups using a linear model studying treatment effect with centre and gender as covariates (fixed effect). However, considering that the criterion deviates from the normal distribution, a non-parametric analysis, based on Hodges-Lehmann's estimate and Mann-Whitney test, was used (complementary analyses).
- Emotional Processing: two separate analyses of variance (ANOVA) models were used to estimate treatment effects with terms for Visit (Day 7, Day 55) on each evaluated criteria. Other initial factors in the model included main effect of treatment (4 levels), site (2 levels) and gender (2 levels).
- Motivation (Tasks 1, 2 & 3): analysis of variance models were used to estimate treatment effects. Other analyses were used to study the interaction and other potential factors influencing the evaluated parameters.
- Sexual acceptability: total score values at each visit were compared between some treatment groups, using a linear model studying treatment effect with centre, gender and baseline as covariates (fixed effect), overall and by gender. Estimate of the difference (standard error) between adjusted group means was provided with its 95% confidence interval and p-value.

Motivation score, Gait task, individual items scores of the PRSexDQ and Sexual Functioning Satisfaction-VAS score, STAI-STATE anxiety questionnaire, Hospital Anxiety Depression (HAD) Scale, MOOD VAS, Social Adaptation Self-Evaluation Scale (SASS) as well as Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) were presented using descriptive statistics in terms of values at each visit and changes from baseline to each post-baseline visit if applicable.

SAFETY ANALYSES

Description of adverse events (total and emergent), vital signs, and biology parameters were provided in the Safety Set.

OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO PHARMACODYNAMICS OR SAFETY

For BDNF and VEGF measurements, descriptive statistics were provided on the whole study period by treatment group in the Safety Set.

PHARMACOKINETICS

The individual saliva concentrations were fit to an existing population pharmacokinetic model which had been developed for agomelatine (██████████). As agomelatine was measured in saliva and not in plasma, a known correlation between agomelatine plasma and saliva concentrations was used to back-calculate plasma concentrations from saliva concentrations, in order to derive individual plasma pharmacokinetic parameters. The following pharmacokinetic parameters were obtained: AUC₂₄, C_{max}, t_{max} and t_{1/2,z}.

Since no population pharmacokinetic model was available for escitalopram, the plasma PK parameters of escitalopram were not estimated.

SUMMARY - CONCLUSIONS**STUDY POPULATION AND OUTCOME:**

	Agomelatine 25 mg (N = 33)	Agomelatine 50 mg (N = 32)	Escitalopram 20 mg (N = 36)	Placebo (N = 32)	All (N = 133)
Included (randomised)	33	32	36	32	133
Withdrawn due to	4 (12.1)	-	7 (19.4)	2 (6.3)	13 (9.8)
adverse event	2 (6.1)	-	2 (5.6)	-	4 (3.0)
protocol deviation	1 (3.0)	-	4 (11.1)	-	5 (3.8)
non-medical reason	1 (3.0)	-	1 (2.8)	2 (6.3)	4 (3.0)
Completed the D0-D56 period	29 (87.9)	32 (100.0)	29 (80.6)	30 (93.8)	120 (90.2)
Per Protocol Set (PPS)	32 (97.0)	32 (100)	32 (88.9)	32 (100)	128 (96.2)
Safety Set	33 (100)	32 (100)	36 (100)	32 (100)	133 (100)
PK Set	31 (93.3)	32 (100)	-	-	63 (47.4)

%: expressed as percentage of the participants from the Randomised Set

SUMMARY - CONCLUSIONS (Cont'd)**STUDY POPULATION AND OUTCOME (Cont'd):**

A total of 137 participants were selected, and 133 were included and randomly assigned to one of the 4 groups. Considering the rules for replacing participants during the study (*i.e.* in case a participant withdrew before D35 (W5), he/she was to be replaced by another participant), the distribution of randomised participants according to the treatment dispensed at inclusion was well balanced: 33 participants in the agomelatine 25 mg group (including one participant replaced), 32 in the agomelatine 50 mg group, 36 in the escitalopram 20 mg group (including four participants replaced) and 32 in the placebo group.

Over the D0-D56 period, the rate of withdrawals was higher in the escitalopram group than in the others groups. This difference was mainly due to withdrawals resulting from protocol deviation, which were more frequent in the escitalopram group than in the other groups (see Table above). Finally the percentage of included and randomised participants who completed the study at D56 was 87.9% in the agomelatine 25 mg group, 100% in the agomelatine 50 mg group, 80.6% in the escitalopram 20 mg group and 93.8% in the placebo group.

In the Randomised Set, participants were 23.3 ± 4.3 years old on average ranging from 18 to 42 years, half were female (49.6%).

At baseline, treatments groups were comparable in term of verbal intelligence quotient, personality and trait anxiety with a mean National Adult Reading Test (NART) total score of 118.3 ± 5.1 , Revised-Eysenck Personality Questionnaire (EPQR) Extraversion, Neuroticism, Psychoticism and Lie scores of 17.1 ± 3.9 , 5.5 ± 4.0 , 5.6 ± 3.4 and 7.7 ± 4.0 , respectively, and State-Trait Anxiety Inventory (STAI)-TRAIT total score of 30.3 ± 5.2 , without relevant differences between groups.

Participants did not feel emotionally blunted on average (mean ODQ Section 1 score = 3.0 ± 4.5 , median 1.0). There was no relevant difference between groups for ODQ Section 1 score.

The mean motivation score at baseline was 7.7 ± 1.0 (median 8.0), with no relevant difference between either group or between genders. Regarding gait tasks, mean walking times were: 15.6 ± 1.8 s for usual pace, 18.0 ± 3.9 s for usual pace with the cognitive task, 10.7 ± 1.3 s for fast walking, and 12.2 ± 1.7 s for fast walking with the cognitive task, with no relevant difference either between groups or between genders.

For sexual acceptability the analyzed population was defined as the subset of participants of the PPS with physical sexual activity at baseline and at least one post baseline visit and includes 110 participants (82.7%). The mean PRSexDQ total score was 0.5 ± 1.3 at inclusion, and the mean sexual functioning VAS score was 88.4 ± 11.1 mm (median 90.0 mm), indicating that participants were largely satisfied with their sexual functioning.

Overall at baseline, participants did not present cognitive and physical impairment, with a mean MGH-CPFQ total score of 14.6 ± 1.9 . The mean SASS score was 48.6 ± 4.9 , corresponding to "normal" social adaptation/functioning.

Participants did not show any signs of depression (HAD depression score ranged from 0 to 6, mean score = 0.9 ± 1.3) and had no anxiety at baseline (mean HAD anxiety score = 3.6 ± 2.5 and mean STAI STATE score = 27.4 ± 6.1).

Mood VAS showed that on average, participants felt happy, calm and alert, and did not feel sad, hostile or anxious.

No relevant differences were observed between treatment groups or between genders for sexual activity, cognitive and physical functioning and subjective scales.

In the Randomised Set, mean treatment exposure was 59.7 ± 11.9 days (median 63.0 days), and was shorter in the escitalopram 20 mg group (54.6 ± 19.5 days) than in the others groups (60.1 ± 10.1 days in the agomelatine 25 mg group, 62.8 ± 1.4 days in the agomelatine 50 mg group and 61.8 ± 4.7 days in the placebo group). This difference was due to the four participants of the escitalopram 20 mg group withdrawn from the study at D3 (3 volunteers) and D7 (1 volunteer), not included in the Per Protocol Set and replaced. Mean global compliance was $98.8 \pm 2.8\%$, with no relevant difference between treatment groups.

PHARMACODYNAMIC RESULTS:***Emotional blunting***

No statistically significant difference either between agomelatine (25 mg and 50 mg) and placebo or between agomelatine (25 mg and 50 mg) and escitalopram or escitalopram *versus* placebo, was observed in the PPS for ODQ total score at any visit during the study.

As regards ODQ-VAS, in the PPS no relevant differences were observed either between baseline and D55, or between groups in overall population.

The gold standard question on the level of blunting showed that at the end of the treatment period (D55) in the PPS, 10.3%, 13.3%, 17.2% and 17.2% of participants, respectively in the agomelatine 25 mg, 50 mg, escitalopram 20 mg and placebo groups, felt mild or moderate emotional effect of the treatment.

Emotional processing:

- Facial Expression Recognition Task (FERT)
 - D7: In overall population, results on target sensitivity indicated a decrease in facial expression recognition following agomelatine 25 mg ($p = 0.030$) and 50 mg ($p = 0.064$) in comparison with escitalopram 10 mg. Compared to placebo, escitalopram 10 mg showed a tendency for higher misclassifications to happy faces ($p = 0.068$) as well as a decreased response bias towards labeling faces as disgust ($p = 0.027$) and as surprise ($p = 0.042$). Compared to placebo, agomelatine 25 mg presented a response bias towards labeling faces as happy (misclassifications: $p = 0.022$; response bias $p = 0.015$). Misclassifications and response bias were higher at the dose of agomelatine 25 mg compared to escitalopram 10 mg (respectively $p = 0.016$ and $p = 0.023$).
 - D55: no significant treatment effects were observed in overall population.
- Faces Dot-Probe Task (FDOT), Emotional Categorisation Task (ECAT), Emotional Memory Free Recall Task (EREC), Emotional Memory Forced Recognition task (EMEM): on D7 and D55, no effect of treatment was observed in overall population.

Motivation:

- The mean motivation score showed no relevant differences either between baseline and D56 or between groups in the PPS.
- Regarding gait tasks, no main differences on mean changes from baseline to each visit were observed between treatments except some tendencies in the following criteria:
 - A slight lower decrease in walking time for usual pace with the cognitive task from baseline to each post-baseline value was observed with the 3 active treatment groups, and especially with escitalopram 20 mg group as compared to placebo group (at D56: -3.04 ± 1.97 s in the agomelatine 25 mg group, -3.37 ± 2.38 s in the agomelatine 50 mg group, -2.83 ± 2.44 s in the escitalopram 20 mg group, and -4.99 ± 5.99 s in the placebo group).
 - A slight greater decrease in walking time for fast walking with the cognitive task from baseline to each post-baseline value was observed with the agomelatine 50 mg group as compared to the other groups, especially escitalopram 20 mg group (at D56: -0.766 ± 1.213 s in the agomelatine 25 mg group, -1.270 ± 1.092 s in the agomelatine 50 mg group, -0.536 ± 1.208 s in the escitalopram 20 mg group, and -0.837 ± 1.086 s in the placebo group).
- Basic probabilistic learning task (Task 1)
 - Accuracy :

Regarding treatment effects, on D3 agomelatine 25 mg elicited higher accuracy ($87.6 \pm 7.6\%$) than escitalopram 10 mg ($82.2 \pm 9.0\%$) ($p = 0.01$). On D14, agomelatine 50 mg elicited higher accuracy ($91.1 \pm 6.8\%$) than placebo ($87.2 \pm 8.3\%$) ($p = 0.038$), agomelatine 25 mg ($86.1 \pm 10.6\%$) ($p = 0.012$), and marginally than escitalopram 20 mg ($87.5 \pm 8.1\%$) ($p = 0.057$). At D56, escitalopram 20 mg elicited higher accuracy ($90.3 \pm 6.2\%$) than placebo ($86.4 \pm 8.8\%$) ($p = 0.035$), and marginally than agomelatine 50 mg ($89.7 \pm 4.5\%$) ($p = 0.053$).

SUMMARY – CONCLUSIONS (Cont'd)**PHARMACODYNAMIC RESULTS (Cont'd):**

There was an interaction of treatment with visit and stimulus valence ($F(6,230) = 2.24, p = 0.041$). With the positive pair: on D3 agomelatine 25 mg ($91.0 \pm 11.0\%$) elicited higher accuracy than escitalopram 10 mg ($82.9 \pm 13.6\%$) ($p = 0.013$). On D14, agomelatine 50 mg ($93.0 \pm 7.0\%$) elicited higher accuracy than both escitalopram 20 mg ($87.4 \pm 12.0\%$) ($p = 0.025$) and agomelatine 25 mg ($85.9 \pm 15.1\%$) ($p = 0.020$). On D56, there was a tendency for all three antidepressants to elicit higher accuracy than placebo.

There was an interaction of treatment with task phase and visit ($F(6,230) = 3.37, p = 0.003$). During the learning phase: on D3 both agomelatine 25 mg ($81.9 \pm 9.4\%$) and agomelatine 50 mg ($80.7 \pm 8.4\%$) elicited higher accuracy than escitalopram 10 mg ($73.8 \pm 10.7\%$) ($p = 0.003$ and $p = 0.007$ respectively). On D14, agomelatine 50 mg ($85.3 \pm 8.9\%$) elicited a higher accuracy than escitalopram 20 mg ($80.6 \pm 9.7\%$) ($p = 0.046$). On D56, there was no difference between treatment groups. During the exploitation phase: on D3, there was no difference between treatment groups. On D14, agomelatine 50 mg ($96.7 \pm 6.0\%$) elicited higher accuracy than agomelatine 25 mg ($91.0 \pm 11.4\%$) ($p = 0.016$). On D56, accuracy with antidepressant treatments was higher than placebo ($90.6 \pm 10.5\%$) (for escitalopram 20 mg: $96.3 \pm 4.6\%$ - $p = 0.012$; agomelatine 25 mg: $95.0 \pm 6.5\%$ - $p = 0.061$; and agomelatine 50 mg: $96.0 \pm 5.1\%$ - $p = 0.013$).

- Reaction time :

There was a marginal interaction of treatment and valence on reaction time (F value = 2.54, $p = 0.060$). With the negative pair, reaction time was shorter in the agomelatine 25 mg group (845.8 ± 210.9 ms) and in the agomelatine 50 mg group (852.4 ± 165.3 ms) than in the placebo group (931.6 ± 202.4 ms) ($p = 0.042$ and 0.043 , respectively) and marginally so compared to the escitalopram 20 mg group (930.5 ± 220.4 ms) ($p = 0.052$ and 0.055 , respectively).

- Complex probabilistic learning task (Task 2)

- Accuracy:

Regarding treatment effects, there was an interaction of treatment with visit and stimulus valence ($F(6,234) = 2.98, p < 0.01$). Indeed, with the positive symbol, agomelatine 25 mg elicited higher accuracy ($78 \pm 8.9\%$) than all other treatment groups on D3 (placebo: $71 \pm 15\%$ - $p = 0.02$, escitalopram 10 mg: $71 \pm 16\%$ - $p = 0.03$, and agomelatine 50 mg: $72 \pm 13\%$ - $p = 0.039$). On D14, agomelatine 25 mg elicited higher accuracy ($80 \pm 9.9\%$) than escitalopram 20 mg ($73 \pm 51\%$) ($p = 0.04$). There was no significant difference between treatment groups on D56. There was no significant difference across treatment groups with the negative symbol.

- Negative Feedback sensitivity (NFS):

NFS in the agomelatine 25 mg group was significantly lower ($28 \pm 8.6\%$) than in the placebo group ($35 \pm 8.8\%$) ($p = 0.006$).

- Risky choices:

As regards treatment, there was an interaction of treatment with visit ($F(6,234) = 2.98, p = 0.008$). Indeed, on D3, agomelatine 25 mg elicited more risky actions ($57 \pm 10\%$) than placebo ($52 \pm 11\%$) ($p = 0.032$) or escitalopram 10 mg ($52 \pm 11\%$) ($p = 0.013$). On D14, agomelatine 25 mg elicited more risky actions ($53 \pm 10\%$) than escitalopram 20 mg ($50 \pm 7.9\%$) ($p = 0.036$), or agomelatine 50 mg ($28 \pm 8.6\%$) ($p = 0.049$), but not more than placebo ($53 \pm 9.9\%$) ($p = 0.85$). On D56, no treatment differences were observed at the exception that agomelatine 50 mg ($48 \pm 12\%$) elicited less risky actions than placebo ($p = 0.0056$). Increase in risky action occurred exclusively on the positive symbol.

- Number of reversals: there was neither main effect of treatment nor any interaction between treatment and visit.

- Reaction time:

There was a main effect of treatment ($F(3,117) = 4.88, p = 0.003$): average reaction time was shorter in the agomelatine 25 mg group (505.80 ± 81.1 ms) than in any other treatment groups ($p = 0.002, p = 0.047$ and $p = 0.002$ against placebo (578.48 ± 101.3 ms), escitalopram 20 mg (552.32 ± 101.6 ms) and agomelatine 50 mg (588.66 ± 118.8 ms) groups, respectively). There was an interaction of treatment and valence $F(3,117) = 4.3, p = 0.006$: agomelatine 25 mg elicited shorter reaction time than all other treatment groups ($p < 0.001, p = 0.012, p < 0.001$ against placebo, escitalopram 20 mg and agomelatine 50 mg treatment groups respectively with the negative symbol, and $p < 0.001, p = 0.007, p < 0.001$ with the positive symbol). Agomelatine 50 mg group elicited longer reaction time than escitalopram 20 mg group with the negative symbol ($p = 0.006$) but not with the positive symbol ($p = 0.18$).

SUMMARY – CONCLUSIONS (Cont'd)**PHARMACODYNAMIC RESULTS (Cont'd):**

- For motivation and effort task (task 3), treatments affected the following criteria:
 - Monetary payoff: payoff was higher in the escitalopram 20mg group (35.9 ± 1.2 pounds average over visits, all visits pooled) as compared to the placebo group (30.1 ± 1.4 pounds average over visits) ($p = 0.003$), agomelatine 50 mg group (32.2 ± 1.4 pounds, average over visits) ($p = 0.051$). This better performance was stable over time, was mostly driven by the effects of treatment on mean effort duration and on incentives effect on effort duration.
 - Mean effort duration was longer in the escitalopram 20 mg group ($10.2 \text{ s} \pm 0.6$ seconds, average over visits) than in the placebo group ($7.6 \text{ s} \pm 0.6$ seconds, average over visits) ($p = 0.002$) and the agomelatine 50 mg group ($8.0 \text{ s} \pm 0.6$ seconds, average over visits) ($p = 0.007$).
 - Effect of incentives on effort duration, for which there was a trend toward a treatment effect ($p = 0.079$): there was a steeper modulation of effort duration by incentives in the escitalopram 20 mg group (1.9 ± 0.3 , average over visits) as compared to placebo (1.1 ± 0.2 , average over visits) ($p = 0.023$).
 - The effect of incentives on rest duration was less pronounced in the agomelatine 50 mg group (-0.15 ± 0.04) than in both agomelatine 25 mg ($p = 0.011$) and escitalopram 20 mg ($p = 0.043$) groups.

Sexual acceptability

The PRSexDQ total score in participants having a sexual activity at baseline and at least at one post-baseline visit, was statistically significantly lower in both agomelatine groups than in the escitalopram 20 mg group at all visits during the treatment period (see Table below) and at the follow-up visit.

Similar results were observed in healthy males subjects, with statistically significant lower total scores in both agomelatine groups than in the escitalopram 20 mg group at D14, D35, D55 and DEND (p-values ranging between < 0.0001 and 0.017). In healthy females, statistically significant lower total score was observed in the agomelatine 25 mg group (at D14 and D35) and agomelatine 50 mg group (at D35) as compared to escitalopram 20 mg group.

The PRSexDQ total score in participants having a sexual activity at baseline and at least at one post-baseline visit, was statistically significantly higher in the escitalopram 20 mg group than in the placebo group at all visits during the treatment period (see Table below) and at the follow-up visit. Similar results were observed in the subgroups of males and females.

Regarding individual item scores during the treatment period, the score for delayed orgasm/ejaculation was slightly greater in the escitalopram 20 mg group than in the agomelatine 25 mg and 50 mg groups at D14 (median 0.5 in the escitalopram 20 mg group *versus* 0.0 in both agomelatine 25 mg and 50 mg groups) and at D55 (median 1.0 *versus* 0.0 in both agomelatine groups). The frequency of participants with fair tolerance tended to be greater in the escitalopram 20 mg group than in the other groups (14.3% in the escitalopram 20 mg group *versus* none, 4.0% and none in the agomelatine 25 mg, 50 mg and placebo groups, respectively).

No relevant changes were detected in the agomelatine 25 mg and 50 mg groups like in the placebo group for the mean sexual functioning satisfaction (SFS-VAS) score during treatment period. In the escitalopram 20 mg group, the mean (median) SFS-VAS score decreased of -10.0 ± 18.2 (-5.0) mm at D55: -3.3 ± 10.6 (-6.0) mm in males and -15.7 ± 21.6 (-5.0) mm in females.

SUMMARY – CONCLUSIONS (Cont'd)
PHARMACODYNAMIC RESULTS (Cont'd):

PRSexDQ total score: Comparison between each dose of agomelatine and escitalopram and between escitalopram and placebo by visit in the Per Protocol Set*

		Agomelatine 25 mg (N = 27)	Agomelatine 50 mg (N = 25)	Escitalopram 20 mg (N = 28)	Placebo (N = 30)
Baseline	n	27	25	28	30
	Mean ± SD	0.4 ± 0.8	0.3 ± 0.8	0.8 ± 2.2	0.3 ± 0.6
D14	n	23	22	24	29
	Mean ± SD	0.2 ± 0.4	0.9 ± 2.1	3.2 ± 3.3	0.2 ± 0.5
		<i>escitalopram versus agomelatine</i>		<i>escitalopram versus placebo</i>	
	E (SE) (1)	2.8 (0.5)	2.0 (0.5)	2.7 (0.5)	
	95% CI (2)	[1.7; 3.8]	[0.9; 3.0]	[1.7; 3.7]	
	p-value (3)	< 0.0001	0.0004	< 0.0001	
D35	n	25	25	26	29
	Mean ± SD	0.7 ± 1.3	0.7 ± 1.8	3.5 ± 3.2	0.5 ± 1.2
		<i>escitalopram versus agomelatine</i>		<i>escitalopram versus placebo</i>	
	E (SE) (1)	2.7 (0.6)	2.6 (0.6)	2.8 (0.5)	
	95% CI (2)	[1.6; 3.8]	[1.5; 3.8]	[1.7; 3.9]	
	p-value (3)	< 0.0001	< 0.0001	< 0.0001	
D55	n	24	24	25	28
	Mean ± SD	1.1 ± 2.0	0.8 ± 1.6	3.0 ± 3.1	0.4 ± 0.8
		<i>escitalopram versus agomelatine</i>		<i>escitalopram versus placebo</i>	
	E (SE) (1)	1.9 (0.6)	2.1 (0.6)	2.5 (0.6)	
	95% CI (2)	[0.7; 3.0]	[0.9; 3.2]	[1.4; 3.6]	
	p-value (3)	0.0016	0.0005	< 0.0001	

* In participants with sexual activity at baseline and at least at one post-baseline visit until D55
 Analysis of variance model on factor treatment with centre, gender and baseline as covariates (fixed effect)

(1) Estimate (standard error) of the difference between adjusted group means: escitalopram 20 mg minus agomelatine 25 mg or escitalopram 20 mg minus agomelatine 50 mg or escitalopram 20 mg minus placebo

(2) 95% confidence interval of the estimate

(3) p-value for the difference between adjusted group means

Subjective scales (HAD and STAI STATE), SASS scale and Physical and cognitive functioning
 In the PPS no changes were observed on these criteria during the study.

SUMMARY – CONCLUSIONS (Cont'd)**SAFETY RESULTS:****Emergent adverse events****Overall summary of emergent adverse events on treatment in the Safety Set**

		Agomelatine 25 mg (N = 33)	Agomelatine 50 mg (N = 32)	Escitalopram 20 mg (N = 36)	Placebo (N = 32)
Participants having reported					
At least one EAE	n (%)	27 (81.8)	24 (75.0)	31 (86.1)	27 (84.4)
At least one treatment-related EAE	n (%)	12 (36.4)	10 (31.3)	22 (61.1)	12 (37.5)
At least one severe EAE	n (%)	2 (6.1)	1 (3.1)	1 (0.9)	3 (3.6)
At least one EAE leading to treatment discontinuation	n (%)	2 (6.1)	-	2 (5.6)	-
At least one serious EAE	n (%)	2 (6.1)	-	-	-
At least one treatment-related serious EAE	n (%)	1 (3.0)	-	-	-
Treatment discontinuation due to serious EAE	n (%)	2 (6.1)	-	-	-

n: number of volunteers affected

During the treatment period in the Safety Set, the percentage of participants with at least one emergent adverse event showed no relevant difference between treatment groups (see Table above).

The most frequently affected system organ classes (in at least 15% of participants) on agomelatine during the treatment period in the Safety Set were nervous system disorders, infections and infestations, gastrointestinal disorders, psychiatric disorders and general disorders and administration site conditions. It was also the case in the escitalopram and the placebo groups except for the last one.

Infections and infestations were more common in the agomelatine 25 mg group (45.5% of participants affected) than in the placebo group (37.5%), and similarly reported in the agomelatine 50 mg, escitalopram 20 mg groups and placebo group (34.4%, 30.6% and 37.5%, respectively).

The percentages of participants with nervous system disorders, gastrointestinal disorders and psychiatric disorders were similar to or lower in the agomelatine 25 mg group (42.4%, 18.2% and 18.2%, respectively), and the agomelatine 50 mg group (40.6%, 15.6% and 15.6%, respectively) than in the placebo group (40.6%, 25.0% and 21.9%, respectively). Inversely, they were greater (at least 2 more participants) in the escitalopram 20 mg group (61.1%, 36.1% and 30.6%, respectively) than in the placebo group.

The percentage of participants with general disorders and administration site conditions was higher in the agomelatine 25 mg group (15.2%) and the escitalopram 20 mg group (13.9%) than in the placebo group (9.4%).

During the treatment period, the most frequent emergent adverse events on agomelatine (reported in at least 5 participants in any agomelatine group) were:

- Headache, reported in 18.2% of patients in the agomelatine 25 mg group, 25.0% in the agomelatine 50 mg group, 36.1% in the escitalopram 20 mg group, and 21.9% in the placebo group.
- Somnolence: 21.2%, 12.5%, 13.9% and 6.3%, respectively.
- Upper respiratory tract infection: 18.2%, 9.4%, 11.1%, and 6.3%.
- Nasopharyngitis: 15.2%, 6.3%, 16.7%, and 25.0%.

Few participants experienced severe emergent adverse events during the treatment period: 2 participants in the agomelatine 25 mg group (diarrhoea and nightmare in one subject and ovarian cyst torsion in the other one), 1 participant in the agomelatine 50 mg group (upper respiratory tract infection), 1 in the escitalopram 20 mg groups (headache), and 3 participants in the placebo group (dry mouth, abnormal dreams and ejaculation failure, respectively).

In both agomelatine groups, the most common system organ classes with treatment-related emergent adverse events were nervous system disorders and psychiatric disorders. Both system organ classes were similarly or less affected in the agomelatine 25 mg and 50 mg groups than in the placebo group except for nervous system disorders in the agomelatine 25 mg group. Both frequencies in the escitalopram were higher than in the placebo group and than in the agomelatine 25 mg and 50 mg groups.

SUMMARY – CONCLUSIONS (Cont'd)**SAFETY RESULTS (Cont'd):**

No death was reported during the study.

Two participants, both in the agomelatine 25 mg group (6.1%), had emergent serious adverse events. One participant had two serious adverse events considered as treatment-related by the investigator (ALAT and ASAT increased, see below "liver acceptability"). The other participant experienced not treatment-related severe ovarian cyst torsion. For both participants, emergent serious adverse events led to study drug withdrawal and resolved.

Two participants, both in the escitalopram 20 mg group (5.6%), experienced 7 non-serious emergent adverse events leading to study treatment discontinuation. Five events (agitation and tremor in one participant and anxiety, dizziness and restless legs in the other participant) were considered as treatment-related by the investigator.

Laboratory tests

In the Safety Set, neither clinically relevant changes over time nor differences between groups were detected for biochemical and haematological parameters during the study except for the mean CPK increase in the escitalopram 20 mg group (55.1 ± 166.1 IU/L *versus* 4.1 ± 69.8 IU/L in the placebo group). The median CPK was 17.0 IU/L and the Q3 was 66 IU/L (max 691 IU/L) in the escitalopram 20 mg group at study end visit, and no PCSA value of CPK was reported.

Few emergent PCSA biochemical values were reported, all in the escitalopram 20 mg group (3 PCSA for urea and 1 for triglycerides) and none was considered as clinically significant by the investigator.

There was no emergent PCSA haematological value during the treatment period.

Liver acceptability

As regards liver acceptability, emergent PCSA values of ALAT or ASAT were reported in 2 participants of the agomelatine 25 mg group at D14 visit.

PCSA value of ALAT (3.5 ULN) was associated with out-of-reference-range value of ASAT (2.2 ULN) in 1 participant and both abnormal values were reported as serious related emergent adverse events. The participant recovered after study drug withdrawal (56 days after the last intake values decreased to 0.5 ULN for ALAT and 0.8 ULN for ASAT). This case was reviewed by an independent expert scientific committee who considered these increases being due to a recent CMV infection instead of the studied drug.

The other participant reported high PCSA value for ASAT (3.0 ULN) associated with ALAT value above the upper limit of reference range (1.1 ULN). No adverse event was reported. At retest (two days later on treatment), values for ASAT and ALAT returned within the normal range.

Vital signs and BMI

In the Safety Set, neither clinically relevant mean changes over the treatment period nor differences between groups were detected for supine blood pressures and heart rate.

In the Safety Set, there were no clinically relevant differences in mean weight or BMI between baseline and follow-up visit in any group, nor relevant differences between the treatment groups.

BDNF and VGEF results**BDNF**

In the PPS, the median level of serum BDNF was slightly higher at last post-baseline assessment than at baseline in the agomelatine 25 mg (from 13702.4 pg/ml at baseline to 15751.9 pg/ml at the last post-baseline assessment), agomelatine 50 mg (from 11727.4 pg/ml to 13795.6 pg/ml) and placebo (from 14914.7 pg/ml to 15445.5 pg/ml) groups, with a greater increase on agomelatine than on placebo. In the escitalopram 20 mg group, the median level was lower at last post-baseline assessment (13502.0 pg/ml) than at baseline (14052.3 pg/ml).

As regards plasma level, the median BDNF was higher at the last post-baseline assessment on treatment than at baseline in the three active treatment groups, and inversely in the placebo group. This treatment effect was mainly observed in the agomelatine 25 mg group (from 1136.1 pg/ml at baseline to 2143.6 pg/ml at the last post-baseline assessment) and escitalopram 20 mg group (from 1044.2 pg/ml to 1575.1 pg/ml).

SUMMARY – CONCLUSIONS (Cont'd)**SAFETY RESULTS (Cont'd):****VEGF**

In the PPS, the median level of serum VEGF was slightly higher at last post-baseline assessment than at baseline in the agomelatine 50 mg group (from 342.5 pg/ml at baseline to 423.0 pg/ml at the last post-baseline assessment) and placebo group (from 507.3 pg/ml to 568.1 pg/ml); and was smaller in the agomelatine 25 mg (from 503.3 pg/ml to 453.7 pg/ml) and escitalopram 20 mg (from 525.6 pg/ml to 502.1 pg/ml) groups.

As regards plasma level, the median VEGF was slightly smaller at last post-baseline assessment than at baseline in all groups without relevant differences between them.

Pharmacokinetic results**Descriptive statistics of agomelatine pharmacokinetic parameters in plasma by dose**

Agomelatine dose (mg)	N	AUC ₂₄ ⁽¹⁾ (ng.h/mL)	C _{max} ⁽¹⁾ (ng/mL)	t _{max} ⁽²⁾ (h)	t _{1/2,z} ⁽¹⁾ (h)
25	31 ⁽³⁾	19.6 ± 20.2 (13.6)	12.8 ± 15.7 (7.55)	1.25 (0.20-4.0)	2.07 ± 0.166 (2.04)
50	32	65.5 ± 113 (32.2)	27.4 ± 42.6 (10.0)	1.25 (0.10-5.0)	2.13 ± 0.262 (2.06)

⁽¹⁾: mean ± SD (median)

N: number of subjects

⁽²⁾: median (min-max)

⁽³⁾: One subject from the 25 mg group did not undergo PK sampling

The mean and median plasma pharmacokinetic parameters based on the simulated plasma concentrations showed that similar t_{max} and t_{1/2,z} values were obtained for 25 and 50 mg doses, and the AUC₂₄ and C_{max} increased approximately proportionally with the dose between 25 and 50 mg. At 25 mg, the median AUC₂₄ and C_{max} values in this study (13.6 ng.h/mL and 7.55 ng/mL, respectively) were similar to the median AUC₂₄ and C_{max} values in the previous combined population pharmacokinetic analysis (13 ng.h/mL and 5.3 ng/mL, respectively). At 50 mg, the median AUC₂₄ in this study (32.2 ng.h/mL) was 1.9-fold lower than the AUC₂₄ value in the combined population pharmacokinetic analysis (60 ng.h/mL) and the C_{max} value in this study (10.0 ng/mL) was 2.5-fold lower than the C_{max} value in the combined population pharmacokinetic analysis (25 ng/mL). However, these observations were within the known variability of agomelatine.

CONCLUSION

This multicentric, randomised, double-blind, placebo-controlled study conducted in healthy volunteers showed that no emotional blunting was induced by agomelatine (25 mg or 50 mg), escitalopram or placebo during the study. Also there was no statistically significant difference between treatments groups.

Results obtained with the Emotional Test Battery failed to demonstrate main treatment effects in the overall population except for the facial expression recognition task (FERT) where, after 7 days treatment, a decreased bias towards labeling faces as disgust and as surprise was observed with escitalopram 10 mg as compared to placebo, whereas a bias towards misclassifying faces as happy was observed with agomelatine 25 mg in comparison to placebo.

As regards gait tasks, descriptive statistics showed no beneficial effects of treatments, except a slightly higher decrease in walking time for fast walking with the cognitive task in the agomelatine 50 mg group as compared to the other groups, especially to escitalopram 20 mg group.

As regards basic probabilistic learning task, an early beneficial effect on accuracy was observed with agomelatine 25 mg (D3) and agomelatine 50 mg (D14) compared to escitalopram 10-20 mg, respectively on D3 and D14. This effect was primarily driven by an increased sensitivity to positive, rewarding stimuli, and arose in the learning phase of the task.

As regards complex probabilistic learning task, an early beneficial effect on accuracy was observed with agomelatine 25 mg compared to escitalopram 10-20 mg (D3 and D14) and placebo (D3), which was specific to positive stimuli. This was achieved with an increased ability to disregard misleading negative feedback with agomelatine 25 mg while at the same time improving reaction time. This earlier beneficial cognitive effect of agomelatine 25 mg may allow patients to quickly relearn positive associations and help them overcome a negative depressed mindset.

Regarding the motivation and effort task, escitalopram 10-20 mg led to a better payoff in the task by both increasing the time spent on effort and by spending longer effort for high-value *versus* low-value trials. Agomelatine 25 mg tended to have similar effects to escitalopram 20 mg, but to a lesser extent, whereas agomelatine 50 mg had effects more similar to placebo.

As regards sexual acceptability (PRSexDQ), this study confirmed the statistically significantly better acceptability of agomelatine 25 mg and 50 mg than the SSRI escitalopram 20 mg, in both males and females. This agomelatine effect as compared to escitalopram effect was higher in men.

No relevant effects of treatments were observed on plasma and serum BDNF or VEGF levels with the exception of an increase between baseline and last post-baseline assessments of plasma BDNF level after agomelatine 25 mg and escitalopram 20 mg treatments.

The safety profile of agomelatine 25-50 mg reported in this study was in line with the known safety profile of agomelatine. Two cases of reversible transaminases increases (maximum values 3.5 ULN and 3 ULN) were reported in the agomelatine 25 mg dose regimen. The safety profile of escitalopram 20 mg/d followed its SmPC.

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