



<i>Document title</i>	<b>Clinical Study Synopsis Report</b>
<i>Study title</i>	<b>Early effect of agomelatine on general interest in outpatients with Major Depressive Disorder. A 12-week, randomised, double-blind, multicentre study with parallel groups: agomelatine (25 mg/day given orally blinded potential adjustment to 50 mg/day) versus escitalopram (10 mg/day given orally with blinded potential adjustment to 20 mg/day).</b>
<i>Study drug</i>	<b>S 20098</b>
<i>Studied indication</i>	<b>Major Depressive Disorder</b>
<i>Development phase</i>	<b>III</b>
<i>Protocol code</i>	<b>CL3-20098-083</b>
<i>Study initiation date</i>	<b>28 June 2011</b>
<i>Study completion date</i>	<b>26 April 2013</b>
<i>Main coordinator</i>	<b>[REDACTED] - Romania</b>
<i>Company / Sponsor</i>	<b>Institut de Recherches Internationales Servier (I.R.I.S.) 50 rue Carnot 92284 Suresnes Cedex - France</b>
<i>Responsible medical officer</i>	<b>[REDACTED]</b>
<i>GCP</i>	<b>This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.</b>
<i>Date of the report</i>	<b>Final version of 6 December 2013</b>

**CONFIDENTIAL**

## 2. SYNOPSIS

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<b>Name of Finished Product:</b> Valdoxan®	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Agomelatine (S20098)	<b>Page:</b>	
<b>Title of study: Early effect of agomelatine on general interest in outpatients with Major Depressive Disorder.</b> A 12-week, randomized, double-blind, multicentre study with parallel groups: agomelatine (25 mg/day given orally with blinded potential adjustment to 50 mg/day) <i>versus</i> escitalopram (10 mg/day given orally with blinded potential adjustment to 20 mg/day). Protocol No.: CL3-20098-083 – EudraCT No. 2010-023576-10		
<b>Coordinator:</b> [REDACTED], Romania		
<b>Study centres:</b> In all, 29 centres in Romania included at least one patient.		
<b>Publication (reference):</b> Not applicable.		
<b>Studied period:</b> Initiation date: 28 June 2011 Completion date: 26 April 2013		<b>Phase of development of the study:</b> III
<b>Objectives:</b> <b>Primary objective:</b> to assess the early effect of agomelatine compared to escitalopram on general interest using a Visual Analogue Scale (VAS) reflecting item 13 (General interest) of the Quick Inventory of Depressive Symptomatology (16-item) Self Report (QIDS-SR16) scale after a 1-week treatment period in outpatients suffering from Major Depressive Disorder (MDD), with a current Major Depressive Episode (MDE) of moderate to severe intensity. <b>Secondary objectives:</b> to compare agomelatine and escitalopram's effects on Concentration/decision making, Energy level, Daytime sleepiness, Severity of depression, Global clinical benefit, Social functioning, Emotional experiences; and to provide additional safety and tolerability data on agomelatine.		
<b>Methodology:</b> This was a phase III, multicentre, national, randomised, double-blind study, with two parallel groups: agomelatine 25 mg o.d. with a potential dose adjustment to 50 mg o.d. <i>versus</i> escitalopram 10 mg o.d. with a potential dose adjustment 20 mg o.d. Adjustment was done in case of insufficient improvement at W2. The criteria for increasing the dose at W2 were defined by I.R.I.S., based on clinical considerations and literature data, before the study beginning and kept blinded to the investigator and the patient. Randomisation was balanced, non adaptive, with stratification on the centre. Treatment randomisation and allocation were centralized with an Interactive Web Response System (IWRS). This study was performed in strict accordance with Good Clinical Practice.		
<b>Number of patients:</b> Planned: 300 patients (150 by treatment group). Included: 287 patients (144 in the agomelatine group and 143 in the escitalopram group).		
<b>Diagnosis and main criteria for inclusion:</b> Male or female out-patients, aged between 18 and 65 years (inclusive), fulfilling Diagnostic and Statistical Manual of Mental Disorders, 4 <sup>th</sup> Ed., Text Revision (DSM-IV-TR) criteria for Major Depressive Disorder, single episode or recurrent, with a current episode ( $\geq 4$ weeks, $\leq 12$ months) of moderate to severe intensity. At selection and inclusion, Hamilton Depression Rating Scale 17 items (HAM-D-17) total score was to be $\geq 22$ and no more than a 20% decrease in HAM-D total score between selection and inclusion, Clinical Global Impression Severity of illness (CGI-S) $\geq 4$ , Hospital Anxiety and Depression (HAD) - depression subscore $\geq 11$ , QIDS-SR16 item13 (General interest) score $\geq 2$ and Sheehan Disability Scale (SDS) total score $\geq 12$ (or $\geq 8$ when item "work" was not applicable, as specified in Amendment No. 2).		

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<b>Name of Active Ingredient:</b> <b>Agomelatine (S20098)</b>	<b>Page:</b>	
<b>Study drug:</b> Agomelatine, capsules of 25 or 50 mg. One capsule o.d. at bedtime. For patients receiving agomelatine 25 mg/day at inclusion, a potential adjustment to 50 mg/day might occur at W2, in case of insufficient improvement. Once adjusted (or not) at W2, the dose was maintained up to W13. Batch No.: Agomelatine 25 mg: L0037212; Agomelatine 50 mg: L0037213.		
<b>Reference product:</b> Escitalopram capsules of 5 mg, 10 mg or 20 mg. One capsule o.d. at bedtime. For patients receiving escitalopram 10 mg/day at inclusion, a potential adjustment to 20 mg/day might occur at W2 in case of insufficient improvement. Once adjusted (or not) at W2, the dose was maintained up to W12. At W12, patients previously treated with escitalopram 10 mg/day received escitalopram 5 mg/day for 1 week (tapering period) and patients previously treated with escitalopram 20 mg/day received 10 mg/day for the first three days, then 5 mg for the 4 following days (tapering period recommended to avoid possible withdrawal reactions).		
<b>Duration of treatment:</b> <ul style="list-style-type: none"> <li>- 4 to 10-day run-in period without study treatment (from selection visit (ASSE) to W0).</li> <li>- 12-week double-blind treatment period (from W0 to W12).</li> <li>- 1-week double-blind tapering period (from W12 to W13).</li> <li>- 1-week follow-up period without study treatment after W13 or after premature study withdrawal.</li> </ul>		

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<p><b>Criteria for evaluation:</b></p> <p><b>Efficacy measurements:</b></p> <ul style="list-style-type: none"> <li>- General interest score obtained from the VAS reflecting item 13 of the QIDS-SR16 scale: rated by the patient at each visit from W1 to W12 or in case of premature withdrawal. It was the primary efficacy criterion.</li> <li>- Scores obtained from the Concentrations/decision making and Energy level VAS: rated by the patient at each visit from W1 to W12, or in case of premature withdrawal.</li> <li>- Scores obtained from the Daytime Sleepiness VAS: rated by the patient at each visit from inclusion to W12, or in case of premature withdrawal.</li> <li>- HAM-D-17 total score: rated by the investigator at each visit from selection to W12, or in case of premature withdrawal, and at the follow-up visit for patients having completed the W0-W13 period.</li> <li>- Quick Inventory of Depressive Symptomatology (16-item) Clinician-rated (QIDS-C16) total score: rated by the investigator at inclusion and at W12, or in case of premature withdrawal.</li> <li>- QIDS-SR16 total score: rated by the patient at each visit from selection to W12, or in case of premature withdrawal.</li> <li>- CGI Severity of illness and Global improvement scores: rated by the investigator from selection to W12 (CGI item 2 not assessed at selection and inclusion and CGI item 1 not assessed at W1, W2 and W6) , or in case of premature withdrawal.</li> <li>- HAD Anxiety and Depression sub-scores: rated by the patient at selection, inclusion and W12, or in case of premature withdrawal.</li> <li>- SDS: Work, Social life and Family life scores, number of days lost and number of days underproductive: rated by the patient at selection, inclusion and W12, or in case of premature withdrawal.</li> <li>- Social Adaptation Self-evaluation Scale (SASS) total score: rated by the patient at inclusion and W12, or in case of premature withdrawal.</li> <li>- Scores obtained from the Emotional experiences VAS: rated by the patient at W0, W2 and W12, or in case of premature withdrawal.</li> </ul> <p><b>Safety measurements</b></p> <ul style="list-style-type: none"> <li>- Adverse events reported at each visit.</li> <li>- Laboratory tests: biochemical (including liver function parameters) and haematological tests available at inclusion and planned at the withdrawal visit in case of premature withdrawal.</li> <li>- Liver function parameters: prescribed at W2 (added by Amendment No. 2), W6 and W12 to be available one week later. Additional liver function tests were prescribed at W6 visit in order to perform liver function test 8 weeks after the inclusion visit (added by Amendment No. 3 but no patient was concerned by this amendment).</li> <li>- Physical examination: <ul style="list-style-type: none"> <li>• Blood pressure and heart rate at selection, inclusion and W12, or in case of premature withdrawal.</li> <li>• Body weight and BMI measured at selection, inclusion and W12, or in case of premature withdrawal. Height was measured at selection.</li> </ul> </li> </ul>		

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<p><b>Statistical methods:</b></p> <p><b>Efficacy analysis</b></p> <p><b>Primary criterion</b></p> <ul style="list-style-type: none"> <li>- Main analysis</li> </ul> <p>The superiority of agomelatine over escitalopram on patient general interest after 1 week of treatment was assessed from the value at W1 of the VAS score reflecting item 13 (General interest) of the QIDS-SR16 scale, in patients of the Full Analysis Set, using a two-way analysis of variance model on factors treatment (fixed effect) and centre (random effect) and without interaction.</p> <ul style="list-style-type: none"> <li>- Sensitivity analysis</li> </ul> <p>A two-sided Student's t-test for independent samples was performed on scores at W1 as sensitivity analysis to the adjustment for centre.</p> <p>A Hodges-Lehmann estimation of the difference between treatment groups associated with a Mann-Whitney test for independent samples was performed on scores at W1 as sensitivity analysis to the normality assumption (semiparametric approach).</p> <ul style="list-style-type: none"> <li>- Secondary analysis</li> </ul> <p>The evolution of the General interest score obtained from the VAS was described by visit and for last value over the W0-W12 period, in patients of the FAS and its subset of more severely depressed patients (Sub-FAS with baseline HAM-D total score <math>\geq 25</math>).</p> <p><b>Secondary criteria</b></p> <p>In order to assess the antidepressant efficacy of agomelatine as compared to escitalopram, the difference between treatment groups was estimated in the FAS on the change from baseline to W1 and to the last post-baseline value of HAM-D total score over W0-W12, using a two-way analysis of covariance model on factor treatment with centre (random class effect) and baseline HAM-D total score (continuous effect) as covariates, and without interaction. The estimate of the difference and its two-sided 95% confidence interval were positioned in relation to the fixed pre-defined non-inferiority margin of 1.5.</p> <p>The difference between treatment groups was also estimated in patients of the FAS on the response to treatment derived from HAM-D total score considering the last post-baseline value over the W0-W12 period.</p> <p>The evolution of HAM-D total score and of response to treatment was described in the FAS and its subset of more severely depressed patients over W0-W12.</p> <p>A description of the HAM-D total score was also provided over W12-Wend by treatment group in patients of the FAS with a value at W12 and Wend, and having performed the tapering period between W12 and W13 without intake of any treatment likely to interfere with the efficacy evaluation.</p> <p>The evolution of scores obtained from the VAS on Concentration/decision making, Energy level and Daytime sleepiness was described over W0-W12, in patients of the FAS.</p> <p>Moreover, the effect of agomelatine as compared to escitalopram on global clinical benefit, anxiety and depression symptoms, social functioning and emotional experiences, was described from the evolution of CGI, QIDS-C16 and QIDS-SR16, HAD, SDS and SASS and VAS on emotional experiences scores, respectively, over W0-W12 in patients of the FAS.</p> <p><b>Safety analysis</b></p> <p>Descriptive statistics were provided in the Safety set by treatment group (<i>i.e.</i> agomelatine <i>versus</i> escitalopram) over the ASSE-W13/Wend period for serious adverse events, emergent adverse events and laboratory parameters and over the W0-W12 period for physical examination.</p>		

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<b>SUMMARY - CONCLUSIONS</b>			
<b>STUDY POPULATION AND OUTCOME</b>			
<b>Disposition of patients</b>			
<b>Status</b>	<b>Agomelatine</b>	<b>Escitalopram</b>	<b>All</b>
<b>W0-W12</b>			
<b>Included and randomised</b>	<b>n</b>	<b>144</b>	<b>143</b>
<b>Withdrawn due to</b>	<b>n (%)</b>	<b>21 (14.6)</b>	<b>22 (15.4)</b>
adverse event	n (%)	4 (2.8)	7 (4.9)
lack of efficacy	n (%)	4 (2.8)	3 (2.1)
non-medical reason	n (%)	13 (9.0)	9 (6.3)
protocol deviation	n (%)	-	3 (2.1)
<i>Performed the follow-up visit</i>	<i>n (%)</i>	<i>4 (2.8)</i>	<i>15 (10.5)</i>
<b>Completed the W0-W12 period</b>	<b>n (%)</b>	<b>123 (85.4)</b>	<b>121 (84.6)</b>
<b>W12-W13</b>			
<b>Entered the W12-W13 period</b>	<b>n (%)</b>	<b>122 (84.7)</b>	<b>120 (83.9)</b>
<b>Completed the W12-W13 period</b>	<b>n (%)</b>	<b>122 (84.7)</b>	<b>242* (84.3)</b>
<i>Performed the follow-up visit</i>	<i>n (%)</i>	<i>121 (84.0)</i>	<i>118 (82.5)</i>
<b>Analysis sets</b>			
<b>Randomised set</b>	<b>n</b>	<b>144</b>	<b>143</b>
<b>Full Analysis Set (FAS)</b>	<b>n (%)</b>	<b>143 (99.3)</b>	<b>139 (97.2)</b>
Sub-FAS with baseline HAM-D total score $\geq 25$	n (%)	103 (71.5)	101 (70.6)
<b>Safety Set</b>	<b>n (%)</b>	<b>144 (100)</b>	<b>141 (98.6)</b>
<i>*Two patients (one in each group) did not enter the W12-W13 period</i>			
<i>%: % of the Randomised Set</i>			
<p>A total of 417 patients were selected for the study, and 287 patients were included and randomly assigned to one of the two treatment groups according to the Interactive Web Response System (IWRS) procedure. Distribution was well balanced (see Table above).</p> <p>In the Randomised Set, among the 268 randomised patients continuing in the study after the W2 visit (138 in the agomelatine group and 130 in the escitalopram group), 57 patients (21.3%) had a dose increase due to insufficient improvement: 30 patients (21.7%) in the agomelatine group <i>versus</i> 27 patients (20.8%) in the escitalopram group.</p> <p>No patient was lost to follow-up during the study. The rate of withdrawals over the W0-W12 period was similar in the two groups (14.6% of the patients in the agomelatine group <i>versus</i> 15.4% in the escitalopram group). The main reason for withdrawal was non medical reason in both groups (9.0% in the agomelatine group and 6.3% in the escitalopram group). Among the 244 patients (85.0%) who completed the W0-W12 period, 242 (84.3%) entered the tapering period and completed the study at W13 (122 patients, <i>i.e.</i> 84.7%, in the agomelatine group and 120 patients, <i>i.e.</i> 83.9%, in the escitalopram group).</p> <p>In the Randomised Set, patients were aged from 20 to 65 years with a mean <math>\pm</math> SD of <math>46.7 \pm 9.6</math> years. Most of them were female (82.2%). According to the DSM-IV-TR criteria, 68.3% of patients were diagnosed as recurrent MDD (63.2% of the patients in the agomelatine group <i>versus</i> 73.4% in the escitalopram group), and the other ones were diagnosed as MDD, single episode (31.7%). About half of patients (47.4%) had a MDE of moderate intensity, and 52.6% a MDE of severe intensity without psychotic features. Melancholic features were observed in 36.2% of patients. Mean number of depressive episodes was <math>2.4 \pm 1.7</math> episodes including the current one, ranging from 1 to 10. Mean duration of the current MDE was <math>3.1 \pm 2.3</math> months (median 2.3 months). Previous psychotropic drug treatment was reported in 53.0% of patients, mainly Selective Serotonin Reuptake Inhibitors (SSRIs, 23.0%), other antidepressants (34.1%), anxiolytics (13.9%), and hypnotics and sedatives (10.1%).</p>			

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<p><b>SUMMARY – CONCLUSIONS (Cont'd)</b>  <b>STUDY POPULATION AND OUTCOME (Cont'd)</b>  At inclusion the mean HAM-D total score was <math>26.1 \pm 2.4</math>. The mean CGI severity of illness score was <math>4.5 \pm 0.6</math> (median 4.0) corresponding to “moderately ill” patients. At inclusion, the mean HAD depression sub-score was <math>16.2 \pm 2.8</math>. All patients had a depression score <math>\geq 11</math> except one patient who had a corresponding protocol deviation. The mean HAD anxiety sub-score was <math>10.7 \pm 3.8</math>. In all, 50.9% of patients (47.2% in the agomelatine group <i>versus</i> 54.6% in the escitalopram group) felt at least moderately anxious (anxiety sub-score <math>\geq 11</math>).</p> <p>The mean QIDS-SR16 total score was <math>17.3 \pm 2.5</math>, which was consistent with the mean QIDS-C16 total score (mean score <math>17.0 \pm 2.5</math>). According to the item 13 of QIDS-SR16 (general interest), 66.2% of patients (61.1% for agomelatine <i>versus</i> 71.3% for escitalopram group) showed interest in only one or two of their formerly pursued activities and 33.8% (38.9% for agomelatine <i>versus</i> 28.7% for escitalopram group) had virtually no interest in formerly pursued activities throughout the past 7 days before inclusion.</p> <p>According to SDS, on average, patients felt markedly disrupted by symptoms for the 3 domains: work and activity (<math>6.7 \pm 1.3</math>), social life (<math>6.9 \pm 1.4</math>), and family life and home responsibilities (<math>6.7 \pm 1.3</math>). On average during the week prior to selection, <math>3.3 \pm 2.2</math> days were lost and <math>4.5 \pm 1.8</math> days were underproductive.</p> <p>The mean SASS total score was <math>25.0 \pm 6.0</math>, corresponding to social maladjustment.</p> <p>No clinically relevant differences between the treatment groups were observed for demographic, disease characteristics, and efficacy criteria at baseline.</p> <p>Baseline characteristics in the FAS and in the Sub-FAS with baseline HAM-D total score <math>\geq 25</math> were similar to those observed in the Randomised Set apart from the criteria defining the subset and criteria related.</p> <p>In the Randomised Set, mean treatment duration was <math>7.0 \pm 1.1</math> days (median 7.0 days) over the W0-W1 period, and <math>77.7 \pm 21.3</math> days (<i>i.e.</i> approximately 11.1 weeks) over the W0-W12 period. In the Safety Set, mean treatment duration was <math>84.3 \pm 22.5</math> days (median 91.0 days) over the W0-W13 period. Treatment durations were similar between groups.</p> <p>Mean global compliance was <math>97.4 \pm 13.5\%</math> over the W0-W1 period, and <math>96.1 \pm 15.2\%</math> over the W0-W12 period. Global compliance showed no relevant difference between the treatment groups.</p>		

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<b>SUMMARY – CONCLUSIONS (Cont'd)</b>			
<b>EFFICACY RESULTS</b>			
- <b>PRIMARY CRITERION: General interest from the VAS reflecting item 13 of the QIDS-SR scale.</b>			
After one week of treatment, in the FAS, the mean VAS General interest score showed no clinically and statistically significant difference between groups (main analysis, see Table below). Sensitivity analysis showed the same results.			
<b>VAS General interest score (mm): Description at W1 - Between-group comparison in the FAS</b>			
		<b>Agomelatine (N = 143)</b>	<b>Escitalopram (N = 139)</b>
W1	n	142	139
	Mean ± SD	49.6 ± 16.9	49.4 ± 17.9
	Median	51.0	51.0
	Min ; Max	3 ; 96	5 ; 91
<b>Statistical analysis</b>			
<i>Main analysis<sup>(1)</sup></i>			
	E (SE) <sup>(1.1)</sup>	0.15 (2.00)	
	95% CI*	[-3.79 ; 4.10]	
	p-value**	0.940	
<i>Sensitivity analysis to the adjustment for centre<sup>(2)</sup></i>			
	E (SE) <sup>(2.1)</sup>	0.14 (2.08)	
	95% CI*	[-3.95 ; 4.23]	
	p-value**	0.947	
<i>Sensitivity analysis to the normality assumption<sup>(3)</sup></i>			
	E (SE) <sup>(3.1)</sup>	0.00 (1.53)	
	95% CI*	[-3.00 ; 3.00]	
	p-value**	0.826	
<i>(1) Analysis of variance model on factor treatment with centre as covariate (random effect):</i>			
<i>(1.1) Estimate (Standard Error) of the difference between adjusted treatment group means: agomelatine minus escitalopram</i>			
<i>(2) Two-sided Student's t-test for independent samples:</i>			
<i>(2.1) Estimate (Standard Error) of the difference between treatment group means: agomelatine minus escitalopram</i>			
<i>(3) Semiparametric analysis:</i>			
<i>(3.1) Estimate (Standard Error) of Hodges-Lehmann for the difference between treatment groups: agomelatine minus escitalopram (Mann-Whitney test)</i>			
<i>*Two-sided 95% Confidence Interval of the estimate; **Two-sided p-value</i>			
Over the W0-W12 period, the mean VAS General interest score progressively increased in both groups (mean scores at the last post-baseline value were 70.9 ± 21.3 and 74.6 ± 19.2 in the agomelatine and escitalopram groups, respectively).			
Similar results were observed in patients more severely depressed at inclusion (Sub-FAS with baseline HAM-D total score ≥ 25).			
- <b>SECONDARY ASSESSMENT CRITERIA</b>			
<b>VAS on Concentration/decision making and Energy level</b>			
In the FAS, VAS scores on concentration/decision making and energy level analyzed over W0-W12 improved in both groups. At the last assessment over W0-W12, mean scores in the agomelatine and escitalopram groups were as follows:			
<ul style="list-style-type: none"> <li>• Concentration / decision making score: 69.7 ± 22.1 mm versus 72.4 ± 21.7 mm, respectively.</li> <li>• Energy level score: 70.3 ± 21.7 mm versus 75.1 ± 19.5 mm, respectively.</li> </ul>			



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<p><b>SUMMARY – CONCLUSIONS (Cont'd)</b> <b>EFFICACY RESULTS (Cont'd)</b></p> <p><b>VAS on Daytime sleepiness</b> Daytime sleepiness assessed in the FAS improved in both groups over W0-W12. Mean changes between baseline and the last post-baseline assessment over the W0-W12 period in the agomelatine and escitalopram groups were as follows:</p> <ul style="list-style-type: none"> <li>• Daytime sleepiness score: <math>-19.9 \pm 30.0</math> mm <i>versus</i> <math>-20.3 \pm 28.1</math> mm, respectively.</li> <li>• Sleepy score: <math>21.0 \pm 28.1</math> mm <i>versus</i> <math>21.0 \pm 30.4</math> mm, respectively.</li> <li>• Confused score: <math>24.2 \pm 27.6</math> mm <i>versus</i> <math>28.4 \pm 24.1</math> mm, respectively.</li> </ul> <p><b>Hamilton Depression Rating Scale-17 items (HAM-D)</b> At week 1, the decrease from baseline in the HAM-D total score was <math>-3.7 \pm 3.4</math> in the agomelatine 25 mg group and <math>-3.5 \pm 4.0</math> in the escitalopram 10 mg group. At last post-baseline assessment, the decrease from baseline in the HAM-D total score was <math>-14.2 \pm 6.8</math> in the agomelatine 25-50 mg group and <math>-14.9 \pm 7.2</math> in the escitalopram 10-20 mg group without relevant difference (E(SE) = <math>-0.64</math> (0.75), 95% CI [-2.11 ; 0.83]). The percentage of responders (decrease in HAM-D total score of at least 50% from baseline) showed no relevant difference between groups at the last post-baseline assessment over W0-W12 (62.9% and 68.4% of patients in the agomelatine and escitalopram groups, respectively; E(SE) = <math>-5.41\%</math> (5.65), 95% CI [-16.47 ; 5.66]). Similar results were observed in the Sub-FAS with baseline HAM-D total score <math>\geq 25</math>.</p> <p><b>Clinical Global Impression (CGI)</b> Mean CGI severity of illness and global improvement scores, in the FAS, decreased over W0-W12 in both treatment groups. Scores at the last post-baseline assessment over the W0-W12 period were as follows:</p> <ul style="list-style-type: none"> <li>• CGI severity of illness score: <math>2.4 \pm 1.1</math> <i>versus</i> <math>2.2 \pm 1.1</math>, in the agomelatine and escitalopram groups respectively.</li> <li>• CGI global improvement score: <math>1.8 \pm 1.1</math> <i>versus</i> <math>1.7 \pm 1.0</math>, respectively.</li> </ul> <p><b>Quick Inventory of Depressive Symptomatology (16-Item) (QIDS)</b> Over the W0-W12 period, the mean QIDS-C16 (clinician-rated) decreased in both groups between baseline and last post-baseline assessment (mean changes of <math>-9.9 \pm 4.6</math> and <math>-10.2 \pm 4.5</math> in the agomelatine and escitalopram groups, respectively). The results obtained after self-evaluation (QIDS-SR16) were consistent with those obtained after clinician assessment (with mean decreases of <math>-10.0 \pm 4.8</math> and <math>-10.0 \pm 5.1</math>, respectively).</p> <p><b>Sheehan Disability Scale (SDS)</b> In the FAS, over the W0-W12 period, the 3 mean SDS scores similarly decreased in the agomelatine and escitalopram groups as follows:</p> <ul style="list-style-type: none"> <li>• Work and activity: <math>-3.7 \pm 2.3</math> <i>versus</i> <math>-3.8 \pm 2.2</math>, respectively.</li> <li>• Social life: <math>-3.8 \pm 2.5</math> <i>versus</i> <math>-3.9 \pm 2.4</math>, respectively.</li> <li>• Family life and home responsibilities: <math>-3.8 \pm 2.6</math> <i>versus</i> <math>-3.9 \pm 2.4</math>, respectively.</li> </ul> <p>As well as for the number of days lost and number of underproductive days:</p> <ul style="list-style-type: none"> <li>• Number of days lost: <math>-2.4 \pm 2.5</math> <i>versus</i> <math>-2.5 \pm 2.3</math>, respectively.</li> <li>• Number of underproductive days: <math>-2.9 \pm 2.3</math> <i>versus</i> <math>-3.2 \pm 2.1</math>, respectively.</li> </ul>		

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<b>SUMMARY – CONCLUSIONS (Cont'd)</b>		
<b>EFFICACY RESULTS (Cont'd)</b>		
<b>Hospital Anxiety Depression scale (HAD)</b>		
In the FAS, over the W0-W12 period, the mean HAD depression and anxiety sub-scores decreased between baseline and last post-baseline assessment in the agomelatine and escitalopram groups, as follows:		
<ul style="list-style-type: none"> <li>• HAD Depression sub-score: <math>-9.8 \pm 5.1</math> versus <math>-10.0 \pm 5.3</math>, respectively.</li> <li>• HAD Anxiety sub-score: <math>-5.1 \pm 4.6</math> versus <math>-6.1 \pm 4.7</math>, respectively.</li> </ul>		
<b>Social Adaptation Self-evaluation Scale (SASS)</b>		
In the FAS, over the W0-W12 period, the mean SASS score increased in both groups. The mean score changes between baseline and last post-baseline assessment were $13.0 \pm 9.7$ and $12.8 \pm 8.8$ in the agomelatine and escitalopram groups, respectively.		
<b>VAS on emotional experiences</b>		
Over the W0-W12 period, items on emotional experiences improved in both agomelatine and escitalopram groups in the FAS. Mean score changes between baseline and last assessment were as follows:		
<ul style="list-style-type: none"> <li>• “My emotions lack intensity”: <math>-10.0 \pm 33.7</math> mm versus <math>-12.7 \pm 37.3</math> mm.</li> <li>• “More a spectator than a participant”: <math>-31.1 \pm 35.2</math> mm versus <math>-33.9 \pm 31.8</math> mm.</li> <li>• “Don’t react to others emotion as before”: <math>-19.3 \pm 36.9</math> mm versus <math>-22.0 \pm 34.0</math> mm.</li> <li>• “Don’t care for responsibilities as before”: <math>-36.5 \pm 34.4</math> mm versus <math>-41.5 \pm 33.6</math> mm.</li> <li>• “Unpleasant emotions toned down/different”: <math>3.1 \pm 38.0</math> mm versus <math>5.4 \pm 41.8</math> mm.</li> </ul>		
<b>SAFETY RESULTS</b>		
<b>- Emergent adverse events</b>		
<b>Overall summary of emergent adverse events in the Safety Set</b>		
	<b>Agomelatine (N = 144)</b>	<b>Escitalopram (N = 141)</b>
<b>During the 13-week treatment period</b>		
Patients having reported		
at least one emergent adverse event	n (%)	44 (30.6)
at least one treatment-related emergent adverse event	n (%)	16 (11.1)
at least one severe emergent adverse event	n (%)	2 (1.4)
at least one emergent adverse event leading to treatment discontinuation	n (%)	2 (1.4)
	n (%)	6 (4.2)
	n (%)	9 (6.4)
<b>During the study</b>		
Patients having experienced		
at least one serious adverse event	n (%)	2 (1.4)
at least one emergent serious adverse event	n (%)	3 (2.1)
at least one emergent treatment-related serious adverse event	n (%)	2 (1.4)
at least one serious emergent adverse event leading to treatment discontinuation	n (%)	-
	n (%)	1 (0.7)
	n (%)	2 (1.4)
	n (%)	2 (1.4)
Patients with treatment discontinuation due to a non-serious emergent adverse event	n (%)	4 (2.8)
Patients who died	n (%)	7 (5.0)
	n (%)	-
	n (%)	-

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<p><b>SUMMARY – CONCLUSIONS (Cont'd)</b> <b>SAFETY RESULTS (Cont'd)</b></p> <p>During the 13-week treatment period in the Safety Set, the percentage of patients who reported at least one emergent adverse event was lower in the agomelatine group than in the escitalopram group (30.6% <i>versus</i> 39.0%).</p> <p>The most frequently affected system organ classes (in more than 5% of patients) in the agomelatine group were nervous system disorders (11.1% of patients), infections and infestations (7.6% of patients), investigations and psychiatric disorders (each 6.3% of patients), similarly reported in the escitalopram group (10.6%, 6.4%, 7.1% and 7.1%, respectively); and gastrointestinal disorders, less common in the agomelatine than in the escitalopram group (7.6% and 17.7%, respectively). In addition, in the escitalopram group, skin and subcutaneous tissue disorders were reported in 5.7% of patients, and were less common in the agomelatine group (0.7%).</p> <p>The most frequent emergent adverse events (in at least 3% of patients) in the agomelatine group were headache (6.3%), nausea (4.2%) and dizziness (3.5%). Compared to escitalopram, the incidences were lower in the agomelatine group for nausea (4.2% <i>versus</i> 10.6%), similar for headache (6.3% <i>versus</i> 7.8%), and higher for dizziness (3.5% <i>versus</i> 0.7%).</p> <p>In the escitalopram group, in addition to the adverse events described above, the other most frequent emergent adverse events (in at least 3% of patients) were ALAT increased (4.3%), hyperhidrosis (3.5%), and diarrhoea (4.3%), all less frequent in the agomelatine group (2.8%, 0.7% and none, respectively).</p> <p>Patients had mostly emergent adverse events of mild to moderate intensity in both groups (95.0% in agomelatine group <i>versus</i> 95.9% in escitalopram group).</p> <p>The percentage of patients with at least one emergent adverse event rated as severe was low in both treatment groups: 2 patients (1.4%) had 4 severe emergent adverse events in the agomelatine group and 2 patients (1.4%) had 5 severe emergent adverse events in the escitalopram group. Severe emergent adverse events were related to psychiatric disorders (in 2 patients in the agomelatine group and 1 in the escitalopram group), gastrointestinal disorders (in 1 patient in each group) and nervous system disorders (in 1 patient in each group).</p> <p>The percentage of patients with at least one emergent adverse event considered to be related to the study treatment by the investigator was lower in the agomelatine group (11.1%) than in the escitalopram group (24.8%): gastrointestinal disorders (3.5% <i>versus</i> 12.8%), nervous system disorders (3.5% <i>versus</i> 5.7%), investigations, (2.8% <i>versus</i> 5.7%), and psychiatric disorders (2.1% <i>versus</i> 4.3%).</p> <p>No death was reported during the study.</p> <p>During the 13-week treatment period, 2 patients in each group (1.4%) experienced at least one non-fatal serious emergent adverse event.</p> <p>None of the serious emergent adverse events was considered to be related to the study treatment in the agomelatine group, and one in the escitalopram group. In all patients, these serious emergent adverse events led to treatment discontinuation.</p> <p>In both groups, emergent serious adverse events were mainly related to psychiatric disorders (2 patients with depression in the agomelatine group and 1 patient with major depression leading to suicide attempt in the escitalopram group). All patients recovered at the end of the study.</p>		

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<p><b>SUMMARY – CONCLUSIONS (Cont'd)</b></p> <p><b>SAFETY RESULTS (Cont'd)</b></p> <p>The percentage of patients withdrawn from the study due to non serious emergent adverse events was lower in the agomelatine group (2.8%, 4 patients) than in the escitalopram group (5.0%, 7 patients). Non-serious adverse events leading to treatment discontinuation were most frequently related to psychiatric disorders.</p> <p><b>- Liver acceptability</b></p> <p>During the ASSE-W13 period, the percentage of patients with at least one emergent Potentially Clinically Significant Abnormal (PCSA) value of liver parameter was 2.1% (3 patients) in the agomelatine group and 1.4% (2 patients) in the escitalopram group. In both groups, emergent PCSA values were related to ALAT, GGT and bilirubin as follows:</p> <ul style="list-style-type: none"> <li>• In the agomelatine group: One patient had emergent PCSA high value of ALAT (3.2 ULN) after 12 weeks of treatment associated with ASAT and GGT values upper than the limit of reference range (1.9 ULN and 1.3 ULN respectively). Another patient had emergent PCSA high value of GGT (3.7 ULN) after 9 weeks of treatment, then an emergent PCSA high value of ALAT (3.4 ULN) after 13 weeks of treatment, associated with ASAT, GGT and ALP upper than the limit of reference range (1.1 ULN, 2.6 ULN and 1.3 ULN respectively). Adverse events were reported in both patients, and were considered as related to concomitant treatment by the investigator (related to paracetamol for one patient and rosuvastatin for the other one). Both patients recovered (after the last intake of agomelatine). One patient, who had total bilirubin upper than the limit of reference range at baseline (1.1 ULN), had emergent PCSA values for bilirubin (total and free: 2.4 and 2.1 ULN, respectively) after 6 weeks of treatment. An adverse event coded as blood bilirubin increased was reported and considered as possibly related to the study treatment by the investigator. At the end of the study, the patient recovered (after the last intake of agomelatine).</li> <li>• In the escitalopram group: One patient had emergent PCSA value for ALAT (4.6 ULN) after 6 weeks of treatment associated with ASAT and ALP above the limit of reference range (2.4 ULN and 1.1 ULN respectively), which were reported as adverse events of moderate intensity, and considered to be related to the study treatment by the investigator. Two days later, the patient recovered on treatment. One patient with a medical history of hyperbilirubinaemia and bilirubin values above the limit of reference range at baseline (1.5 ULN), had emergent PCSA high values for bilirubin (total and conjugated: 2.3 and 2 ULN, respectively) after 12 weeks of treatment. An adverse event coded as hyperbilirubinaemia of moderate intensity was reported and considered as treatment-related. At the end of the study the patient was recovering.</li> </ul> <p><b>- Vital signs and Body Mass Index (BMI)</b></p> <p>Over the W0-W12 period, there were no relevant changes in mean sitting blood pressures and heart rate, as well as in mean weight between baseline and last post-baseline value, in all treatment groups. As regards BMI, most patients remained in the same BMI class over the W0-W12 period (86.8% of patients in the agomelatine group and 84.4% in the escitalopram group).</p>		

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<p><b>CONCLUSION</b></p> <p>This multicenter, double-blind, randomised study conducted in patients with MDD showed no clinically and statistically significant difference between agomelatine 25 mg o.d. and escitalopram 10 mg o.d. on the patient's general interest after 1 week of treatment, as assessed using the VAS on General interest reflecting item 13 of the QIDS-SR16 scale. Both treatments improved the patient's general interest over the W0-W12 period.</p> <p>Antidepressant effect of agomelatine 25-50 mg o.d. over W0-W12 was confirmed on the HAM-D total score and HAM-D responders. This therapeutic benefit was not different from the effect of escitalopram 10-20 mg o.d.</p> <p>The tolerance of agomelatine 25-50 mg o.d. during the 13-week treatment period was in accordance with its known safety profile. No unexpected adverse event was reported. Moreover agomelatine was better tolerated than escitalopram 10-20 mg o.d., particularly for gastrointestinal disorders. Regarding liver acceptability, emergent ALAT values (<math>\geq 3</math> ULN) were reported on agomelatine as well as on escitalopram.</p>		
<b>Date of the report: 6 December 2013</b>		