Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Effects of agomelatine versus escitalopram on emotional experiences in outpatients suffering from Major Depressive Disorder.** **An exploratory, randomised, double-blind, international, multicentre study with parallel groups: agomelatine (25** to 50 **mg/day) versus escitalopram (10 to 20 mg/day) over a 6-month period.**
Test drug code	**Agomelatine – S 20098**
Indication	**Major Depressive Disorder**
Development phase	**Phase III (Phase II for Brazil)**
Protocol code	**CL3-20098-060**
Study initiation date	**11 July 2012**
Study completion date	**03 October 2014**
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **Servier Canada Inc.** **235, Armand-Frappier Blvd.** **Laval, Québec, H7V 4A7 - CANADA**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**03 September 2015**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** **Valdoxan®** **Name of Active Ingredient:** **Agomelatine (S 20098)**		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Effects of agomelatine *versus* escitalopram on emotional experiences in outpatients suffering from Major Depressive Disorder.
An exploratory, randomised, double-blind, international, multicentre study with parallel groups: agomelatine (25 to 50 mg/day) versus escitalopram (10 to 20 mg/day) over a 6-month period.
Protocol No.: CL3-20098-060
EudraCT No : 2011-005320-17The description of the study protocol given hereafter includes the modifications of the 6 substantial amendments to the protocol.

Main coordinator:
[redacted]

Study centres:
In all, 40 centres in 5 countries included at least one patient: 6 centres (25 included patients) in Australia, 8 centres (73 patients) in Brazil, 8 centres (97 patients) in Canada, 8 centres (104 patients) in South Africa, and 10 centres (99 patients) in UK.

Publication (reference):
Not applicable

Studied period:	**Phase of development of the study:**
Initiation date (first visit first patient): 11 July 2012 (first consent: 05 July 2012) Completion date: 03 October 2014	Phase III (Phase II for Brazil)

Objectives:
The objectives of the present exploratory study were to differentiate the effects treatment of agomelatine, as compared to escitalopram in MDD patients, on the:

- Short-term, mid-term and long-term emotional experiences with the ODQ (Price et al, in press) and Visual Analogue Scales (VAS) on some specific items of the ODQ.
- Relative pattern of improvement in positive and negative affects, using the Positive Affect and Negative Affect Schedule (PANAS, Watson and Clark, 1988).
- Return of pleasure, using the Snaith-Hamilton Pleasure Scale (SHAPS, Snaith *et al.*, 1995).
- Antidepressant efficacy with the HAM-D 17-item total score (Hamilton, 1967), the Clinical Global Impression scale (CGI, Guy, 1976) and the Hospital Anxiety Depression scale (HAD, Zigmond *et al.*, 1983).
- Personality traits using the sub-scales Neuroticism and Extraversion of the "Neuroticism, Extraversion, Openness-Five Factor Inventory" (Revised NEO-FFI, McCrae and Costa, 2004).

The possible correlations between personality traits, relative pattern of improvement in negative and positive affects, return of pleasure, antidepressant efficacy and the evolution in emotional experiences was to be assessed in the whole study population and in remitted patients.
Usual safety parameters and liver enzyme parameters were to be thoroughly assessed throughout the study.
A pharmacogenetic sub-study was also to be conducted in order to evaluate associations between polymorphisms in candidate genes and the efficacy and safety of agomelatine. Results will be provided in a separate report.

Methodology:
This was an exploratory phase III (phase II for Brazil), randomised, comparative *versus* escitalopram, double-blind, multicentre international study in parallel groups performed in outpatients suffering from Major Depressive Disorder and requiring an antidepressant treatment.
The treatment (agomelatine or escitalopram) was assigned at inclusion by balanced, non-adaptative randomisation with stratification on the centre and on the ODQ total score. Treatment randomisation and allocation were centralized with an Interactive Response System (IRS).
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned: 500 patients, *i.e*. 250 per treatment group.
Included: 398 patients, *i.e*. 199 per group (recruitment difficulties leading to a strategic decision from the Sponsor to stop study).

Diagnosis and main criteria for inclusion:
Male or female outpatients, aged between 18 (or legal age of majority in the country) and 65 years (inclusive), fulfilling the Diagnosis and Statistical Manuel of Mental Disorders, 4th Ed., Text Revision (DSM-IV TR) criteria for Major Depressive Disorder. At selection, Hamilton Depression Rating Scale 17 items (HAM-D-17) was to be ≥ 22, Clinical Global Impression (CGI) severity of illness (item 1) ≥ 4, Hospital Anxiety and Depression scale (HAD) with Depression score ≥ 11 and Depression score > Anxiety score. At inclusion,
HAM-D 17-item total score was to be still ≥ 22, any HAM-D 17-item total score decrease between ASSE and W0 ≤ 20%, and CGI severity of illness was to be still ≥ 4.

Test drug:
Agomelatine capsules of 25 and 50 mg. One capsule once daily at bedtime.
From W0 to W2: one capsule of agomelatine 25 mg.
From W2 to W24: in case of insufficient response at W2, the dose could be increased in blind conditions (neither the investigator nor the patient knew whether the dose had been increased), using pre-defined criteria, to agomelatine 50 mg. Patients with a sufficient improvement remained on the same treatment at the initial dose until W24. Whether or not the dose was increased, the patient continued to take one capsule once daily.
From W24 to W25 or during the week after withdrawal (tapering period): one capsule of placebo o.d.
Batch numbers:
Agomelatine 25 mg: L0042640, L0046099, L0048525, L0048401, L0050483, L0051478, L0053264.
Agomelatine 50 mg: L0043057, L0046107, L0048527, L0051391, L0051481, L0053266.

Comparator (Reference product and/or placebo):
Escitalopram capsules of 5, 10 and 20 mg. One capsule once daily at bedtime.
From W0 to W2: one capsule of escitalopram 10 mg.
From W2 to W24: in case of insufficient response at W2, the dose could be increased in blind conditions (neither the investigator nor the patient knew whether the dose had been increased), using pre-defined criteria, to escitalopram 20 mg. Patients with a sufficient improvement remained on the same treatment at the initial dose until W24. Whether or not the dose was increased, the patient continued to take one capsule once daily.
From W24 to W25 or during the week after withdrawal (tapering period):

- Patients previously on escitalopram 20 mg received escitalopram 10 mg for 3 days followed by 4 days on escitalopram 5 mg.
- Patients previously on escitalopram 10 mg received escitalopram 5 mg for 3 days followed by 4 days on placebo.

Duration of treatment:

- 3 to 14 days run-in period without treatment from ASSE to W0.
- 24-week double-blind treatment period (from W0 to W24).
- 7-day double-blind treatment tapering period (mandatory from W24 to W25 and recommended at withdrawal visit in case of premature discontinuation).
- 7-day as a maximum follow-up period without treatment after W25 or after premature withdrawal.

Criteria for evaluation:

Efficacy measurements:
No primary criterion has been defined for this exploratory study.

Emotional experiences:

- ODQ (Oxford Depression Questionnaire) at inclusion (W0, before drug intake), after 2 weeks, 1 month, 3 months and 6 months of treatment, and at the follow-up visit or at the withdrawal visit in case of premature withdrawal from the study.
- ODQ-VAS (Visual Analogue Scale) on specific ODQ items at inclusion (W0, before drug intake) and at each visit afterwards (except at W25 visit).

Positive and negative affects:
Positive Affect and Negative Affect Schedule (PANAS) assessed at inclusion (W0, before drug intake), after 1 month, 3 months and 6 months of treatment, and at the follow-up visit or at the withdrawal visit in case of premature withdrawal from the study.

Return of pleasure:
Snaith-Hamilton Pleasure Scale (SHAPS) total score assessed at inclusion (W0, before drug intake), after 1 month, 3 months and 6 months of treatment, and at the follow-up visit or at the withdrawal visit in case of premature withdrawal from the study.

Antidepressant efficacy:

- HAM-D 17-item total score assessed at each visit.
- Clinical Global Impression scale (CGI) item 1 (severity of illness) and item 2 (global improvement) assessed at each visit (except item 2, only to be assessed from 2 weeks of treatment and afterwards).
- Hospital Anxiety Depression scale (HAD) assessed at selection visit, after 3 months and 6 months of treatment or at the withdrawal visit in case of premature withdrawal from the study.

Safety measurements:

- Adverse events assessed at each visit
- Laboratory parameters (haematology and biochemistry including liver parameters): results available for W0, W16, W25 visits and at withdrawal from the study. Only liver parameters available for W4, W8, and W12 visits.
- Clinical examination: sitting blood pressure, heart rate, body weight and body mass index at selection, W0, W12, and W24 visits.
- 12-lead-ECG available before inclusion, at W24 and WEND visits.

Other measurements:

Pharmacogenetic sub-study (will be provided in a separate report).

Statistical methods:

Efficacy analysis:
No primary efficacy criterion was defined for this exploratory study.
The type I error was set at $\alpha = 5\%$ (bilateral situation).

ODQ: Descriptive statistics were provided by treatment group, in patients of the FAS, RMFAS (remitted FAS: patients with a W24 HAM-D 17 item total score ≤ 7) and RPFAS (responder FAS: decrease from baseline $\geq 50\%$ at W24). Moreover, in order to estimate the difference between agomelatine and escitalopram on emotional experiences after 4-week, 12-week and 24-week treatment periods, agomelatine was compared to escitalopram in the RMFAS and RPFAS on the change from baseline to W4, W12 and W24 of ODQ total score, GR-ED and RP-NC scores, using a three-way analysis of variance (ANOVA) model. Analysis included the fixed, categorical effect(s) of treatment, ODQ total score class ([0 ; 64] and]64 ; 80]), and the random, categorical effect(s) of centre.

Statistical methods (Cont'd):

ODQ-VAS on specific items: Descriptive statistics were provided by treatment group, in patients of the FAS, RMFAS and RPFAS. Moreover, in order to estimate the difference between agomelatine and escitalopram on emotional experiences after 4-week, 12-week and 24-week treatment periods, agomelatine was compared to escitalopram in the RMFAS and RPFAS on the change from baseline to W4, W12 and W24 of ODS-VAS items, using a three-way analysis of variance (ANCOVA) model. Analysis included the fixed, categorical effect(s) of treatment, ODQ total score class ([0 ; 64] and]64 ; 80]), and the random, categorical effect(s) of centre, as well as the continuous, fixed covariate(s) of baseline ODQ VAS.

PANAS positive and negative affects scores and SHAPS total score: descriptive statistics expressed as value at baseline, at each post-baseline visit and change from baseline to each post-baseline visit.

To evaluate the ***possible correlation between emotional experiences***, Pearson correlation coefficient and Spearman Ranked-order correlation associated to a scatterplot were calculated between:

- ODQ total score/ODQ VAS and PANAS Positive/Negative scores at baseline, W4, W12, W24 and WEND.
- ODQ total score/ODQ VAS and SHAPS total score at baseline, W4, W12, W24 and WEND.
- ODQ total score/ODQ VAS and NEO-FFI Extraversion/Neuroticism scores at baseline.

HAM-D 17-item total score: Descriptive statistics were provided by treatment group, in patients of the FAS. Moreover, in order to estimate the difference between agomelatine and escitalopram on depressive symptoms after 6-week and 24-week treatment periods, agomelatine was compared to escitalopram in the FAS on the change from baseline to W6 and W24 using a three-way analysis of covariance (ANCOVA) model. Analysis included the fixed, categorical effect(s) of treatment, ODQ total score class ([0 ; 64] and]64 ; 80]), and the random, categorical effect(s) of centre, as well as the continuous, fixed covariate(s) of baseline HAM-D total score. In addition, agomelatine was compared to escitalopram in the FAS on the response to treatment at W6 and W24.

HAD (depression and anxiety scores): Descriptive statistics expressed as value at baseline, at each post-baseline visit and change from baseline to each post-baseline visit.

CGI: Descriptive statistics expressed as value at baseline (only for CGI Severity of illness score), at each post-baseline visit, and also for Global improvement score as response to treatment (defined as a score equal to 1 or 2) at each post-baseline visit.

Study outcome and safety analysis: Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Status		ALL (N = 398)	Agomelatine (N = 199)	Escitalopram (N = 199)
Included	**n**	**398**	**199**	**199**
In conformity with the protocol	n	357	178	179
With protocol deviation(s) before or at inclusion	n	41	21	20
Completed the W0-W24 period	**n (%)**	**275 (69.10)**	**140 (70.35)**	**135 (67.84)**
Entered the W24-W25 period	n (%)	272 (68.34)	138 (69.35)	134 (67.34)
Did not enter the W24-W25 period	n (%)	3 (0.75)	2 (1.01)	1 (0.50)
Performed the follow-up visit	n (%)	3 (0.75)	2 (1.01)	1 (0.50)
Withdrawn Due To	**n (%)**	**123 (30.90)**	**59 (29.65)**	**64 (32.16)**
Adverse Event	n (%)	40 (10.03)	14 (7.04)	26 (13.07)
Protocol deviation	n (%)	12 (3.01)	6 (3.02)	6 (3.02)
Lack of efficacy	n (%)	22 (5.53)	17 (8.54)	5 (2.51)
Non-medical reason	n (%)	48 (12.06)	22 (11.06)	26 (13.07)
Recovery, improvement	n (%)	1 (0.25)	-	1 (0.50)
Performed the tapering period	n (%)	28 (7.04)	16 (8.04)	12 (6.03)
Performed the follow-up visit	n (%)	27 (6.78)	15 (7.54)	12 (6.03)
Did not perform the tapering period	n (%)	95 (23.87)	43 (21.61)	52 (26.13)
Performed the follow-up visit	n (%)	46 (11.56)	21 (10.55)	25 (12.56)
Completed the W24-W25 period	**n (%)**	**275* (69.10)**	**142 (71.36)**	**133 (66.83)**
Performed the tapering period	n (%)	275 (69.10)	142 (71.36)	133 (66.83)
Performed the follow-up visit	n (%)	272 (68.34)	141 (70.85)	131 (65.83)
Withdrawn on W24-W25 period	**n (%)**	**2 (0.50)**	**-**	**2 (1.00)**
Protocol deviation	n (%)	1 (0.25)	-	1 (0.50)
Non-medical reason	n (%)	1 (0.25)	-	1 (0.50)
Performed the tapering period	n (%)	1 (0.25)	-	1 (0.50)
Performed the follow-up visit	n (%)	-	-	-
Did not perform the tapering period	n (%)	1 (0.25)	-	1 (0.50)
Performed the follow-up visit	n (%)	1 (0.25)	-	1 (0.50)
FAS		390	194	196
RMFAS		188	92	96
RPFAS		243	123	120
SS		397	199	198

%: Expressed as percentage of the patients from the Included/Randomised Set
Including 2 patients withdrawn during the W0-W24 period and 2 patients notified as not entering the W24-W25 period

A total of 398 patients were included and randomly assigned to one of the 2 groups: 199 patients in the agomelatine group and 199 in the escitalopram group. Of them, 275 patients (69.1%) completed the W0-W24 period: 140 patients (70.4%) in the agomelatine group, and 135 patients (67.8%) in the escitalopram group. Among them, 272 patients, *i.e.* 138 in the agomelatine group and 134 in the escitalopram group entered the W24-W25 period.

Overall, 123 patients (30.9%) were withdrawn during the W0-W24 period: 59 patients (29.6%) in the agomelatine group and 64 patients (32.2%) in the escitalopram group. Of these 123 patients, 28 patients performed the tapering period. The main reason (apart from non-medical reason) for withdrawal was adverse events, the rate of withdrawal due to AEs being lower in the agomelatine group (7.0%) than in the escitalopram group (13.1%).

BASELINE CHARACTERISTICS

At selection, in the Randomized Set (RS), the mean ± SD age was 41.1 ± 12.3 years ranging from 18 to 65 years. Two thirds of patients were female. Overall, 85.6% of patients were Caucasian.

In the RS, all patients presented with MDD according to DSM-IV TR criteria, as required in the selection criteria.

Most patients suffered from recurrent MDD (61.8%), a single episode being observed in 38.2% of patients.

Most of the current episodes were moderate (61.3%), severe (without psychotic features) episodes being reported in 38.7% of patients. Most patients presented with melancholic features (64.1%).

The duration of MDD ranged from 2.1 to 43.8 years with a mean ± SD of 13.22 ± 8.76 years. The duration of the current episode ranged from 1 to 12 months with a mean ± SD of 5.3 ± 2.8 months.

SUMMARY – CONCLUSIONS (Cont'd)
BASELINE CHARACTERISTICS (Cont'd)

Mean values at baseline of the various assessed scales, in the RS, are presented in the table below.
No relevant difference was observed between the treatment groups in demographic and disease characteristics at baseline.

Summary of efficacy criteria at inclusion in the Randomised Set

		Agomelatine (N = 199)	Escitalopram (N = 199)	All (N = 398)
ODQ total score	Mean ± SD	60.633 ± 12.194	59.759 ± 12.498	60.196 ±12.339
ODQ GR+EQ score	Mean ± SD	26.467 ± 8.067	25.809 ± 8.171	26.138 ± 8.116
ODQ PR+NC score	Mean ± SD	34.447 ± 5.180	33.950 ± 5.791	34.198 ± 5.493
ODQ VAS 1*	Mean ± SD	68.5 ± 27.1	67.1 ± 27.8	67.8 ± 27.4
ODQ VAS 2*	Mean ± SD	65.1 ± 26.9	62.3 ± 28.6	63.7 ± 27.8
ODQ VAS 3*	Mean ± SD	76.2 ± 25.3	73.9 ± 26.8	75.1 ± 26.1
PANAS positive score	Mean ± SD	15.5 ± 5.0	15.5 ± 4.9	15.5 ± 4.9
PANAS negative score	Mean ± SD	32.5 ± 8.1	31.2 ± 8.2	31.8 ± 8.2
SHAPS total score	Mean ± SD	39.1 ± 5.2	38.6 ± 6.2	38.9 ± 5.7
HAM-D total score	Mean ± SD	25.4 ± 2.6	25.5 ± 2.4	25.5 ± 2.5
CGI severity of illness score	Mean ± SD	4.5 ± 0.6	4.6 ± 0.6	4.6 ± 0.6
HAD depression score	Mean ± SD	16.3 ± 2.7	16.5 ± 2.6	16.4 ± 2.7
HAD anxiety score	Mean ± SD	9.9 ± 3.2	9.9 ± 3.3	9.9 ± 3.3

**VAS 1: my emotions lack intensity*
VAS 2: I don't react to other people emotions as much as I did before my illness/problem
VAS 3: my emotions are numbed/dulled/flattened compared to before I develop my illness/problem

Demographic and other baseline characteristics were similar in the FAS, the Remitted FAS (RMFAS: W24 HAM-D 17-item total score ≤ 7) and the Responder FAS (RPFAS: decrease from baseline ≥ 50% at W24).

EXTENT OF EXPOSURE
Over the W0-W24 period, in the Randomised Set, the treatment duration ranged between 1 and 187 days with a mean (± SD) of 138.7 ± 53.4 days (median of 168.0 days) and the mean ± SD overall compliance was of 93.6 ± 14.8%. No relevant difference between the treatment groups was observed.
Over the tapering period, in the Randomised Set of patients having performed the tapering period, the treatment duration ranged between 0 and 10 days with a mean (± SD) of 6.8 ± 0.8 days (median of 7 days), and the mean ± SD overall compliance was of 93.7 ± 16.4 %, without relevant difference between the treatment groups.

EFFICACY RESULTS

As it was an exploratory study, no primary efficacy criterion was defined.

Efficacy was assessed using self- rating questionnaires (ODQ, PANAS, SHAPS, and HAD) and scales completed by the investigator (antidepressant efficacy: HAM-D 17 items, and CGI).

SUMMARY – CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

Changes from baseline to W24 (LOCF) are summarised in the table below.

Changes from baseline to W24 (LOCF) of efficacy assessments in the FAS

W24 (LOCF) - baseline	Agomelatine (N = 199)	Escitalopram (N = 198)
ODQ total score		
n	194	196
Mean ± SD	-26.242 ± 25.198	-28.138 ± 25.202
ODQ GR-ED sub-score		
n	194	196
Mean ± SD	-9.670 ± 12.324	-10.097 ± 13.149
ODQ-PR NC sub-score		
n	194	196
Mean ± SD	-16.861 ± 13.829	-18.041 ± 13.473
ODQ-ED score		
n	194	196
Mean ± SD	-5.088 ± 6.912	-5.444 ± 7.006
ODQ-GR score		
n	194	196
Mean ± SD	-4.582 ± 7.052	-4.653 ± 7.401
ODQ-NC score		
n	194	196
Mean ± SD	-8.155 ± 6.967	-8.357 ± 6.860
ODQ-PR score		
n	194	196
Mean ± SD	-8.706 ± 7.515	-9.684 ± 7.238
ODQ-VAS 1		
n	194	196
Mean ± SD	-30.4 ± 40.0	-29.1 ± 41.2
ODQ-VAS 2		
n	194	196
Mean ± SD	-27.7 ± 35.6	-26.2 ± 39.0
ODQ-VAS 3		
n	194	196
Mean ± SD	-36.9 ± 39.9	-36.0 ± 41.7
SHAPS total score		
n	192	191
Mean ± SD	-10.7 ± 10.3	-11.8 ± 9.8
PANAS positive score		
n	192	191
Mean ± SD	11.1 ± 11.1	13.4 ± 11.4
PANAS negative score		
n	192	191
Mean ± SD	-10.0 ± 11.5	-11.6 ± 9.6
HAM-D total score		
n	194	196
Mean ± SD	-16.3 ± 8.6	-17.3 ± 7.7
CGI severity of illness score		
n	194	196
Mean ± SD	2.3 ± 1.3	2.1 ± 1.4
CGI global improvement score		
n	194	196
Mean ± SD	1.9 ± 1.2	1.7 ± 1.1
HAD depression score		
n	185	186
Mean ± SD	-8.7 ± 6.2	-10.0 ± 5.6
HAD anxiety score		
n	185	186
Mean ± SD	-1.0 ± 6.1	-2.2 ± 5.3

SUMMARY – CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

Regarding emotional experiences, the mean ODQ total score decreased, *i.e.* improved, from baseline to each post-baseline visit (W2, W4, W12, W24), without relevant difference between the two treatment groups, in the FAS. The same evolution was obtained for GR-ED (General Reduction in emotions – Emotional Detachment from others), PR-NC (Positive Reduction in emotions – Not Caring), ED, GR, NC, and PR mean scores. A decrease of the mean scores was also observed for each of the 3 items of the ODQ VAS without relevant difference between the treatment groups.

In the same way, the mean SHAPS total score decreased, *i.e.* improved, from baseline to each post-baseline visit (W2, W4, W12, W24), without relevant difference between the 2 treatment groups, in the FAS. An improvement was also observed in the PANAS positive and negative mean scores from baseline to each post-baseline visit (W4, W12, W24), without relevant differences between the groups.

The self-rating questionnaire mean scores remained stable between W24 and Wend in patients having values at these assessment times, having performed the tapering period, and without intake of any treatment which could interfere with the efficacy evaluation.

Similar efficacy results as in the FAS were observed in the RMFAS and RPFAS, whichever the scale.

It can be noticed that results in the RMFAS were better than those in the FAS/RPFAS whichever the treatment group.

In the same line, the mean HAM-D total score improved from baseline to each post-baseline visit (W2, W4, W6, W8, W12, W16, W20, W24). Considering the rate of responders according to the HAM-D scale (defined as decrease from baseline $\geq$ 50%), the rate was similar in the two treatment groups: 72.7% in the agomelatine group and 75.5% in the escitalopram group at W24 (LOCF). Consistently, the rate of remitters (defined as a HAM-D total score $\leq$ 7) increased in both groups with the visit, in the FAS, the percentage of remitters being 51.0% in the agomelatine group and 58.7% in the escitalopram group at W24 (LOCF).

When the antidepressant efficacy was assessed using the CGI scale, the severity of illness decreased through the visits in both groups and was similar in the 2 treatment groups at W24, in the FAS. The response to treatment according to the CGI (global improvement score equal to 1 or 2) showed that the percentage of responders (LOCF) was 75.3% in the agomelatine group and 81.6% in the escitalopram group at W24.

In the FAS, over W0-W24, the HAD depression and anxiety scores decreased, *i.e.* improved, from baseline to each post-baseline visit (W12/W24), without relevant difference between the 2 treatment groups.

In order to estimate the possible correlations between emotional experiences, correlations between ODQ total score / ODQ VAS and PANAS / SHAPS / NEO-FFI were looked for. It can be noted that the correlations between the ODQ (total score or VAS) and the other scales were weak at baseline. Under treatment, in the FAS, rather strong correlations were observed between ODQ total score and PANAS positive/negative scores, SHAPS total score, and NEO-FFI neuroticism/extraversion scores at each time point. Similar correlations were observed with the 3 items of the ODQ VAS except for the PANAS negative score with weaker correlations. Similar results were evidenced in the RPFAS and roughly similar results in the RMFAS.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Emergent adverse events**

Overall summary of AEs in the Safety Set

		Agomelatine (N = 199)	Escitalopram (N = 198)
Patients having reported			
at least one emergent adverse event	n (%)	134 (67.3)	145 (73.2)
at least one treatment-related emergent adverse event	n (%)	70 (35.2)	97 (49.0)
Patients having experienced			
at least one serious adverse event (including death)	n (%)	10 (5.0)	18 (9.1)
at least one serious emergent event (including death)	n (%)	9 (4.5)	17 (8.6)
at least one treatment-related serious adverse event	n (%)	1 (0.5)	5 (2.5)
Patients with treatment withdrawal			
due to an emergent adverse event	n (%)	15 (7.5)	26 (13.1)
due to an emergent serious adverse event	n (%)	4 (2.0)	8 (4.0)
due a treatment-related emergent adverse event	n (%)	7 (3.5)	20 (10.1)
due a treatment-related emergent serious adverse event	n (%)	1 (0.5)	4 (2.0)
Patients who died	n (%)	-	-

During the W0-W24 period, in the Safety Set, the incidence of patients presenting with at least one EAE was slightly lower in the agomelatine group (67.3%) than in the escitalopram group (73.2%).
The most frequently affected (>10% of patients) system organ classes (SOC) in both groups were nervous system disorders, infections and infestations, gastrointestinal disorders, and psychiatric disorders. Nervous system disorders were reported less frequently in the agomelatine group than in the escitalopram group (25.6% of patients and 31.3%, respectively), as well as gastrointestinal disorders (20.6% of patients and 30.3%, respectively) and skin and subcutaneous disorders (5.0% of patients and 9.6%, respectively). Conversely, the incidence of infections and infestations was higher in the agomelatine group (25.6% of patients) than in the escitalopram group (19.7%).
The most frequently reported EAEs (> 5.0%) in the agomelatine group were headache and nausea which were also the most commonly reported in the escitalopram group. The incidence of headache was similar in the treatment groups (15.6% of patients in the agomelatine group and 17.2% in the escitalopram group) while the incidence of nausea was lower in the agomelatine group than in the escitalopram group (7.0% and 17.2%, respectively).

Emergent adverse events were mainly mild or moderate in the agomelatine group as well as in the escitalopram group. The incidence of severe EAEs was lower in the agomelatine group (5.8%) than in the escitalopram group (9.7%).

The incidence of treatment-related EAEs was lower in the agomelatine group (35.2%) than in the escitalopram group (49.0%).

No death was reported during the study.

During the W0-W24 period, 9 patients in the agomelatine group (4.5%) and 17 patients in the escitalopram group (8.6%) reported emergent serious adverse events. The incidence of SEAEs leading to treatment withdrawal was lower in the agomelatine group than in the escitalopram group (2.0% and 4.0%, respectively) as well as the incidence of SEAEs related to the study drug (0.5% and 2.5%, respectively).
The incidence of emergent (serious and non-serious) adverse events leading to premature treatment withdrawal was lower in the agomelatine group (15 patients [7.5%]) than in the escitalopram group (26 patients [13.1%]).

Safety was also assessed in patients entering the W24-W25/WEND period. Emergent adverse events were reported in 12.1% in the agomelatine group and 17.8% in the escitalopram group. The most frequently affected (> 3% of patients) system organ classes (SOC) in the agomelatine group were nervous system disorders (3.6%) and psychiatric disorders (3.6%) as well as in the escitalopram group (5.9% of patients each). The most frequently reported EAEs in the agomelatine group were headache (3.6%) and insomnia (2.9%).Withdrawal syndromes were reported only in the escitalopram group (5 patients – 3.7%). The other most frequently reported EAEs in the escitalopram group were headache, irritability, and paraesthesia, each in 2.2% of patients. The incidence of severe EAEs was lower in the agomelatine group (5.3% of EAEs) than in the escitalopram group (13.5%). No SEAE was reported during the W24-W25/WEND period.

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

- **Laboratory tests**

In the SS, neither clinically relevant changes over time nor difference between groups were detected for biochemical and haematological parameters.

Emergent PCSA biochemical values were sparse in both groups and for each parameter, except for high triglycerides reported in 7.4% of patients in the agomelatine group and 2.3% in the escitalopram group. It should be noted that these PCSA values in the agomelatine group mainly (11/13 patients) occurred in patients with values already out of reference range at baseline (3/4 in the escitalopram group) and, in 4/13 patients, PCSA values were observed in non-fasting samples (2/4 in the escitalopram group).

Emergent PCSA haematological values were also sparse in both groups.

Regarding liver acceptability, PCSA values of liver parameters were observed in 4 patients in the agomelatine group and 1 patient in the escitalopram group (hepatitis alcoholic). In the agomelatine group, 1 patient had PCSA values of ALT and AST (EAE leading to drug withdrawal, recovered, related to study drug according to the investigator), 1 patient had PCSA values of AST and out-of-reference range values of ALT (EAE recovered on treatment, not related to study drug), 1 patient had PCSA values of ALT, associated with out-of-reference range values of GGT and ALP (hepatitis reported as EAE, drug withdrawn, recovered, related to study drug), and 1 patient had PCSA values of indirect bilirubin with out-of-reference range values of GGT and ALT (no EAE reported, drug not withdrawn, returned to out-of-reference range on treatment).

- **Other safety evaluation**

Neither clinically relevant nor differences between groups in mean changes between baseline and last post-baseline values were detected during the W0-W24 period, in the SS, for weight, sitting blood pressure, and heart rate.
Regarding BMI during the W0-W24 period in the SS, the rate of patients within the normal range at baseline and overweighed at the last post-baseline value was slightly lower in the agomelatine group (2.67%) than in the escitalopram group (4.23%). Similarly, the rate of patients overweighed at baseline and obese at the last post-baseline value was slightly lower in the agomelatine group (1.60%) than in the escitalopram group (4.23%).
In the SS, 3.21% of overweighed patients at baseline in the agomelatine group and 2.65% in the escitalopram group were within the normal range at last post-baseline assessment. During the same period, 1.60% of obese patients in the agomelatine group at baseline, and 2.12% in the escitalopram group were overweighed at the last assessment.

In patients with available ECG data during the W0-W24 period, no emergent clinically significant abnormality was reported.

CONCLUSION

This exploratory phase III, randomised, double-blind, multicentre, international study in parallel groups conducted in patients suffering from major depressive disorder, showed similar improvement in emotional experiences (ODQ scores and VAS), positive and negative affects (PANAS), return of pleasure (SHAPS) and similar antidepressant efficacy (HAM-D, CGI, HAD) with agomelatine (25 or 50 mg) and escitalopram (10 or 20 mg), over a 24-week period of treatment.
The safety profile of agomelatine after a 24-week treatment was satisfactory. The severity, seriousness, cases of treatment discontinuation and relationship to study treatment of emergent adverse events were lower in the agomelatine group than in the escitalopram group. Four patients in the agomelatine group and one patient in the escitalopram group had potentially clinically significant abnormal values of liver function tests. The good tolerability of agomelatine was confirmed in this study.

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