Document title	**Clinical Study Report Synopsis**
Study title	**Evaluation of efficacy and clinical benefit of agomelatine (25 to 50 mg/day) over 6-month treatment period in patients with Major Depressive Disorder.** **A randomised, double-blind, international multicentre study with parallel groups *versus* duloxetine (60 mg/day). Twenty-four weeks of treatment.**
Study drug	**Agomelatine (S 20098)**
Studied indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-062**
Study initiation date	**18 May 2009**
Study completion date	**04 August 2010**
Main coordinator	[redacted] [redacted]**Budapest - Hungary**
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** **Laboratorios Servier, S.L.** **Avenida de los Madronos 33** **28043 Madrid - Spain**
Responsible medical officer	[redacted]**(I.R.I.S.)**
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 23 September 2011**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

Title of study:

Evaluation of efficacy and clinical benefit of agomelatine (25 to 50 mg/day) over 6-month treatment period in patients with Major Depressive Disorder.

A randomised, double-blind, international multicentre study with parallel groups *versus* duloxetine (60mg/day). Twenty-four weeks of treatment.

Protocol No.: CL3-20098-062

International coordinator: [redacted], Hungary) was also national coordinator in Hungary.

National coordinators: [redacted], Australia), [redacted], Brazil), [redacted], Canada), [redacted], Greece), [redacted], Italy), [redacted], Portugal), [redacted], South Africa), [redacted], Spain), [redacted], United Kingdom).

Study centres:

In all, 51centres located in 10 countries included at least one patient: Australia (6 centres – 48 patients), Brazil (3 centres – 48 patients), Canada (5 centres – 41 patients), Greece (2 centres – 3 patients), Hungary (6 centres – 60 patients), Italy (6 centres – 33 patients), Portugal (4 centres – 29 patients), South Africa (6 centres – 55 patients), Spain (7 centres – 35 patients), United Kingdom (6 centres – 66 patients).

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 18 May 2009 Completion date: 04 August 2010	III

Objectives: to assess long-term efficacy and the global clinical benefit of agomelatine compared to duloxetine in depressed outpatients.

Primary objective: to demonstrate the superiority of long-term antidepressant efficacy of agomelatine compared to duloxetine on HAM-D total score expressed as response to treatment (HAM-D 17 total score decrease from baseline ≥ 50%) over a 6-month period.

Secondary objectives: to further describe the global clinical benefit of agomelatine, to further describe the effect on depressive symptoms, sleep patterns, social functioning and quality of life, to provide additional safety and tolerability data on agomelatine, and to evaluate the influence of genetic factors on efficacy and safety of agomelatine in a pharmacogenetic sub-study.

Methodology:

Phase III multicentre international study with therapeutic benefit, randomized, double-blind, parallel groups, comparative *versus* duloxetine 60 mg using a flexible dosage of agomelatine 25 mg/day, increased to 50 mg/day in case of insufficient improvement at W2. The criteria for increasing the dose were defined by the sponsor, based on clinical considerations, before the study beginning, and kept blinded to the investigator and the patient. The randomisation was balanced (non adaptive), with stratification on the centre. The randomisation, the treatment allocation and the dose increase were done centrally using an Interactive Response System (IRS). This study was performed in strict accordance with Good Clinical Practice.

Number of patients:

Planned: 400 patients, 200 patients by group

Included: 418 patients (202 in the agomelatine group and 216 in the duloxetine group)

Diagnosis and main criteria for inclusion:

Male or female out-patients, aged between 18 (or legal age of majority in the country) and 65 years (inclusive), and fulfilling DSM-IV TR criteria for Major Depressive Disorder of moderate or severe intensity. At selection, HAM-D 17 items total score was to be ≥ 22 and HAD depression score ≥ 11. At inclusion, HAM-D 17 items total score was still to be ≥ 22 and no more than a 20% of decrease in HAM-D total score between selection and inclusion, and CGI severity of illness was to be ≥ 4.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

Study drug:

Agomelatine, tablets of 25 mg, masked in capsule, 1 or 2 tablets per day, single administration, p.o., in the evening.

Patients received 25 mg/day (1 capsule containing 1 tablet of 25 mg, and one placebo capsule) from W0 with possible increase to 50 mg/day in double-blind conditions (1 capsule containing 2 tablets of 25 mg and one placebo capsule) from W2, in case of insufficient improvement. Once adjusted (or not) at W2, the dose was maintained up to W24. Between W24 and W25 (mandatory), or in case of premature withdrawal (recommended), patients received the dose received at W2 for additional 7 days in order to blind the tapering period needed only for duloxetine.

Batch No.: L0026869, L0029629, L0026871, L0029631

Reference product:

Duloxetine, capsules of 30 mg and 60 mg masked in capsule, 1 capsule per day, single administration, p.o., in the evening.

Patients received 60 mg/day (1 capsule containing 1 capsule of 60 mg and one placebo capsule) from W0 to W24. From W24 to W25 (mandatory) or in case of premature withdrawal (recommended), patients received 1 capsule containing 30 mg/day and one placebo capsule.

Duration of treatment:

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

Criteria for evaluation:

Efficacy measurements

On depression

- Hamilton Depression Rating Scale-17 items (HAM-D) was rated by the investigator at each visit from the selection visit to W24, and Wend for patients completed at W25, or in case of premature withdrawal. The primary efficacy criterion was the HAM-D total score. The main analytical approach was the response to treatment defined as HAM-D total score decrease from baseline ≥ 50%.
- Clinical Global Impressions scale (CGI) was rated by the investigator at each visit from the inclusion visit (only item 1) to W24, and Wend for patients completed at W25, or in case of premature withdrawal.

On sleep

- Pittsburgh Sleep Quality Index (PSQI) was rated by the patient at W0 and W24 or in case of premature withdrawal between W0 and W24.
- Leeds Sleep Evaluation Questionnaire (LSEQ) was rated by the patient at W1 and W2 or in case of premature withdrawal between W0 and W2.

Other measurements

- Sheehan Disability Scale (SDS) was rated by the patient at selection, W2, W6, W12 and W24, or in case of premature withdrawal between W0 and W24.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

Criteria for evaluation (Cont'd):

Safety measurements

- Adverse events reported at each visit.
- Laboratory tests: blood samplings were prescribed at selection in order to have the results at W0, at or just before W2, at W6, W12, W20 and W24, and in case of withdrawal between W0 and W24 (included), in order to have the results at Wend.
- Physical examination: vital signs, *i.e.* sitting blood pressure after a 5 minutes' rest (DBP, SBP) and heart rate were measured at selection, W0, W6, W24 and Wend or in case of premature withdrawal. Body weight and Body Mass Index were measured at selection, W0, W6, W24 or in case of premature withdrawal. Waist/hip circumference was measured at W0 and W24 or in case of premature withdrawal in patients having a BMI $\geq$ 30 kg/m² at selection only. Height was measured at selection.
- 12-lead ECGs: one ECG was prescribed at selection in order to have the result for inclusion, at W24 in order to have the result at W25, or in case of withdrawal between W0 and W24 (included) in order to have the result for Wend.
- Arizona Sexual Experiences Scale (ASEX) was completed by the patient at W0, W4 and W24 or in case of premature withdrawal between W0 and W24.
- Oxford Questionnaire on emotional Side-effects of Antidepressants (OQESA) was completed by the patient at W0, W4, W12, W24 or in case of premature withdrawal between W0 and W24. It was only completed by the English-speaking patients.

Other measurements

- Euroqol Questionnaire (EQ-5D) was rated by the patient at each visit between W0 and W24, at Wend, or in case of premature withdrawal between W0 and W24.
- Socioeconomic questions were rated by the patient at each visit between W0 and W24, at Wend, or in case of premature withdrawal between W0 and W24.

Statistical methods:

Efficacy analysis

Primary criterion

In addition to descriptive statistics for all analytical approaches of the primary criterion on the W0-W24 and W0-W6 periods in the FAS, the following analyses were performed:

- Main analysis

A stepwise strategy (superiority test preceded by a non-inferiority test) was used. First, the non-inferiority of agomelatine to duloxetine was studied taking into account a fixed pre-defined non-inferiority margin of 8%. Then, in the case of a significant non-inferiority test (p to be compared to 2.5%), the superiority of agomelatine to duloxetine would be studied.

For both steps, the same logistic regression model with country (fixed effect) and baseline HAM-D total score (continuous variable) as covariates and no interaction was used, on the response to treatment taking into account the last post-baseline until W24, in the FAS.

- Sensitivity analyses

Two sensitivity analyses were planned:

- A logistic regression model as for the main analysis in the Randomised Set on the response to treatment at W24 using a "best or worst case imputation" for missing responses at W24.
- An unadjusted logistic regression model in the FAS on the response to treatment considering the last post-baseline value until W24.

For these two sensitivity analyses, the same stepwise strategy as for the main analysis was set up, and the fixed pre-defined non-inferiority margin of 8% was considered.

A complementary analysis was performed on the response to treatment in more severily depressed patients (HAM-D total score $\geq$ 25 at W0) using the same methodology as the one used for the main analysis.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

Statistical methods (Cont'd):
Efficacy analysis (Cont'd)

- Secondary analyses

The same analysis strategy as the main analysis was implemented on the response to treatment taking into account the last post-baseline value until W6.
Moreover, the superiority of agomelatine to duloxetine was also assessed on the change from baseline to last post-baseline value until W24, setting up a stepwise strategy, *i.e.* the superiority test was preceded by a non-inferiority test using a fixed pre-defined non-inferiority margin of 1.5. For both steps, a two-way analysis of covariance model with centre (random effect) and baseline as covariates and no interaction was implemented in the FAS. The same analysis strategy was also applied with country (fixed effect) and baseline as covariates.

Secondary criteria
For each analytical approach of secondary criteria, descriptive statistics were provided in the FAS on the W0-W24 (W0-W2 for LSEQ) period, and also on the W0-W6 period for CGI and SDS.
The superiority of agomelatine to duloxetine was also assessed on the response to treatment based on CGI-I taking into account the last value until W24, setting up a stepwise strategy (fixed pre-defined non-inferiority margin of 8%). For both steps, an unadjusted logistic regression model was implemented in the FAS.
Moreover, the efficacy of agomelatine was compared to duloxetine on the value at W1 and the last value for the LSEQ Getting off to sleep and Quality of sleep scores, using a two-sided Student's t-test for independent samples (at the 5% significance level).

Safety analysis
Descriptive statistics were provided in the Safety Set by treatment group over the ASSE-W25/Wend period for emergent adverse events and laboratory parameters, and over the W0-W24/Wend period for vital signs and ECG. For ASEX, descriptive analysis was performed by gender and overall, in the Safety Set, Remitted Set and Remitted OQESA W24 Set over the W0-W24 period. For OQESA, descriptive analysis was performed in the OQESA Set and its two subsets (OQESA W24 Set, and Remitted OQESA W24 Set) over the W0-W24 period.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

Status		**Agomelatine**	**Duloxetine**	**All**
Included and randomised	**n**	**202**	**216**	**418**
W0-W24 period				
Lost to follow-up	**n (%)**	**1 (0.5)**	**-**	**1 (0.2)**
Withdrawn due to	**n (%)**	**74 (36.6)**	**63 (29.2)**	**137 (32.8)**
Adverse event	n (%)	25 (12.4)	20 (9.3)	45 (10.8)
Protocol deviation	n (%)	6 (3.0)	4 (1.9)	10 (2.4)
Lack of efficacy	n (%)	26 (12.9)	18 (8.3)	44 (10.5)
Non-medical reason	n (%)	15 (7.4)	20 (9.3)	35 (8.4)
Cure remission or improvement	n (%)	2 (1.0)	1 (0.5)	3 (0.7)
Completed the W0-W24 period	**n (%)**	**127 (62.9)**	**153 (70.8)**	**280 (67.0)**
W24-W25 period				
Completed the W24-W25 tapering period	**n (%)**	**125 (61.9)**	**151 (69.9)**	**276 (66.0)**
Withdrawn due to	**n (%)**	**2 (1.0)**	**2 (0.9)**	**4 (1.0)**
Adverse event	n (%)	1 (0.5)	-	1 (0.2)
Protocol deviation	n (%)	1 (0.5)	2 (0.9)	3 (0.7)
W0-W25 period				
Performed the tapering period after premature withdrawal	**n (%)**	**31 (15.3)**	**20 (9.3)**	**51 (12.2)**
Performed the follow-up visit	*n (%)*	*183 (90.6)*	*189 (87.5)*	*372 (89.0)*
Main analysis Sets				
Randomised Set	n	202	216	418
Full Analysis Set (FAS)	n (%)	198 (98.0)	212 (98.1)	410 (98.1)
Safety Set	n (%)	199 (98.5)	214 (99.1)	413 (98.8)

% according to randomised patients

Overall, 418 patients were randomised: 202 patients to the agomelatine group and 216 patients to the duloxetine group. Among the 190 agomelatine-randomised patients continuing in the study after the W2 visit, 40 patients (21.1%) in the agomelatine group had a dose increase. During the study, one patient in the agomelatine group was lost to follow-up at W24. During the W0-W25 period, the rate of withdrawal was higher in the agomelatine group than in the duloxetine group (37.6% *versus* 30.1%). This difference was mainly related to a higher frequency of withdrawals for adverse events (12.9% *versus* 9.3%) and for lack of efficacy (12.9% *versus* 8.3%) in the agomelatine group. Finally, the percentage of randomised patients who completed the study at W25 was 61.9% in the agomelatine group and 69.9% in the duloxetine group.

Randomised patients were 42.8 ± 12.1 years old on average (± SD), ranging from 18 to 65 years. Most of them were female (72.3%). According to the DSM-IV-TR criteria, 74.6% of patients were diagnosed as recurrent MDD, and the other ones had single episode (25.4%). In all, 67.0% of patients had a moderate MDD, and 33.0% a severe MDD without psychotic feature. Melancholic features were observed in 66.0% of patients. Mean number of depressive episodes was 2.9 ± 2.2 including the current one, ranging from 1 to 15. Mean duration of the current MDE was 5.5 ± 4.1 months (median 4.1 months). Previous psychotropic drug treatment was reported in 57.4% of patients, mainly SSRIs (30.6%).

No clinically relevant differences between the treatment groups were observed for demographic and disease characteristics at baseline except for the percentage of patients with severe MDD which was lower in the agomelatine group than in the duloxetine group (29.7% *versus* 36.1%).

Regarding the severity of depression at inclusion, the mean HAM-D total score was 26.3 ± 2.7, and the mean CGI severity of illness score was 4.6 ± 0.6 corresponding to “markedly” ill patients.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Regarding the sleep quality over the past month before inclusion, the mean PSQI total score was 12.9 ± 3.5.
According to SDS, on average, the patients felt markedly disrupted by symptoms for the 3 domains: work (7.2 ± 2.0), social life (7.4 ± 2.0), and family life and home responsibilities (7.3 ± 1.9). On average, 2.8 ± 2.7 days were lost, and 4.3 ± 2.4 days were underproductive in the week before the assessment.
The mean EQ-5D index was 0.41 ± 0.32, and the mean EQ-5D VAS score was 43.9 ± 18.2 at inclusion.
No clinically relevant differences between the treatment groups were observed for all efficacy criteria at baseline.

Regarding safety criteria, the ASEX total score over the last week before inclusion ranged between 6 and 30 with a mean of 19.7 ± 5.0 (n = 158) at inclusion corresponding to a somewhat difficult sexual activity. In all, 210 patients (50.4%) had sexual activity in the past week, and 331 patients (87.3%) had at least one sexual dysfunction at inclusion. No clinically relevant differences between the treatment groups were observed.

In randomised English-speaking patients (n = 177), at inclusion, the mean OQESA total score, the mean RP-NC sub-score (reduction in positive emotion score and not caring score), and the mean GR-ED sub-score (general reduction in emotion score and emotional detachment from others score) were lower in the agomelatine group than in the duloxetine group as follows:

- Total score: 56.54 ± 13.65 *versus* 61.48 ± 12.37.
- RP-NC sub-score: 33.49 ± 5.68 *versus* 35.40 ± 4.79.
- GR-ED sub-score : 23.05 ± 9.99 *versus* 26.07 ± 9.55.

Baseline characteristics in the FAS were similar to those observed in the Randomised Set.
In the Randomised Set, mean treatment duration was 137.1 ± 54.8 days (median 168.0 days) over the W0-W24 period. Global compliance was 93.6 ± 15.7% over the W0-W24 period. Treatment duration and global compliance showed no relevant difference in both groups.

EFFICACY RESULTS

- **Primary criterion: HAM-D total score**
  - **Response to treatment (main expression)**

A responder to treatment was defined as a patient with a decrease in HAM-D total score of at least 50% from baseline.
In the FAS, the response to treatment at the last post-baseline assessment over the W0-W24 period was 69.7% in the agomelatine group and 78.3% in the duloxetine group. Considering the pre-defined non-inferiority margin of -8%, agomelatine was not statistically non-inferior to duloxetine (E (SE) = -9.21% (4.46); 95%CI = [-17.95 ; -0.47]%, p = 0.607, main analysis). These results were confirmed by the sensitivity analyses.
In more severily depressed patients (HAM-D total score ≥ 25 at W0) (N = 289), unplanned complementary analysis showed results in the same line as those in the FAS with a smaller difference between the treatment groups (E (SE) = -3.72% (5.34) ; 95%CI = [-14.18 ; 6.74]%, p = 0.211).
Over the W0-W6 period, the results were in the same line as those over the W0-W24 period.

  - **Mean change from baseline**

In the FAS, the mean ± SD decrease from baseline at the last post-baseline assessment over the W0-W24 period was -15.8 ± 8.6 in the agomelatine group, and -18.0 ± 8.5 in the duloxetine group. Considering the pre-defined non-inferiority margin of -1.5, agomelatine was not statistically non-inferior to duloxetine (E(SE) = -2.33 (0.79), 95% CI = [-3.88 ; -0.79], p = 0.855).
Over the W0-W6 period, descriptive results were in the same line as those over the W0-W24 period.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **CGI**
  - **Severity of illness score**

In the FAS, the mean CGI severity of illness score decreased from baseline to the last post-baseline value over the W0-W24 period in both treatment groups:

- From 4.6 ± 0.6 and 4.6 ± 0.7 (median 5.0 in each group) in the agomelatine and duloxetine groups, respectively.
- To 2.4 ± 1.4 and 2.0 ± 1.4 (median 2.0 and 1.0) in the agomelatine and duloxetine groups, respectively.

  - **Global improvement score**

In the FAS, the mean CGI global improvement score decreased over the W0-W24 period in both treatment groups:

- From 3.3 ± 0.8 and 3.2 ± 0.9 (median 3.0 in each group) at W1 in the agomelatine and duloxetine groups, respectively.
- To 2.0 ± 1.3 and 1.7 ± 1.2 (median 1.0 in each group) in the agomelatine and duloxetine groups, respectively at the last assessment.

The percentage of responders according to CGI (global improvement score = 1 or 2) at the last assessment over the W0-W24 period was 72.7% and 78.8% in the agomelatine and duloxetine groups, respectively. Considering the pre-defined non-inferiority margin of -8%, agomelatine was not statistically non-inferior to duloxetine (E (SE) = -6.05% (4.23) ; 95%CI = [-14.34 ; 2.25]%, p = 0.322).

  - **Efficacy index**

In the FAS, the mean CGI efficacy index increased over the W0-W24 period in both treatment groups:

- From 1.50 ± 0.82 and 1.33 ± 0.79 (median 1.00 in each group) in the agomelatine and duloxetine groups, respectively at W1.
- To 2.83 ± 1.31 and 3.00 ± 1.29 (median 3.00 and 4.00) in the agomelatine and duloxetine groups, respectively at the last assessment.

For the 3 CGI scores over the W0-W6 period, the results were in the same line as those over the W0-W24 period.

- **LSEQ**
  - **Getting off to sleep score**

In the FAS, the mean LSEQ getting off to sleep was 44.61 ± 17.79 mm in the agomelatine group and 44.83 ± 18.77 mm in the duloxetine group at W1, and 41.69 ± 17.83 mm in the agomelatine group and 42.52 ± 17.87 mm in the duloxetine group at the last assessment over the W0-W2 period without statistically significant differences between the two treatment groups at both assessments (p = 0.906, and p = 0.642, respectively).

  - **Quality of sleep score**

In the FAS, the mean LSEQ quality of sleep score was statistically significantly lower on agomelatine than on duloxetine at W1 (E (SE) = 6.95mm (2.17); 95%CI = [2.68 ; 11.22]mm, p = 0.001). At the last assessment over the W0-W2 period, the difference in favour of agomelatine showed a trend to statistical significance (E (SE) = 3.67mm (2.20) ; 95%CI = [-0.66 ; 8.00]mm, p = 0.097).

  - **Sleep awakening score**

In the FAS, the mean LSEQ sleep awakening score showed no relevant differences between the treatment groups at W1 (46.31 ± 17.21 mm *versus* 46.12 ± 20.29 mm) and for the last assessment over the W0-W2 period (44.99 ± 19.97 mm *versus* 44.89 ± 21.14 mm).

  - **Integrity of behaviour score**

In the FAS, the mean LSEQ integrity of behaviour score showed no relevant differences between the treatment groups at W1 (51.03 ± 18.38 mm *versus* 52.81 ± 19.05 mm) and for the last assessment over the W0-W2 period (48.94 ± 20.88 mm *versus* 48.34 ± 20.16 mm).

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **PSQI**

In the FAS, the mean PSQI total score decreased between the baseline and the last post-baseline assessment over the W0-W24 period without relevant difference between the treatment groups (-5.4 ± 4.9 in the agomelatine group and -5.5 ± 5.1 in the duloxetine group).

- **SDS**

In the FAS, the mean decrease in SDS total score between W0 and the last post-baseline assessment over the W0-W24 period was lower in the agomelatine group than in the duloxetine group (-9.7 ± 9.1 *versus* -12.2 ± 9.0). Results for the 3 mean SDS scores were in the same line:

- Work: -3.3 ± 3.3 in the agomelatine group *versus* -4.0 ± 3.2 in the duloxetine group.
- Social life: -3.2 ± 3.4 *versus* -4.4 ± 3.3, respectively.
- Family life and home responsibilities: -3.1 ± 3.4 *versus* -4.1 ± 3.4, respectively.

Results observed over the W0-W6 period were in the same line.

SAFETY RESULTS

- **Emergent adverse events**

Main safety results in the Safety Set (N = 413)

		Agomelatine (N = 199)	**Duloxetine (N = 214)**
Patients having reported			
at least one emergent adverse event	n (%)	145 (72.9)	166 (77.6)
at least one treatment-related emergent adverse event	n (%)	114 (57.3)	140 (65.4)
Patients having experienced			
at least one serious adverse event	n (%)	7 (3.5)	3 (1.4)
at least one emergent serious adverse event	n (%)	7 (3.5)	1 (0.5)
at least one treatment-related emergent serious adverse event	n (%)	1 (0.5)	-
Patients withdrawn			
due to an emergent adverse event	n (%)	23 (11.6)	19 (8.9)
due to a serious emergent adverse event	n (%)	5 (2.5)	1 (0.5)
due a treatment-related non serious emergent adverse event	n (%)	22 (11.1)	13 (6.1)
due a treatment-related serious emergent adverse event	n (%)	1 (0.5)	-
Patients who died	n (%)	-	-

Over the W0-W25/Wend period in the Safety Set, the percentage of patients with at least one emergent adverse event was slightly lower in the agomelatine group than in the duloxetine group (72.9% *versus* 77.6%).

The most frequently affected system organ classes (in more than 20% of patients) in the agomelatine group were nervous system disorders (33.2%), gastrointestinal disorders (31.7%), psychiatric disorders (21.1%), and infections and infestations (20.6%). No relevant differences were observed between the treatment groups except for nervous system disorders, and gastrointestinal disorders which were less common in the agomelatine group than in the duloxetine group (33.2% *versus* 36.0%, and 31.7% *versus* 44.9%, respectively).

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

The most frequent emergent adverse event in the agomelatine group was headache with a higher frequency than in the duloxetine group (18.1% *versus* 14.0%). In the duloxetine group, it was nausea with a higher frequency than in the agomelatine group (6.5% in the agomelatine group *versus* 24.3% in the duloxetine group).

The other most frequent emergent adverse events (reported in at least 6% of patients) in the agomelatine group were dry mouth and dizziness which were less frequent in the agomelatine group than in the duloxetine group (9.5% *versus* 11.7%, and 6.0% *versus* 7.5%, respectively), and diarrhoea and nasopharyngitis which were more frequent in the agomelatine group than in the duloxetine group (6.5% *versus* 3.7%, and 6.0% *versus* 3.3%, respectively). In addition, in the duloxetine group, there were somnolence and constipation, both less frequent in the agomelatine group (5.0% *versus* 12.6%, and 2.5% *versus* 7.9%, respectively), and insomnia similarly reported in both treatment groups (5.5% in the agomelatine group and 6.1% in the duloxetine group).

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 than in the duloxetine group (57.3% in the agomelatine group *versus* 65.4% in the duloxetine group), mainly attributable to gastrointestinal disorders (27.6% *versus* 42.5%, respectively).

Most emergent adverse events were of mild or moderate intensity in both treatment groups (49.8% and 43.4% in the agomelatine group, respectively, and 46.2% and 46.7%, in the duloxetine group). The percentage of patients who experienced at least one emergent adverse event rated as severe was lower in the agomelatine group than in the duloxetine group (10.1% *versus* 15.0%, respectively).

Most emergent adverse events resolved or were improving at the end of the study. The percentage of emergent adverse events not resolved showed no relevant difference between the treatment groups (5.9% and 7.1% in the agomelatine and duloxetine groups, respectively).

No death was reported during the study. In all, 8 patients experienced each one serious emergent adverse event during the treatment period with a higher frequency in the agomelatine group (7 patients, 3.5%) than in the duloxetine group (1 patient, 0.5%).

One emergent serious adverse event in the agomelatine group was considered as related to the study treatment by the investigator (gastrointestinal haemorrhage).

Non-fatal serious emergent adverse events led to study treatment discontinuation in 5 patients (2.5%) in the agomelatine group and 1 patient (0.5%) in the duloxetine group.

In all, emergent non-serious adverse events were responsible for premature treatment withdrawal in 42 patients (10.2%) during the W0-W25/Wend period. The percentage of patients concerned was slightly higher in the agomelatine group than in the duloxetine group: 11.6% (23 patients) in the agomelatine group *versus* 8.9% (19 patients) in the duloxetine group.

- **Laboratory tests**
  - In the Safety Set, biochemical other than liver parameters and haematological parameters did not show any clinically relevant change over time on average in both treatment groups nor relevant difference between them.

    For biochemical parameters, emergent PCSA values were related to potassium, urea, glucose, total cholesterol, and triglycerides. Differences between groups were observed for the percentage of patients with high PCSA values of triglycerides in fasting condition which was lower in the agomelatine group than in the duloxetine group (2.1% *versus* 9.2%). Result was reversed for high PCSA values of urea (2.1% *versus* 1.0%). For haematological parameters, 7 patients (3.5%) in the agomelatine group, and 11 patients (5.1%) in the duloxetine group had at least one PCSA value under treatment. Emergent PCSA values were related to haemoglobin, haematocrit, white blood cells, neutrophils, eosinophils, and platelets. Differences between groups were observed for the percentage of patients with low PCSA and high PCSA values of white blood cells which was lower in the agomelatine group than in the duloxetine group (none *versus* 1.0%, and 0.5% *versus* 2.0%), as well as with high PCSA values of neutrophils and high PCSA values of eosinophils (none *versus* 1.0% for each parameter). Results were reversed for low PCSA values of haemoglobin and haematocrit (1.6% *versus* 0.5%, and 2.1% *versus* 1.0%).

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- Liver acceptability

  During the W0-W25/Wend period, 11 patients (5.5%) in the agomelatine group, and 5 (2.3%) in the duloxetine group had at least one emergent PCSA value of liver parameters with a higher frequency in the agomelatine group.

  Emergent PCSA transaminases (≥ 3 ULN) were reported in 7 patients in the agomelatine group, and 3 patients in the duloxetine group:

- In the agomelatine group:
  - 5 patients had emergent PCSA ALAT (maximum 11.7 ULN):
    - In 2 patients, these emergent PCSA ALAT values were associated with emergent PCSA ASAT (maximum 7.2 ULN).
    - In 3 patients, these emergent PCSA ALAT values were associated with abnormal ASAT without reaching PCSA limit.

    In all patients, total bilirubin and alkaline phosphatase were within the reference range. All patients recovered after treatment withdrawal.
  - 2 patients had emergent PCSA ASAT (maximum 4.0 ULN):
    - In one patient, the emergent PCSA ASAT was associated with abnormal ALAT without reaching PCSA limit. The other liver parameters were normal at all visits. The patient recovered after treatment withdrawal.
    - In the other patient, the emergent PCSA ASAT was associated with normal ALAT and abnormal conjugated bilirubin already present at baseline. At the end of the study, ASAT was within the reference range, and bilirubin increase was still present.
- In the duloxetine group, 3 patients had emergent PCSA ALAT (maximum 4.5 ULN):
  - In one patient, the emergent PCSA ALAT was associated with emergent PCSA ASAT (maximum 12.4 ULN).
  - In 2 patients, the emergent PCSA ALAT was associated with abnormal ASAT without reaching PCSA limit.

The 3 patients recovered, one on treatment, and 2 after treatment withdrawal.

- **Vital signs and BMI**

There were no relevant mean changes in sitting blood pressures and heart rate as well as in weight between baseline and last post-baseline value over the W0-W24/Wend period in the Safety Set in both treatment groups. As regards BMI, the percentage of patients with a BMI increase (change of BMI class) between the baseline and the last post-baseline assessment was lower in the agomelatine group than in the duloxetine group (3.5% *versus* 7.9%).

- **ECG**

One emergent ECG abnormality was considered as clinically significant by the investigator in the duloxetine group (abnormal electrocardiogram T wave in patient who already had an electrocardiogram repolarisation abnormality at W0 considered as clinically significant). In addition, one clinically significant abnormality was reported in an ECG considered as not interpretable (ECG with minor problems). It was extrasystoles in the agomelatine group reported as mild adverse event and considered as possibly related to the study treatment. The patient recovered on treatment.

- **ASEX**

In the Safety Set, the mean ASEX total score and the percentage of patients with at least one sexual dysfunction decreased between the baseline and the last post-baseline assessment over the W0-W24 period in both treatment groups without relevant difference between them:

- Total score: -2.7 ± 3.9 (n = 58) in the agomelatine group, and -1.9 ± 5.8 (n = 54) in the duloxetine group.
- From 90.0% to 70.6% in the agomelatine group, and from 85.1% to 68.9% in the duloxetine group.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Valdoxan®**	**Volume:**	
Name of Active Ingredient: **Agomelatine (S 20098)**	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- OQESA

In the OQESA Set (N = 173), the mean OQESA total score, the 2 subscores, and the 4 dimensions scores decreased between the baseline and the last post-baseline assessment over the W0-W24 period in both treatment groups. The mean decrease was lower in the agomelatine group than in the duloxetine group for all scores except for the GR score as follows:

- Total score: -20.97 ± 23.78 in the agomelatine group and -29.88 ± 26.35 in the duloxetine group.
- RP-NC: -13.33 ± 13.29 and -18.77 ± 15.02, respectively.
- GR-ED: -7.64 ± 12.68 and -11.11 ± 13.30, respectively.
- GR: -4.86 ± 7.40 and -4.95 ± 8.18, respectively.
- RP: -6.90 ± 7.28 and -9.71 ± 7.70, respectively.
- ED: -2.78 ± 7.34 and -6.16 ± 6.87, respectively.
- NC: -6.43 ± 6.77 and -9.06 ± 7.76, respectively.

RESULTS OF OTHER MEASUREMENTS

- EQ-5D

The mean increase in VAS score, and EQ-5D index between the baseline and the last post-baseline assessment over the W0-W24 period showed no relevant differences between the treatment groups:

- +21.6 ± 28.6 in the agomelatine group and +27.9 ± 26.3 in the duloxetine group.
- +0.29 ± 0.41 and +0.36 ± 0.39, respectively.

CONCLUSION

This international, multicentre, double-blind, randomised study conducted in patients with MDD failed to demonstrate any beneficial effect of agomelatine 25-50 mg compared to duloxetine 60 mg after 24 weeks of treatment according to HAM-D response to treatment, however these results deeply contrast with those observed in previous head-to-head comparison agomelatine studies that showed favourable results for patients treated with agomelatine. Meanwhile, the results in the duloxetine group also differ from those found in the literature. For these reasons, the generalisation of the results of this present study should be considered with caution.

On the other hand, the improvement in sleep quality was statistically significantly better on agomelatine than on duloxetine after 7 days of treatment.

Agomelatine 25-50 mg was well tolerated. Moreover, agomelatine was better tolerated than duloxetine for gastrointestinal disorders, particularly nausea.

Date of the report: 23 September 2011