Document title	**Abbreviated Clinical Study Synopsis Report**
Study title	**Efficacy of agomelatine 25 mg/day (with possible increase to 50 mg/day after 8 weeks of treatment) given orally during 16 weeks in patients with Obsessive-Compulsive Disorder.** **A randomised, double-blind, placebo-controlled, parallel groups, international study.**
Study drug	**S 20098 (Agomelatine: Valdoxan®)**
Studied indication	**Obsessive-Compulsive Disorder**
Development phase	**II**
Protocol code	**CL2-20098-072**
Study initiation date	**29 April 2010**
Study completion date	**25 April 2013**
Main coordinator	[redacted] **Israel**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 SuresnesCedex - France** **Laboratorios Servier, S.L** **Departamiento de Investigación y Desarrollo** **Avenida de los Madroños, 33** **28043 Madrid - Spain** **Servier Research and Development** **International Centre for Therapeutic Research, Rowley,** **Wexham Springs, Framewood Road - Wexham** **Slough SL3 6PJ - United Kingdom**
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	**Final version of 17 April 2014**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50, rue Carnot** **92284 Suresnes cedex – 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 (S20098)**	**Page:**	

Title of study: Efficacy of agomelatine 25 mg/day (with possible increase to 50 mg/day after 8 weeks of treatment) given orally during 16 weeks in patients with Obsessive-Compulsive Disorder.
A randomised, double-blind, placebo-controlled, parallel groups, international study.
Protocol No.: CL2-20098-072 – EudraCT No. 2009-016713-20

International coordinator:
[redacted] Israel.

Study centres: In all, 8 centres located in 6 countries included at least one patient: 1 centre in Israel (23 patients), 1 centre in Italy (7 patients), 1 centre in Netherlands (7 patients), 3 centres in Spain (23 patients), 1 centre in Sweden (5 patients) and 1 centre in United Kingdom (9 patients).

Publication (reference): Not applicable.

Studied period: Initiation date: 29 April 2010 Completion date: 25 April 2013	**Phase of development of the study:** II

Objectives:
Primary objective: to evaluate the efficacy of agomelatine (25-50 mg/day) compared to placebo on the reduction of Obsessive and Compulsive (OC) symptoms by using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) after 16 weeks of treatment in patients fulfilling DSM-IV-TR criteria for Obsessive Compulsive Disorders (OCD).
Secondary objective: to evaluate agomelatine effects on:

- The severity of OC symptoms by using the National Institute for Mental Health Obsessive-Compulsive scale (NIMH-OC), the Clinical Global Impression score (CGI) and OC-Visual Analogue Scales (OC-VAS).
- The severity of depressive and anxious symptoms using Montgomery and Asberg Depression Rating Scale (MADRS) and Hamilton Anxiety Rating Scale (HAM-A).
- Sleep using the Leeds Sleep Evaluation Questionnaire (LSEQ).
- Global social functioning using the Sheehan Disability Scale (SDS).
- Safety parameters: Adverse Events (AEs), Blood Pressure (BP), Heart Rate (HR), body weight, Body Mass Index (BMI) and laboratory parameters.

Methodology:
This was a 16-week randomised, double blind placebo-controlled international phase II study with parallel arms using a flexible dosage of agomelatine 25 mg/day increased to 50 mg/day in case of insufficient improvement at W8 (reduction ≤ 20% of the baseline Y-BOCS total score). This potential dose adaptation was done in single-blind conditions.

The treatment (agomelatine or placebo) was assigned at inclusion by balanced (non-adaptive and non-centralized) randomisation with stratification on the centre.
This study was performed in strict accordance with Good Clinical Practices.

Number of patients:
Planned: 80 patients (40 in each group).
Included: 74 patients (39 on agomelatine; 35 on placebo).

Diagnosis and main criteria for inclusion:
Outpatients, male or female, aged between 18 (or legal age for majority in the country) and 65 years inclusive, with a primary diagnosis of OCD according to DSM-IV-TR, previously treated with a first line pharmacological treatment, moderately to severely ill (Y-BOCS total score ≥ 20), with a duration of OCD symptoms of at least one year and requiring a treatment.

Study drug:
Agomelatine, tablet of 25 mg. One or 2 tablets of agomelatine had to be taken orally once a day, in the evening at around 8 p.m.:
- Agomelatine 25 mg/day group: 1 tablet + 1 placebo tablet.
- Agomelatine 50 mg/day group: 2 tablets.

Batch No.: Agomelatine 25 mg: L0029925, L0041218.

Reference product:
Placebo: 2 tablets had to be taken orally once a day, in the evening at around 8 p.m.

Duration of treatment:
- **A run-in period** without treatment of maximum 10 days between selection (ASSE) and inclusion (W0) visits.
- **A double-blind treatment period** of 16 weeks (from W0 to W16).
- **A follow-up period** of 1 week without treatment after the end of the double-blind period or in case of premature withdrawal (WEND visit).

Criteria for evaluation:
Efficacy measurements:
Main criterion: Y-BOCS total score: rated by the investigator at ASSE, W0, W2, W8 and W16 visits or in case of premature withdrawal. It was the primary efficacy criterion, expressed mainly as the change from baseline to last post-baseline value on the W0-W16 period.
Secondary criteria:
- NIMH-OC score: rated by the investigator at ASSE, W0, W2, W8 and W16 visits or in case of premature withdrawal.
- CGI Severity of Illness and Global Improvement scores: rated by the investigator at ASSE and W0 (severity of illness only), W2, W8, and W16, or in case of premature withdrawal.
- OC-VAS: filled in by the patient at ASSE, W0, W2, W8 and W16 visits or in case of premature withdrawal.
- SDS Work, Social life and Family life scores: filled in by the patient at W0, W8 and W16 visits or in case of premature withdrawal.
- HAM-A total score: rated by the investigator at W0 and W16 visits or in case of premature withdrawal.
- LSEQ Getting off to sleep score, Quality of sleep score, Sleep awakening score and Integrity of behaviour score: filled in by the patient at W2, W8 and W16 visits or in case of premature withdrawal.
- MADRS total score: rated by the investigator at ASSE, W0, and W16 visits or in case of premature withdrawal.

Safety measurements:
- Adverse events: at each visit from ASSE to Follow-up (WEND) visits.
- Vital signs and physical examination: Sitting blood pressure (mmHg) *i.e.* systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (bpm) and body weight (kg): at each visit from ASSE to Follow-up (WEND) visits.
- Laboratory parameters: biochemical (including liver function tests) and haematological tests: between ASSE and W0 (*results were to be available at latest for W0 visit), at W8, W12, W16 visits and the withdrawal visit in case of premature withdrawal. According to Amendment N°4, an additional blood sample was to be systematically taken at visit W2 to test liver function parameters.

Pharmacokinetic measurements
The saliva concentrations of agomelatine were to be determined 1h, 2h and 3h after treatment intake in the evening preceding W8 and W12 visits.

Statistical methods:
Efficacy analysis:

Primary criterion

- Main analysis:

The superiority of agomelatine as compared to placebo on the reduction of OC symptoms after a 16-week treatment period was assessed in patients of the Full Analysis Set (FAS) from the change from baseline to last post-baseline value of Y-BOCS total score using an adjusted semi-parametric approach: a Robust General Linear Model was implemented using a rank-based analysis (Wilcoxon scores), on factor treatment with country (fixed effect) and baseline Y-BOCS total score as covariates and without interaction.

- Sensitivity analyses:
  - Sensitivity analysis to adjustment for covariates (unadjusted semi-parametric approach): agomelatine was compared to placebo on the last post-baseline value on the W0-W16 period, using Hodges-Lehmann estimation of the difference between treatment groups and Mann-Whitney test for independent samples,
  - Sensitivity analysis using an adjusted parametric approach (normality assumption): agomelatine was compared to placebo on the change from baseline to last post-baseline value on the W0-W16 period, from a two-way analysis of covariance model on factor treatment with country (fixed effect) and baseline Y-BOCS total score as covariates and without interaction.
- Secondary analyses:
  - Response to treatment derived from Y-BOCS total score *(definition No. 1: Decrease from baseline ≥ 35%, or No. 2: Decrease from baseline ≥ 25%)*: agomelatine was compared to placebo at the last post-baseline value until W16 using Fisher's exact test in the FAS.

In addition, descriptive statistics were provided for remission derived from Y-BOCS total score (Y-BOCS total score ≤ 10) on the W0-W16 period for patients of the FAS.

All the previous efficacy analyses were also performed in the Observed Cases W16 Set (OCW16S).

Secondary criteria:
The agomelatine and placebo groups were compared on the severity of OC symptoms in the FAS (on last post-baseline value) and in the OCW16S (value at W16) on the W0-W16 period for:

- Y-BOCS Obsession and Compulsion sub-scores, NIMH-OC score, CGI Severity of illness and Global improvement scores using a two-sided Student's t-test for independent samples and a Mann-Whitney test with the Hodges-Lehmann estimation of the difference between treatment groups.
- Response to treatment (Global improvement score equal to 1 or 2) using Fisher's exact test. Remission (Severity of illness score as equal to 1 or 2) was also described.

Descriptive statistics were provided for OC-VAS score, MADRS total score, HAM-A total score , LSEQ scores (Getting off to sleep, Quality of sleep, Sleep awakening and Integrity of behaviour scores) and SDS scores (Work, Social life, Family life and home responsibilities scores) on the W0-W16 period for patients of the FAS and OCW16S.

Study outcome and Safety analysis:
Descriptive statistics were provided.

Pharmacokinetic analysis:
A population pharmacokinetic model was developed, pooling the whole PK information available at the time of the analysis. For the CL2-20098-072 study, as agomelatine was measured in saliva and not in plasma, a correlation between plasma and saliva concentrations was used to back calculate plasma concentrations from saliva concentrations. This correlation was estimated as one of the parameters of the newly refined population PK model. Then, the following secondary PK parameters were computed from the individual back-calculated plasma PK profiles obtained with the final PK model including covariates: AUC, C_{max}, t_{max} and $t_{1/2,z}$.

SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

		Agomelatine	Placebo	Whole population
Included (randomised)	**n**	**39**	**35**	**74**
Withdrawn due to	**n (%)**	**19 (48.7)**	**10 (28.6)**	**29 (39.2)**
lost to follow-up	n (%)	-	-	-
adverse event	n (%)	4 (10.3)	1 (2.9)	5 (6.8)
non-medical reason	n (%)	9 (23.1)	3 (8.6)	12 (16.2)
lack of efficacy	n (%)	6 (15.4)	6 (17.1)	12 (16.2)
Completed the W0-W16 period	**n (%)**	**20 (51.3)**	**25 (71.4)**	**45 (60.8)**
Analysis Sets				
Randomised Set (RS)	**n**	**39**	**35**	**74**
Full Analysis Set (FAS)*	**n (%)**	**39 (100)**	**34 (97.1)**	**73 (98.6)**
Observed Cases W16 Set (OCW16S)**	**n (%)**	**21 (53.8)**	**26 (74.3)**	**47 (63.5)**
Safety set (SS)***	**n (%)**	**39 (100)**	**35 (100)**	**74 (100)**
Pharmacokinetic Set (PK Set)	**n (%)**	**26 (66.7)**	**-**	**26 (35.1)**

* *All patients of the RS having taken at least one dose of study medication and having a value at baseline and at least one post-baseline value for the primary efficacy criterion over the W0-W16 period.*
** *All patients of the FAS having a value for the primary efficacy criterion at W16.*
*** *All included patients having taken at least one dose of study medication.*
%::*According to randomised patients.*
n: Number of patients.

A total of 79 patients were selected for the study, and 74 were included and randomly assigned to one of the 2 treatment groups: 39 patients in the agomelatine group and 35 patients in the placebo group.
Most agomelatine-treated patients who continued at W8 (30 patients) had a dose increased to 50 mg/day (25/30 patients, 83.3%).

In the Randomised Set (RS), 19 patients (48.7%) in the agomelatine group and 10 (28.6%) in the placebo group were prematurely withdrawn from the study over the W0-W16 period. The most frequent reasons were both non-medical reason [more frequent in the agomelatine group (23.1%) than in the placebo group (8.6%)] and lack of efficacy (at the same frequency in the 2 groups, respectively 15.4% and 17.1%). No patient was lost to follow-up.

Regarding the main characteristics of patients at baseline in the Randomised Set (see table below), patients were aged from 19 to 65 years with a mean ± SD of 40.1 ± 11.5 years in the agomelatine group and 37.7 ± 12.6 years in the placebo group. There were slightly more females in the agomelatine group (21 patients, 53.8%) and slightly more males in the placebo group (20 patients, 57.1%).

As regards OCD efficacy criteria at baseline in the Randomised Set, there were slight differences between the treatment groups on mean **Y-BOCS total score**, mean **NIMH-OC score**, mean **OC-VAS compulsion sub-score** and mean **MADRS total score**, showing that patients under agomelatine appeared to have a less severe profile than patients under placebo. Indeed, the mean Y-BOCS total score was lower in the agomelatine group (mean ± SD = 24.6 ± 3.8, median = 24.0) than placebo group (mean ± SD = 26.1 ± 3.4, median = 26.0). As for Y-BOCS total score, the mean Y-BOCS obsession sub-score showed a slight difference between agomelatine group (mean ± SD = 12.1 ± 2.7, median = 12.0) and placebo group (mean ± SD = 13.4 ± 1.9, median = 14.0). Similar results were observed for OC-VAS compulsions sub-score at baseline (median = 74.0 mm in the agomelatine group and 80.0 mm in the placebo group). Regarding NIMH-OC score at baseline, 64.1% of patients in the agomelatine group and 42.9% of patients in the placebo group had a NIMH-OC score between 7 and 9, and 33.3% and 48.6%, respectively had a score between 10 and 12, indicating that fewer patients in the agomelatine group presented a severe obsessive-compulsive behaviour compared to the placebo group. Furthermore, the mean MADRS total score was slightly lower in the agomelatine group (mean ± SD = 10.8 ± 5.3, median = 10.0) than in the placebo group (mean ± SD = 12.1 ± 5.8, median = 13.0), indicating that patients in the agomelatine group had less depressive symptoms at baseline.

Baseline characteristics in the FAS were similar to those observed in the RS. No clear relevant differences between groups were detected in the OCW16S compared to the RS for the main characteristics.

In the RS, the mean ± SD treatment duration over the W0-W16 period was 94.0 ± 37.0 days (median = 112 days, *i.e.* 16 weeks) without relevant differences between the treatment groups. Global compliance over the W0-W16 period was satisfactory (mean ± SD = 90.3 ± 18.4%) and showed no relevant difference between groups.

SUMMARY – CONCLUSIONS (CONT'D)
STUDY POPULATION AND OUTCOME

Main baseline* characteristics of patients in the randomised Set

				Agomelatine (N = 39)	Placebo (N = 35)	All (N = 74)
Age (years)			**n**	**39**	**35**	**74**
			Mean ± SD	40.1 ± 11.5	37.7 ± 12.6	39.0 ± 12.0
			Median	38.0	36.0	37.0
			Min ; Max	21 ; 61	19 ; 65	19 ; 65
Gender		Male	n (%)	18 (46.2)	20 (57.1)	38 (51.4)
		Female	n (%)	21 (53.8)	15 (42.9)	36 (48.6)
Duration of OCD since diagnosis (years)			Mean ± SD	8.7 ± 8.2	8.1 ± 7.7	8.4 ± 7.9
			Median	5.0	6.0	5.5
Duration of OCD symptoms (years)			Mean ± SD	19.1 ± 10.7	18.3 ± 11.7	18.7 ± 11.2
			Median	15.6	18.3	17.3
DSM-IV diagnosis criteria for OCD						
Criteria A, Obsessions		Yes	n (%)	39 (100)	35 (100)	74 (100)
Criteria A, Compulsions		Yes	n (%)	38 (97.4)**	35 (100)	73 (98.6)**
Main previous psychotropic treatment for OCD						
Selective serotonin reuptake inhibitors			n (%)	38 (97.4)	34 (97.1)	72 (97.3)
Non-selective monoamine reuptake inhibitors			n (%)	11 (28.2)	4 (11.4)	15 (20.3)
Main OCD efficacy criteria at inclusion			**n**	**39**	**35**	**74**
Y-BOCS total score			Mean ± SD	24.6 ± 3.8	26.1 ± 3.4	25.3 ± 3.7
			Median	24.0	26.0	25.0
			Min ; Max	16 ; 34	20 ; 37	16 ; 37
Y-BOCS Obsession sub-score			Mean ± SD	12.1 ± 2.7	13.4 ± 1.9	12.7 ± 2.5
			Median	12.0	14.0	13.0
Y-BOCS Compulsion sub-score			Mean ± SD	12.4 ± 2.4	12.7 ± 2.2	12.6 ± 2.3
			Median	12.0	13.0	12.0
NIMH-OC score			Mean ± SD	9.3 ± 1.3	9.6 ± 1.4	9.4 ± 1.3
			Median	9.0	10.0	9.0
	Classes	[7-9]	n (%)	25 (64.1)	15 (42.9)	40 (54.1)
		[10-12]	n (%)	13 (33.3)	17 (48.6)	30 (40.5)
CGI Severity of illness score			Mean ± SD	4.6 ± 0.8	4.8 ± 0.7	4.7 ± 0.7
			Median	5.0	5.0	5.0
OC-VAS Obsessions score			Mean ± SD	71.7 ± 22.8	81.0 ± 15.6	76.1 ± 20.1
			Median	79.0	81.0	79.5
OC-VAS Compulsions score			Mean ± SD	69.5 ± 23.6	75.9 ± 23.1	72.5 ± 23.4
			Median	74.0	80.0	76.5
MADRS total score			Mean ± SD	10.8 ± 5.3	12.1 ± 5.8	11.4 ± 5.6
			Median	10.0	13.0	11.5
			Min ; Max	2 ; 23	2 ; 23	2 ; 23
HAM-A total score			Mean ± SD	12.7 ± 6.8	13.9 ± 7.8	13.2 ± 7.3
			Median	12.0	11.0	12.0

* *Baseline = value at selection except for efficacy criteria (value at inclusion).*
** *Patient No. 072 724 0402 00057 did not have compulsions.*
\# *Only values of patients having worked/studied during the past week.*

SUMMARY – CONCLUSIONS (CONT'D)
EFFICACY RESULTS

- Primary efficacy criterion: Y-BOCS Total score

Over the W0-W16 period, in the FAS, the median change of Y-BOCS total score from baseline to the last post-baseline assessment showed no statistically significant difference between groups after adjustment for country and baseline Y-BOCS total score (main analysis, see Table below). Sensitivity analyses showed the same results.

Y-BOCS total score: Description at baseline, at last post-baseline assessment over the W0-W16 period and corresponding change from baseline, and between-group comparisons in the FAS

		Agomelatine (N = 39)	Placebo (N = 34)
Baseline	n	39	34
	Median	24.0	26.0
	Min ; Max	16 ; 34	20 ; 37
Last post-baseline (on W0-W16)	n	39	34
	Median	23.0	22.5
	Min ; Max	12 ; 35	2 ; 39
Last post-baseline (on W0-W16) - Baseline	n	39	34
	Median	0.0	-2.5
	Min ; Max	-11 ; 6	-23 ; 10
Statistical analysis			
Main analysis [(a)]	E (SE) [(1)]	-2.00 (1.67)	
Adjusted semi-parametric analysis			
Last post-baseline (on W0-W16) - Baseline	95% CI [(2)]	[-5.34 ; 1.34]	
	p-value [(3)]	0.236	
Sensitivity analysis			
Unadjusted semi-parametric analysis	E (SE) [(4)]	0.00 (1.53)	
Last post-baseline (on W0-W16)	95% CI [(2)]	[-3.00 ; 3.00]	
	p-value [(5)]	0.769	
Baseline	n	39	34
	Mean ± SD	24.6 ± 3.8	26.1 ± 3.5
Last post-baseline (on W0-W16)	n	39	34
	Mean ± SD	23.3 ± 5.4	23.2 ± 7.4
Last post-baseline (on W0-W16) - Baseline	n	39	34
	Mean ± SD	-1.2 ± 4.2	-2.8 ± 6.1
Sensitivity analysis			
Adjusted parametric analysis [(b)]	E (SE) [(6)]	-1.59 (1.25)	
Last post-baseline (on W0-W16) - Baseline	95% CI [(2)]	[-4.09 ; 0.91]	
	p-value [(3)]	0.209	

(a) Rank-based analysis (Wilcoxon scores) on factor treatment with country (fixed effect) and baseline Y-BOCS total score as covariates.
(b) Analysis of covariance model on factor treatment with country (fixed effect) and baseline Y-BOCS total score as covariates.
(1) Estimate (Standard Error) of the difference between treatment groups: Placebo minus Agomelatine.
(2) Two-sided 95% Confidence Interval of the estimate.
(3) Two-sided p-value.
(4) Estimate (Standard Error) of Hodges-Lehmann for the difference between treatment groups: Placebo minus Agomelatine.
(5) Mann-Whitney test: Two-sided p-value.
(6) Estimate (Standard Error) of the difference between adjusted treatment group means: Placebo minus Agomelatine.

SUMMARY – CONCLUSIONS (CONT'D)

EFFICACY RESULTS

In the OCW16S, the median change of Y-BOCS total score from baseline to W16 assessment was 0.0 in the agomelatine group and -3.0 in the placebo group. This between-group difference was statistically significant: E (SE) = -2.00 (0.99), 95% CI [-3.99 ; -0.01], p = 0.049, after adjustment for country and baseline. No statistically significant between-group difference was observed according to the 2 sensitivity analyses:

- Sensitivity analyses using a parametric approach with adjustment for country and baseline, on the change from baseline to W16: E (SE) = -1.79 (1.58), 95% CI [-4.99 ; 1.42], p = 0.266.
- Sensitivity analyses using a unadjusted semi-parametric approach, on W16 assessment: E (SE) 0.00 (1.53), 95% CI [-3.00 ; 3.00], p = 0.797.

Y-BOCS response to treatment (definition No. 1: decrease from baseline ≥ 35%, or No. 2: decrease from baseline ≥ 25%).

In the FAS, the rate of responders (*decrease from baseline ≥ 35%)* slightly increased over the W0-W16 period in both groups. At the last post-baseline assessment, no statistically significant difference was observed between agomelatine and placebo groups *i.e.*, 3/39 (7.7%) and 4/34 (11.8%) responders respectively; E (SE) = 4.07% (6.98), 95% CI [-9.61 ; 17.76], p =0.698). Similar results were observed for the rate of responders analysed according to the second definition of response to treatment *i.e.*, rate of responders: 5/39 (12.8%) and 6/34 (17.6%) in the agomelatine and placebo groups, respectively; E (SE) = 4.83% (8.45), 95% CI [-11.74 ; 21.39], p = 0.745). Results in OCW16S were in the same line than those in the FAS.

Y-BOCS remission

In the FAS, the rate of remitters (*i.e.* patients having Y-BOCS total score ≤ 10) at the last post-baseline assessment over the W0-W16 period was 0/39 in the agomelatine group and 2/34 (5.9%) in the placebo group. Results were similar in the OCW16S.

- **Secondary efficacy criteria:**
  - **Y-BOCS obsession and compulsion sub-scores**

In the FAS, the mean change of Y-BOCS obsession sub-score from baseline to the last post-baseline assessment over the W0-W16 was -0.4 ± 2.5 (median = 0.0) in the agomelatine group and -1.5 ± 3.3 (median = -2.0) in the placebo group. At the last post baseline assessment, the mean score was 11.7 ± 3.4 in the agomelatine group and 11.9 ± 3.8 in the placebo group (median = 12.0 in both groups), without statistically significant difference between-groups: E (SE) 0.16 (0.85), 95% CI [1.53 ; 1.86], p = 0.847 (parametric analysis) and E (SE) = 0.00 (0.77), 95% CI [-1.00 ; 2.00], p = 0.951 (semi-parametric analysis).

Similar results were reported for the Y-BOCS compulsion sub-scores in the FAS: E (SE) = -0.26 (0.82), 95% CI [-1.89 ; 1.36], p = 0.749 (parametric analysis) and E (SE) = 0.00 (0.77), 95% CI [-2.00 ; 1.00], p = 0.718 (semi-parametric analysis).

Results were similar in the OCW16S.

  - **NIMH-OC**

In the FAS, the mean NIMH-OC score did not change significantly in both groups from baseline to the last post-baseline assessment over the W0-W16 period. At the last post-baseline assessment, the mean score was 8.9 ± 1.7 in the agomelatine group and 8.9 ± 2.5 in the placebo group (median = 9.0 in both groups) without statistically significant difference between groups: E (SE) = -0.07 (0.49), 95% CI [-1.06 ; 0.92], p = 0.891 (parametric analysis). The semi-parametric analysis led to similar conclusion. Results were similar in the OCW16S.

  - **Clinical Global Impression (CGI)**

In the FAS, the mean CGI severity of illness score and global improvement score remained stable over W0-W16 in both treatment groups, without statistically significant difference between agomelatine and placebo groups. At the last assessment over the W0-W16 period, the rate of responders (global improvement score = 1 or 2) was 12.8% in the agomelatine group and 11.8% in the placebo group, without statistically significant difference between groups: E (SE) = -1.06% (7.69), 95% CI [-16.13 ; 14.02], p = 1.000). Concerning the rate of remitters (CGI severity of illness score = 1 or 2) it was 0/39 patients in the agomelatine group and 1/34 patients (2.9%) in the placebo group at the last post-baseline assessment over the W0-W16 period. Results were similar in the OCW16S.

SUMMARY – CONCLUSIONS (CONT'D)
EFFICACY RESULTS

- **OC-VAS**

In the FAS, OC-VAS obsessions score remained stable over W0-W16 in the agomelatine group whereas it improved in the placebo group with a mean change from baseline to the last post-baseline assessment of -0.2 ± 25.3 mm (median = -1.0) in the agomelatine group and -11.9 ± 29.5 mm (median = -4.5) in the placebo group. In the OCW16S, the mean change of obsessions sub-score from baseline to W16 was -0.2 ± 28.4 mm (median = -5.0) in the agomelatine group and -14.7 ± 30.2 mm (median = -5.5) in the placebo group.
Regarding OC-VAS compulsions score, the mean change from baseline to the last post-baseline assessment over the W0-W16 was -3.6 ± 23.7 mm (median = 0.0) in the agomelatine group and -7.4 ± 30.5 mm (median = 0.0) in the placebo group.
Results were similar in the OCW16S.

- **MADRS and HAM-A**

In the FAS, the mean change from baseline to the last post-baseline assessment over the W0-W16 period of MADRS and HAM-A total score showed no relevant difference between groups:

- MADRS total score: 0.9 ± 7.3 (median = 1.0) in the agomelatine group and 2.0 ± 8.3 (median = 1.0) in the placebo group.
- HAM-A total score: -0.3 ± 6.1 (median = 0.0) and -0.0 ± 10.5 (median = 0.0) respectively.

Results were similar in the OCW16S.

- **Leeds Sleep Evaluation Questionnaire (LSEQ)**

In the FAS, at the last assessment over the W0-W16 period (as well at each visit from W2), agomelatine-treated patients felt rather a better getting off to sleep than without medication whereas placebo-treated patients felt rather no change, as follows:

- LSEQ getting off to sleep score at the last assessment: 43.3 ± 24.4 mm (median = 44.7) in the agomelatine group and 54.0 ± 19.5 mm (median = 51.0) in the placebo group.

Quality of sleep score, sleep awakening score and integrity of behaviour score showed no clear change compared to without medication as well as no clinically relevant differences between the agomelatine and placebo groups at the last assessment over the W0-W16 period as follows:

- LSEQ quality of sleep score at the last assessment: 46.8 ± 20.9 mm (median = 49.5) and 54.7 ± 19. mm (median = 50.8), respectively.
- LSEQ sleep awakening score: 55.4 ± 19.8 mm (median = 51.0) and 53.0 ± 18.3 mm (median = 52.0), respectively.
- LSEQ integrity of behaviour score: 53.3 ± 21.5 mm (median = 52.7) and 55.3 ± 23.2 mm (median = 57.7), respectively.

Results observed in the OCW16S were similar to those in the FAS.

- **Sheehan Disability Scale (SDS)**

In the FAS, the 3 mean SDS scores rating the disruption of work, social life, and family life/home responsibilities remained stable from baseline to the last post-baseline assessment over the W0-W16 period in the both groups, without relevant difference between groups, as follows:

- Work disruption score: -0.1 ± 2.7 (median = 0.0) in the agomelatine group and -0.4 ± 2.6 (median = 0.0) in the placebo group.
- Social life score: -0.5 ± 3.1 (median = 0.0) and 0.3 ± 3.7 (median = 0.0) respectively.
- Family life/home responsibilities score: -0.1 ± 2.4 (median = -1.0) and -0.1 ± 2.6 (median = 0.0) respectively.

Results observed in the OCW16S were similar to those reported in the FAS.

SUMMARY – CONCLUSIONS (CONT'D)

SAFETY RESULTS

Overall summary of safety results in the Safety Set

		Agomelatine (N = 39)	Placebo (N = 35)
Patients having reported			
at least one emergent adverse event	n (%)	19 (48.7)	15 (42.9))
at least one treatment-related emergent adverse event	n (%)	7 (17.9)	4 (11.4)
Patients having experienced			
at least one serious emergent adverse event	n (%)	1 (2.6)	1 (2.9)
at least one treatment-related serious adverse event	n (%)	-	-
Patients withdrawn			
due to an emergent adverse event	n (%)	3 (7.7)	2# (5.7)
due to a serious emergent adverse event	n (%)	1 (2.6)	-
due a treatment-related emergent adverse event	n (%)	1 (2.6)	-
Patients who died	n (%)	-	-

 # For 1 patient in the placebo group (No. 072 826 0601 00092) the reason for study withdrawal was lack of efficacy.

Emergent adverse events

In the Safety Set, during the 16-week treatment, the percentage of patients who reported at least one emergent adverse event showed no relevant difference between the two treatment groups: 48.7% in the agomelatine group and 42.9% in the placebo group.

The most frequently affected system organ classes (SOCs) (in more than 10% of patients in any of the treatment groups) were nervous system disorders (9 patients, 23.1% in the agomelatine group *versus* 3 patients, 8.6% in the placebo group) and gastrointestinal disorders (6 patients, 15.4% *versus* 3 patients, 8.6%), both more frequent in the agomelatine group than in the placebo group. In contrast, psychiatric disorders were less common in the agomelatine group (5 patients, 12.8%) than in the placebo group (10 patients, 28.6%). Infections and infestations were at the same frequency in the 2 groups (3 patients, 7.7%, *versus* 4 patients, 11.4%, respectively). Regarding other SOCs, skin and subcutaneous tissue disorders was reported in 3/39 patients (7.7%) in the agomelatine group and 1/35 patient (2.9%) in the placebo group.

The emergent adverse event most frequently reported (in at least 3 patients in any of the treatment groups) were headache (5/39 patients, 12.8%, in the agomelatine group and 1/35 patients, 2.9%, in the placebo group), then depression (2/39 patients, 5.1%, and 3/35 patients, 8.6%) and nasopharyngitis (1/39 patients, 2.6%, and 3/35 patients, 8.6%). In addition, several emergent adverse events were reported in 2 patients (5.1%) in the agomelatine group *versus* none in the placebo group: dizziness, nausea, nightmare, and paraesthesia.

No unexpected emergent adverse events were reported on agomelatine in comparison with the Valdoxan® Summary of Product Characteristics (2013), in these patients suffering from OCD.

Most emergent adverse events were graded as mild or moderate (92.2% in the agomelatine group and 91.2% in the placebo group). Severe emergent adverse events were reported at the same frequency in the agomelatine and placebo groups (7.8% and 8.8% of total emergent adverse events respectively).

As regard to emergent treatment-related adverse events, the percentage of patients concerned was higher in the agomelatine group (17.9%, 7 patients) than in the placebo group (11.4%, 4 patients). The system organ classes most commonly affected corresponded to those cited above: nervous system disorders, (15.4%, 6 patients in the agomelatine group *versus* 2.9%, 1 patient in the placebo group), and gastrointestinal disorders (2 patients in each group, 5.1% and 5.7%, respectively).

No death occurred during the study. One patient in each treatment group had at least one non-fatal serious emergent adverse event. In the agomelatine group, one patient experienced one serious worsening of OCD considered to be related to lack of efficacy of the study treatment, that led to drug withdrawal 9 days after the first drug intake. In the placebo group, the patient hospitalised due to familiar problems, experienced crying, irritability, decrease appetite and 10 other SEAEs related to psychiatric disorders, all considered as not related to treatment. Both patients recovered.

The percentage of patients with non-serious emergent adverse events leading to treatment withdrawal was similar between the agomelatine and placebo groups (2 patients in each group, respectively 5.1% and 5.7%).

SUMMARY – CONCLUSIONS (CONT'D)
SAFETY RESULTS (CONT'D)

Clinical laboratory evaluation

Few biochemical and haematological emergent PCSA values were reported during the ASSE-W16/Wend period in the agomelatine group (1 high PCSA value of triglycerides) and placebo group (1 low PCSA value of glucose and platelet). None of these PCSA values were reported as an adverse event, or considered as clinically relevant by the investigator.

As regards liver acceptability, no emergent PCSA values of liver parameters were reported in the agomelatine group, and one high PCSA value of total bilirubin in the placebo group.

Physical examination

In the Safety Set, there were no clinically relevant mean changes from baseline to last post-baseline value for sitting blood pressure, heart rate and weight over the W0-W16/WEND period in agomelatine and placebo groups.

Analysis of BMI by class showed that most patients remained in the same BMI class between the baseline and the last post-baseline assessment over the W0-W16/WEND period. Moreover, BMI class increases were infrequent in the two treatment groups (3/39 patients, 7.7%, in the agomelatine group and 1/35 patients, 2.9%, in the placebo).

PHARMACOKINETIC RESULTS

Descriptive statistics of the agomelatine pharmacokinetic parameters in plasma per dose

Agomelatine dose (mg)	Week	N	AUC [1] (ng.h/mL)	C_{max} [1] (ng/mL)	t_{max} [2] (h)	$t_{1/2\ z}$ [1] (h)
[redacted]						
[redacted]						

N: Number of patients.
[1]: Mean ± SD (median).
[2]: Median (min ; max).
[3]: Week 12 pharmacokinetic data was not available for three patients (subjects 42, 115 and 116). Three patients (subjects 6, 8 and 17) did not undergo a dose escalation to 50 mg in Week 12, and remained at 25 mg per day. Given the high variability of agomelatine pharmacokinetic parameters and the low number of patients at this dose level in Week 12, no statistics were reported for these three patients at Week 12. Pharmacokinetic parameters for subject 33 at week 12 (50 mg) are omitted from these statistics [redacted]

The population PK model previously built for agomelatine was successfully used to obtain empirical Bayes estimates for the individual patients in the CL2-20098-072 study, based on their measured saliva concentrations of agomelatine. The mean and median plasma PK parameters based on the simulated plasma concentrations showed that similar t_{max} and $t_{1/2,z}$ values were obtained for 25 and 50 mg doses, and the AUC_{24} and C_{max} increased approximately proportionally with the dose between 25 and 50 mg. At 25 mg, the median AUC in this study [redacted] was [redacted]-fold higher than the median AUC in the previous combined population PK analysis [redacted] and the median C_{max} in this study [redacted] was [redacted]-fold higher than the median C_{max} in the combined population PK analysis [redacted]. At 50 mg, the median AUC and C_{max} values in this study [redacted] were similar to the AUC and C_{max} values in the combined population PK analysis [redacted] respectively). However, these observations are within the known variability of agomelatine. No relationship between pharmacodynamics data and agomelatine C_{max} or exposure was investigated as no efficacy of agomelatine was observed in this study.

CONCLUSION

This multicentre, double-blind, placebo-controlled, randomised study conducted in patients with OCD showed no clinically nor statistically significant difference between agomelatine (25-50 mg/day) and placebo on reduction of OC symptoms after 16 weeks of treatment, as assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). In addition, agomelatine had no effect on the severity of OC symptoms according to NIMH-OC score, CGI scores, and OC-VAS sub-scores. An improvement in LSEQ getting off to sleep score was observed on agomelatine over the 16-week treatment period. No effect of agomelatine was observed on work and activity, social and family life (SDS scores).

As regard safety results, the tolerance of agomelatine 25-50 mg/day over the 16-week treatment period was in accordance with its known safety profile. No unexpected adverse event was reported. The severity of adverse events, seriousness and treatment discontinuation showed a similar figure to that observed for the placebo. Liver acceptability of agomelatine was similar to placebo.

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Version of the report: Final version.