I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Abbreviated clinical study report**
Study title	**Response to VALDOXAN® and restoration of social rhythms in Major Depressive Disorder: VALDOXAN® D-Rhythm study. Interventional, phase-IV, multicentre clinical study** **VALDOXAN D-RHYTHM Study**
Study drug	**agomelatine (S20098)** **Valdoxan®**
Studied indication	**Major depressive episode according to DSM-IV-TR criteria**
Development phase	**Phase IV**
Protocol code	**DM4-20098-107**
Study initiation date	**10 October 2009**
Study completion date	**09 September 2010**
Main coordinator	[redacted]
Company / Sponsor	**LES LABORATOIRES SERVIER** **Euthérapie** **35 rue de Verdun** **92284 Suresnes**
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 12 September 2011**
Volume number	**No 1/1**
	~~CONFIDENTIAL~~

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2. SYNOPSIS

Name of Company: ***LES LABORATOIRES SERVIER*** *22 rue Garnier – 92200Neuilly-sur-Seine*	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: ***VALDOXAN® (France)***	**Volume:**	
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Title of study:

Response to VALDOXAN® and restoration of social rhythms in Major Depressive Disorder: VALDOXAN® D-Rhythm study. Interventional, phase-IV, multicentre clinical study.
Protocol No.: DM4-20098-107

National Coordinator: [redacted]

Study centres:

275 French hospital and community psychiatric centres – 187 centres having included at least one patient

Publication: not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 10 October 2009 Completion date: 09 September 2010	IV

Objectives:

The main objective of the study was to assess the relationship between restoration of social rhythms (SRM-II-5) and improvement of Major Depressive Disorder (QIDS-C16) in patients after 8 weeks of treatment with VALDOXAN®. This relationship was, in particular, assessed in patients presenting severe social dysfunction (SDS).

The secondary objectives were:

- To describe the impact of an early restoration (after 2 weeks) of social rhythms (SRM-II-5) on improvement of Major Depressive Disorder (according to QIDS-C16, QIDS-SR16 and CGI-I) in patients treated with VALDOXAN®, after 8 weeks of treatment.
- To describe the social rhythms (SRM-II-5 questionnaire) and sleep-wake rhythms (CSM) of patients at inclusion, according to their socio-demographic characteristics and duration and severity of depression.
- To describe the changes in sleep-wake rhythms (CSM) during treatment.
- To verify the psychometric characteristics of the French version of the QIDS-C16 questionnaire

With regard to the product's safety, the aim was to describe the safety of use and the tolerance profile of VALDOXAN® using reported adverse events, changes in vital signs (including weight and waist measurements), liver laboratory parameters and the number of premature withdrawals due to adverse events.

As part of an ancillary study, a sub-group of patients included by certain pre-selected centres was treated by psychotherapy in combination with VALDOXAN®. These centres were randomised to receive either Social Rhythm Therapy (SRT) or Intensive Clinical Management (ICM).

The principal aim of this ancillary study was to assess the benefit of additional patient care with SRT in comparison with ICM on improvement of depression (QIDS-C16), after 8 weeks of treatment with VALDOXAN®.

The secondary objectives of this ancillary study were:

- To compare the changes in social rhythms (SRM-II-5) in the 2 patient sub-groups (VALDOXAN® + SRT and VALDOXAN® + ICM) after 8 weeks of treatment.
- To compare the change in subjective treatment benefit (as rated by the patients: QIDS-SR16) in the 2 sub-groups (VALDOXAN® + SRT and VALDOXAN® + ICM) after 8 weeks of treatment.

The objective of the pharmaco-genetic profiles assessment was to identify any genetic factors that will enable a responder-patient profile and a predisposition to adverse events to be predicted.

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Methodology:

Interventional, national, phase-IV, multicentre, open-label, flexible-dose (VALDOXAN® 25 or 50 mg/day) study. Randomised, ancillary study, blinded to the type of psychotherapy, in a sub-group of patients.
Study performed in depressed outpatients according to DSM-IV-TR criteria for Major Depressive Episode, not treated on the day of inclusion, assessed over the course of 3 visits and 2 telephone calls:

- W0: inclusion visit and allocation of treatment - VALDOXAN® (1 x 25 mg tablet/day) was begun on the evening of the W0 visit. In the psychotherapy sub-group, patients visited the psychologist on D0 (or D1 or D2 or D3, at the latest)
- W1: telephone call to remind the patient to fill in SRM-II-5.
- W2: visit performed 14 ± 2 days after start of treatment with VALDOXAN® during which its dose may be increased to 50 mg/day, in the event of absence of symptoms improvement.
- W6: telephone call.
- W8: visit performed 56 ± 2 days after start of treatment with VALDOXAN®. At the end of visit W8, those patients who, in the investigator's opinion, had gained some therapeutic benefit (improvement in the symptoms, absence of troublesome adverse events) from the eight weeks of treatment, were proposed to participate in an extension study, if they wished to continue taking the treatment.

As part of the ancillary study, psychotherapy together with VALDOXAN® was offered to patients from certain pre-selected centres in order to assess its potential benefit. These centres were randomly assigned either to the specific psychotherapy (SRT) group or to a non specific psychotherapy (ICM) group corresponding to "placebo" therapy. The patients of these centres, if they agreed, were treated and followed up in the same way as the other patients and, in addition, received a specific (SRT) or non specific (ICM) psychotherapy.
The psychotherapy, irrespective of type, was performed in the form of weekly telephone calls during the W1 to W8 treatment period. These telephone calls were carried out by an independent psychologist. The investigator was not informed of the results of the randomisation in order to maintain the assessments blinded throughout the study.

Number of patients:

Planned: 1600 patients – Ancillary study: 400 patients (200 patients per group)
Selected: 900, Included: 898, Safety Set: 870, Full Analysis Set: 863
Ancillary study: Randomised: 287, Safety Set: 278, Full Analysis Set: 277

Diagnosis and main criteria for inclusion:

Inclusion criteria

- Demographic characteristics
  - Men or women
  - Aged 18 years or over
  - Outpatient follow-up
- Medical and therapeutic criteria
  - Presenting a major depressive episode (MDE) according to DSM-IV-TR criteria
    - single or recurring episode
    - with or without melancholy according to DSM-IV-TR criteria
    - without psychotic feature
    - without catatonic feature
    - having begun at least 2 weeks prior to inclusion
  - Requiring antidepressant treatment
  - Not treated with antidepressant on the day of the inclusion
  - Episode of moderate to severe intensity, with
    - a CGI-S severity score ≥ 4 (at least "moderately ill") and
    - a total QIDS-C16 score ≥ 16
- Informed consent: in compliance with ICH GCP and local regulatory requirements, the patients must have been informed verbally and in writing (information form) of the study procedures and have given their written consent to participate in the study.

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Diagnosis and main criteria for inclusion (cont'd)

Non-inclusion criteria

- General criteria
  - Refusal to sign the informed consent form.
  - Pregnant or breast-feeding woman.
  - Woman of childbearing age not using effective contraception (oral contraceptives, intra-uterine device, contraceptive implant or condoms).
  - Patient unlikely to cooperate fully in the study and/or be compliant, in the investigator's opinion.
  - Patient that is illiterate or incapable of understanding or filling in himself the self-assessment questionnaires.
  - Patient that is participating in another clinical trial simultaneously or having participated in a clinical trial in the 2 months prior to the inclusion visit or having already been included in this study.
  - Shift workers.
- Medical criteria
  - Patient reporting discontinuation symptoms that can be attributed to previous antidepressant treatment.
  - Patient presenting with bipolar disorder, schizoaffective disorder, acute or chronic psychosis, mental retardation, delirious state, dementia.
  - Patient dependent on alcohol or any other drug, except tobacco.
  - Patient not having responded to previous VALDOXAN® treatment.
  - Patient with known hypersensitivity to the active substance or any of the excipients of VALDOXAN®.
  - Patient with lactose intolerance (congenital galactosemia, lactase deficiency, glucose or galactose malabsorption syndrome).
  - Patient at a high risk of suicide in the investigator's opinion.
  - Patient with a known hepatic insufficiency (cirrhosis or progressive hepatic disease).
  - Patient with a known instable or severe somatic pathology that, in the investigator's judgement, has a high impact on the patient's daily life and that could interfere with his/her follow-up, including progressive morbid obesity.
- Therapeutic criteria
  - Concomitant treatment with a powerful CYP1A2 inhibitor (fluvoxamine: Floxyfral®; ciprofloxacin: Ciflox®).
  - Concomitant treatment with a non-selective irreversible monoamine oxidase inhibitor (MAOI).
  - ECT (Electro-Convulsive Therapy) in the 3 previous months or current need for ECT.
  - Light therapy started in the 2 weeks prior to inclusion.
  - Patient undergoing psychoanalytic psychotherapy or cognitive behavioural therapy or systemic therapy at a rate of at least one session per week (only for patients participating in the ancillary study).

Study drug:

Agomelatine 25 mg tablet (VALDOXAN®): 1 tablet per day, taken in the evening, with the possibility of increasing the dose to 50 mg per day (2 tablets taken in the evening), after two weeks of treatment, in the event of absence of improvement of symptoms.

Batch No. S05001

Reference product: *not applicable*

Duration of treatment: 8 weeks

Criteria for evaluation

Effectiveness criteria

Questionnaires used in the **main analysis**: SRM-II-5 (social rhythms) and QIDS-C16 (quick inventory of depressive symptomatology – clinician-rated).

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Criteria for evaluation (cont'd)
Effectiveness criteria (cont'd)
Questionnaires used in the analysis of **secondary criteria**:

- SRM-II-5 (social rhythms)
- QIDS-C16 (quick inventory of depressive symptomatology – clinician-rated) and QIDS-SR16 (patient's perception of the depressive symptomatology)
- CGI-I (global clinical improvement) and CGI-S (severity of the disease)
- CSM (wake/sleep rhythms) and SDS (social dysfunction)

Safety criteria: were the adverse events reported, the change in vital signs and liver function parameters.

Statistical methods:

Efficacy analyses were performed in the Full Analysis Set (all included patients having taken at least one dose of study treatment, and with at least one efficacy criterion available after inclusion visit) for analyses in the framework of the whole study, and in the Ancillary Full Analysis Set (all patients included in the ancillary study having taken at least one dose of study treatment and with at least one efficacy criterion available after inclusion visit) for the analyses in the framework of the ancillary study.

Main analysis: The Pearson correlation coefficient between QIDS-C16 total score and SRM-II-5 score was provided with the corresponding p-value at W8 and for last available value in W1-W8 period (provided that QIDS-C16 was not evaluated more than 2 weeks after SRM-II-5).
As secondary analyses, the same analysis was done in the FAS subgroups "Severe dysfunction at inclusion" (patients with SDS Social life score > 7 and SDS family life and home responsibilities score > 7, and SDS work score > 7 or not rated because the patient did not work/studied in the week before the visit for reasons unrelated to the depressive disorder) and "Very severe depression at inclusion" (QIDS-C16 total score ≥ 20).
Results were also provided in the FAS and in the FAS subgroups "Severe dysfunction at inclusion" and "Very severe depression at inclusion" without patients participating in ancillary study (sensitivity analysis).

Secondary criteria:

- In order to estimate the impact of the level of stability of social rhythms at W2 and the intensity and frequency of the symptoms of depression at W8 and last post-baseline visit, the Pearson correlation coefficients between SRM-II-5 score at W2 and QIDS-C16 total score, QIDS-SR16 total score and CGI-S at W8 and last post-baseline visit were provided.
- In the framework of the whole study, the evolution of secondary criteria during the W1-W8 period was analysed using a single mixed-effects repeated measured model (MMRM) incorporating a coefficient for week with an unstructured covariance matrix for the SRM-II-5 score, within-group comparisons (t-test or Wilcoxon signed-rank test) at W8 and last post-baseline evaluation for QIDS-C16, QIDS-SR16, CGI-S and SDS total score, non adjusted within-group comparisons (t-test or Wilcoxon signed-rank test) and comparisons adjusted on gender and age (covariance analysis) at W8 and last post-baseline evaluation for the CSM.
- In the framework of the ancillary study, SRT group was compared to ICM group using a single MMRM, including terms for effects of psychotherapy, week and an interaction term for psychotherapy and week, with an unstructured covariance matrix for SRM-II-5 score at each post-baseline week, a covariance analysis model including the baseline score value and the psychotherapy group and a non-adjusted analysis (t-test) for QIDS-C16 and QIDS-SR16 at W8 and last post-baseline evaluation, and within-group comparisons (t-test or Wilcoxon signed-rank test) at W8 and last post-baseline evaluation for the SDS total score.
- Psychometric characteristics of the French version of the QIDS-C16 questionnaire verified were: quality of completion (number and percentage of missing values), internal consistency (Cronbach alpha), construct validity (Pearson correlation coefficients each sub-scores and total score, Principal Component Analysis on the sub-scores), clinical validity (analysis of variance according to the model: QIDS-C16 total score = CGI-S), concurrent validity (Pearson correlation coefficients and corresponding p-values between QIDS-C16 and QIDS-SR16 total score and sub-scores) and responsiveness (QIDS16 total score and sub-scores in two subgroups defined according to CGI-I at last value using Student-t test).

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SUMMARY - CONCLUSIONS

Study population and outcome

Disposition of patients		**Ancillary study**		
	Overall study	**SRT**	**ICM**	**Total**
Selected	**900**	**144**	**143**	**287**
Included / Randomised (for ancillary study)	**898**	**144**	**143**	**287**
Withdrawn	**252** (1)	**35**	**34**	**69**
due to adverse event	96	12	10	22
due to consent withdrawal	77	12	9	21
due to lost to follow up	34	4	4	8
due to investigator's decision	43	7	11	18
due to unknown reason	2 (1)	0	0	0
Completed	**646**	**109**	**109**	**218**
Safety Set	**870**	**137**	**141**	**278**
Full Analysis Set (FAS)	**863**	**137**	**140**	**277**

(1) Including 2 patients with unknown status at the end of the study

Main baseline characteristics		**Included Set** (N = 898)
Age (years)	N	898
	Mean ± Std dev	47.0 ± 12.4
	Median (Min ; Max)	48.0 (18 ; 83)
Age in classes		
< 25 years	n (%)	42 (4.7 %)
[25 ; 45 [years	n (%)	316 (35.2 %)
[45 ; 60 [years	n (%)	421 (46.9 %)
[60 ; 75 [years	n (%)	106 (11.8 %)
≥ 75 years	n (%)	13 (1.4 %)
Gender	N	898
Female	n (%)	662 (73.7 %)
Smoking habit	N	898
Smoker	n (%)	335 (37.3 %)
Has stopped smoking	n (%)	73 (8.1 %)
Alcohol habit	N	897
Has stopped	n (%)	45 (5.0 %)
Yes	n (%)	153 (17.1 %)
History of previous MDE	N	898
	n (%)	596 (66.4 %)
Time since the first MDE (years)	N	890
	Mean ± Std dev	10.42 ± 10.95
	Median (Min ; Max)	7.12 (0.0 ; 49.9)
Number of previous MDE	N	856
	Mean ± Std dev	2.2 ± 3.5
	Median (Min ; Max)	1.0 (0 ; 50)
Family history of psychiatric disorders	n (%)	420 (46.9 %)
Current episode duration (months)	N	896
	Mean ± Std dev	16.86 ± 43.78
	Median (Min ; Max)	3.96 (0.0 ; 564.7)
Melancholic characteristics	n (%)	181 (20.2 %)
Psychotropic therapy (1) ongoing at inclusion	n (%)	631 (70.3 %)
Any significant medical or surgical history	n (%)	474 (52.8 %)
Co-morbidities	n (%)	351 (39.1 %)
Other treatments (2) ongoing at inclusion	n (%)	536 (59.7 %)

*(1) Drugs other than antidepressants or psychotherapy (psychotherapy:*19.2 % of the IS patients)
(2) Concomitant treatments other than psychotropics

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Study population and outcome (cont'd)

Baseline values for efficacy criteria			**Included Set** (N = 898)
SRM-II-5 total score [1]		N	499
		Mean ± Std dev	4.67 ± 1.42
		Median (Min ; Max)	4.80 (0.0 ; 7.0)
QIDS-C16 total score [2]		N	898
		Mean ± Std dev	19.0 ± 2.4
		Median (Min ; Max)	19.0 (8 ; 26)
Intensity of depression based on QIDS-C16 total score [2]	Score between 6 and 10	n (%)	1 (0.1 %)
	Score between 11 and 15	n (%)	23 (2.6 %)
	Score between 16 and 19	n (%)	507 (56.5 %)
	Score between 20 and 27	n (%)	367 (40.9 %)
Severe sleep disorders based on QIDS-C16 [3]		N	869
		n (%)	629 (72.4 %)
QIDS-SR16 total score [2]		N	694
		Mean ± Std dev	17.3 ± 4.5
		Median (Min ; Max)	18.0 (1 ; 27)
Intensity of depression based on QIDS-SR16 total score [2]	Score between 0 and 5	n (%)	10 (1.4 %)
	Score between 6 and 10	n (%)	46 (6.6 %)
	Score between 11 and 15	n (%)	151 (21.8 %)
	Score between 16 and 19	n (%)	260 (37.5 %)
	Score between 20 and 27	n (%)	227 (32.7 %)
Severe sleep disorders based on QIDS-SR16 [3]		N	697
		n (%)	496 (71.2 %)
Severity of illness score (CGI-S) [4]		N	898
		Mean ± Std dev	4.9 ± 0.6
		Median (Min ; Max)	5.0 (4 ; 7)
Composite Scale of Morningness total score [5]		N	815
		Mean ± Std dev	33.6 ± 7.3
		Median (Min ; Max)	34.0 (14 ; 55)
Composite Scale of Morningness total score in classes		N	815
	≤ 24	n (%)	92 (11.3 %)
	] 24 ; 43 [	n (%)	637 (78.2 %)
	≥ 43	n (%)	86 (10.6 %)
SDS Work / studies [6]		N	582
		Mean ± Std dev	6.8 ± 2.5
		Median (Min ; Max)	7.0 (0 ; 10)
SDS Social life [6]		N	874
		Mean ± Std dev	7.5 ± 2.0
		Median (Min ; Max)	8.0 (0 ; 10)
SDS Family life and Home responsibilities [6]		N	872
		Mean ± Std dev	7.2 ± 2.1
		Median (Min ; Max)	8.0 (0 ; 10)
SDS total score		N	582
		Mean ± Std dev	21.5 ± 5.6
		Median (Min ; Max)	22.0 (0 ; 30)
Severe dysfunction (SDS scores >7) [7]		N	870
		n (%)	302 (34.7 %)

(1) The SRM-II-5 score ranges between 0 (extremely disturbed social rhythms) and 7 (stable social rhythms)
(2) Intensity of depression according to QIDS-C16 and QIDS-SR16 total scores, which vary from 0 to 27: between 0 and 5: null, between 6 and 10: mild, between 11 and 15: moderate, between 16 and 19: severe, between 20 and 27: very severe.
(3) At least one score = 3 for sleep items 1, 2 or 3
(4) The CGI Severity scale varies from 1 (normal) to 7 (extremely ill)
(5) The CSM score ranges from 13 (extreme eveningness) to 55 (extreme morningness)
(6) Each SDS scores varies from 0 (no disruption) to 10 (extreme disruption).
(7) SDS Social life score and SDS family life and home responsibilities score > 7, and SDS work score > 7 or not rated because the patient did not work/study in the week before the visit for reasons unrelated to the depressive disorder.

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Study population and outcome (cont'd)

Treatments during the study

In the Included Set, the study treatment duration was 49.0 ± 17.0 days - median: 55 days with an excellent compliance. The dose of agomelatine was increased to 50mg/day for 31.7 % of the patients who continued the study treatment after W2 visit. 70.2 % of the patients received at least one concomitant psychotropic treatment during the study treatment period (anxiolytics: 51.2 %, hypnotics and sedatives: 24.2 %, antipsychotics: 5.7 %, psychotherapy: 19.2 %). At the end of the study, the rate of continuation of agomelatine was 60.0 % of the patients, the rate of replacement of agomelatine by another antidepressant 22.5 % of the patients and the rate of stop of any antidepressant 17.4 % of the patients.

Overall, **no clinically significant difference** was observed between the Included Set and the FAS, and between the FAS subgroups ("SDS Severe Dysfunction", "Very Severe Depression", sets of patients taken into account for main analysis at last evaluation or at W8 visit) and the FAS **for the main baseline characteristics**, including the baseline values for efficacy criteria, **and for the treatment during the study**.

Efficacy results

Correlation between the SRM-II-5 score and the QIDS-C16 total score

	Analysis	Main	Secondary		Sensitivity		
At last post-baseline evaluation [1]		**Full Analysis Set** (N = 863)	**SDS severe dysfunction** (N = 291)	**Very Severe Depression** (N = 348)	**FAS without AS*** **patients** (N = 586)	**SDS Severe Dysfunction without AS*** (N = 181)	**Very Severe Depression without AS*** (N = 213)
SRM-II-5 score	N	748	254	297	513	159	182
	Mean ± Std dev	4.8 ± 1.4	4.8 ± 1.5	4.7 ± 1.5	4.8 ± 1.4	4.7 ± 1.5	4.8 ± 1.5
	Median (Min ; Max)	5.0 (0 ; 7)	4.8 (0 ; 7)	4.8 (1 ; 7)	5.0 (0 ; 7)	4.8 (0 ; 7)	4.8 (1 ; 7)
QIDS-C16 score	N	748	254	297	513	159	182
	Mean ± Std dev	10.1 ± 5.7	11.1 ± 6.4	11.5 ± 6.3	10.3 ± 5.7	12.1 ± 6.3	12.2 ± 6.3
	Median (Min ; Max)	9.0 (0 ; 26)	10.0 (0 ; 26)	11.0 (0 ; 26)	10.0 (0 ; 26)	12.0 (0 ; 26)	12.0 (0 ; 26)
Pearson correlation coefficient		**-0.094**	**-0.162**	**-0.104**	**-0.082**	**-0.156**	**-0.087**
p-value (coeff=0)		**0.010**	**0.010**	**0.073**	**0.062**	**0.050**	**0.242**
At W8 [1]							
SRM-II-5 score	N	485	171	189	325	98	109
	Mean ± Std dev	4.97 ± 1.35	4.96 ± 1.38	4.90 ± 1.45	4.97 ± 1.37	4.94 ± 1.45	4.92 ± 1.50
	Median (Min ; Max)	5.20 (0 ; 7)	5.00(0.8 ; 7	5.00 (0.8 ; 7)	5.13 (0.8 ; 7)	4.80 (0.8 ; 7)	5.00 (0.8 ; 7)
QIDS-C16 score	N	485	171	189	325	98	109
	Mean ± Std dev	8.5 ± 5.0	9.3 ± 5.7	9.5 ± 5.6	8.9 ± 5.2	10.5 ± 6.1	10.5 ± 6.0
	Median	7.0 (0 ; 25)	8.0 (0 ; 25)	8.0 (0 ; 25)	8.0 (0 ; 24)	10.0 (0 ; 24)	10.0 (0 ; 24)
Pearson correlation coefficient		**0.006**	**-0.053**	**0.025**	**0.008**	**-0.077**	**0.014**
p-value (coeff=0)		**0.899**	**0.491**	**0.738**	**0.892**	**0.453**	**0.889**

(*) AS: Ancillary Study patients

(1) FAS restricted to patients with available QIDS-C16 score and SRM-II-5 score at last post-baseline evaluation / W8.

The **significant negative correlation between SRM-II-5 and QIDS-C16** observed **at last evaluation** showed that more the level of social rhythms was stable, more the depressive state was mild at the study end.

Secondary efficacy criteria

Correlation between SRM-II-5 at W2 and QIDS-C16 / QIDS-SR16 at W8 and last evaluation.

Correlation between SRM-II-5 at W2 and	QIDS-C16 total score at W8	QIDS-C16 total score at last evaluation	QIDS-SR16 total score at W8	QIDS-SR16 total score at last evaluation
N [*]	641	689	403	671
Pearson correlation coefficient	**-0.084**	**-0.089**	**-0.138**	**-0.146**
p-value (coeff=0)	**0.033**	**0.019**	**0.005**	**<0.001**

(*) FAS restricted to patients with available SRM-II-5 at W2 and available QIDS-C16 / QIDS-SR16 total score at W8 / last evaluation.

This **significant negative correlation between SRM-II-5 at W2 and QIDS-C16 and QIDS-SR16 at W8 and last evaluation** showed that more the level of social rhythms was stable at W2, more the intensity and frequency of the symptoms of depression were weak at the study end.

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Efficacy results (cont'd)

Analyses of the evolution of secondary criteria during the W1-W8 period showed a statistically **significant decrease of the intensity of the depression** (decrease of the QIDS-C16 total score, QIDS-SR16 total score and CGI-S score) and a statistically **significant improvement of the social rhythms** (increase of the SRM-II-5 score), of the **sleep-wake rhythms** (increase of the CSM score) and of **the impact of the disease on the daily activities** of the patient (decrease of the SDS total score).

With the exception of a higher rate of clinical response according to QIDS-SR16 at W8 in the SRT group (50.8 % of the patients) than in the ICM group (41.1 %), efficacy analyses showed no statistically or clinically significant difference in favour of the SRT psychotherapy. Given the differences in the characteristics and baseline values of the efficacy criteria between the two groups, it was not possible to interpret these results.

Safety results

Overall summary of the Safety results	**Safety set (N = 870)**	
At least one	**n**	**% (*)**
Emergent adverse event under treatment (1)	336	38.62
Emergent adverse event under treatment (1) treatment-related	197	22.64
Emergent adverse event under treatment (1) leading to study drug withdrawal	96	11.03
Severe emergent adverse event under treatment (1)	72	8.28
Emergent adverse event after treatment (2)	11	1.26
Nervous system disorder emergent under treatment (1)	112	12.87
Nervous system disorder emergent under treatment (1) and treatment-related	72	8.28
Nervous system disorder emergent under treatment (1) leading to study drug withdrawal	26	2.99
Psychiatric disorder emergent under treatment (1)	105	12.07
Psychiatric disorder emergent under treatment (1) and treatment-related	60	6.90
Psychiatric disorder emergent under treatment (1) leading to study drug withdrawal	59	6.78
Gastrointestinal disorder emergent under treatment (1)	97	11.15
Gastrointestinal disorder emergent under treatment (1) and treatment-related	71	8.16
Gastrointestinal disorder emergent under treatment (1) leading to study drug withdrawal	19	2.18
Events Requiring Immediate Notification (3) (ERIN) during the study	35	4.02
Emergent (4) ERIN	33	3.79
Emergent ERIN under treatment (1)	29	3.33
Emergent ERIN after treatment (2)	5	0.57
Emergent (4) death	0	0
Emergent (4) non-fatal ERIN	33	3.79
Emergent (4) psychiatric (5) ERIN	20	2.30
Emergent (4) Suicidal event with acting out	8	0.92
Emergent (4) Suicidal event with acting out treatment-related	0	0
Emergent (4) Suicidal event with acting out related to lack of efficacy	2	0.23
Hospitalisation for emergent (4) aggravation of depression	8	0.92
Hospitalisation for emergent (4) aggravation of depression treatment-related	0	0
Hospitalisation for emergent (4) aggravation of depression related to lack of efficacy	3	0.34
Hepatic disorder with transaminases increase (6)	15	1.72
Emergent (4) hepatic disorder with transaminases increase	7	0.81
Emergent (4) hepatic disorder with transaminases increase treatment-related	4	0.46

(1) which occurred between the first study drug intake and the last study drug intake + 1 day or which occurred before the first study drug intake and which worsened or became serious between the first study drug intake and the last study drug intake + 1 day.

(2) all adverse events which occurred after the last study drug intake + 1 day or which occurred between the first study drug intake and the last study drug intake + 1 day and which worsened or became serious after the last study drug intake + 1 day.

(3) ERIN included SAE and increase of transaminases higher than 3 ULN at two successive determinations, suicide attempt without seriousness criterion, pregnancy and overdose.

(4) Event which occurred after the first study drug intake without limit of time after the last study drug intake

(5) MedDRA SOC "Psychiatric disorders" and MedDRA PT "Intentional overdose"

(6) MedDRA PT: hepatitis, transaminases increased, alanine aminotransferase increased

Name of Company: ***LES LABORATOIRES SERVIER*** *22 rue Garnier – 92200Neuilly-sur-Seine*	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: ***VALDOXAN® (France*)**	**Volume:**	
Name of Active Ingredient: ***agomelatine (S20098)***	**Page:**	

Safety results (cont'd)

No clinically significant change in systolic and diastolic blood pressure, heart rate, weight, body mass index and abdominal perimeter was observed at W2, W6 and last post-baseline evaluation.

CONCLUSION

In this study, of which the main objective was to assess the relationship between restoration of social rhythms (SRM-II-5) and improvement of Major Depressive Disorder (QIDS-C16) after 8 weeks of treatment with Valdoxan®, a statistically significant negative correlation was showed between the SRM-II-5 score and the QIDS-C16 at last post-baseline evaluation and between the SRM-II-5 at W2 and the QIDS-C16 and QIDS-SR16 at W8 and last post-baseline evaluation. More the level of social rhythms was stable, more the depressive state was mild at the end of the study.

Analysis of secondary efficacy criteria showed a global improvement of patients' status, an improvement of depressive symptoms, a decrease of the impact of the disease on daily activities and an improvement of the social rhythms (evaluated by the SRM-II-5) and sleep-wake rhythms (assessed by the CSM). Overall, efficacy results tended to be better in the patients whose sleep-wake rhythm was "Morningness" and less good in the patients whose sleep-wake rhythm was "Eveningness".

The nature and the frequency of emergent adverse events were in accordance with the safety profile of agomelatine. Most frequent emergent adverse events were nervous system disorders (12.9 %), psychiatric disorders (12.1 %) and gastrointestinal disorders (11.2 %). Emergent events requiring immediate notification were reported in 3.8 % of the patients. The most frequent of these events were psychiatric disorders (2.3 %), mainly hospitalisations for aggravation of depression (0.9 %), or anxiety (0.6 %), and suicidal events with acting out (0.9 % - 8 suicide attempts). Emergent hepatic disorders with transaminases increase were observed in 0.8 % of the patients.

Date of the report: 12 September 2011