Document title	**Abbreviated clinical study report**
Study title	**Clinical long-term effects of Valdoxan® (25 or 50 mg) in depressed patients. Clinical, national, interventional, phase IV, multicentre, open study.** **Valdoxan® D-EXTENSION Study**
Study drug	**Agomelatine (S20098)** **Valdoxan®**
Studied indication	**Major depressive episode according to DSM-IV-TR criteria**
Development phase	**Phase IV**
Protocol code	**DM4-20098-112**
Study initiation date	**02 June 2009**
Study completion date	**13 October 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 25 November 2011**
Volume number	**N1/1**
	~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: ***LES LABORATOIRES SERVIER***	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: Clinical long-term effects of Valdoxan® (25 or 50 mg) in depressed patients. Clinical, national, interventional, phase IV, multicentre, open study. Valdoxan® D-EXTENSION Study
Protocol No.: DM4-20098-112

National Coordinator: [redacted]

Study centre*(s)*:
714 French psychiatry centres (hospital or private practice) having participated in the Valdoxan® D-Change or D-Rhythm studies – 641 centres having included at least one patient in D-Extension study

Publication: not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 02 June 2009 Completion date: 13 October 2010	IV

Objective:
The objective was to **evaluate the clinical long-term effects of Valdoxan®** (25 or 50 mg/day) in the patients having participated in the Valdoxan® D-Change or D-Rhythm study, using:

- For efficacy, the documentation provided by:
  - CGI-I (Clinical Global Impression-Improvement) scale - for the evaluation of the patients' clinical condition by the clinician.
  - CGI-EI (Clinical Global Impression-Efficacy Index) scale - for the therapeutic effect/side effects ratio.
  - The PGI-I (Patient Global Impression of Improvement) self-administered questionnaire - for the patient's own evaluation of his/her condition.
  - The QIDS-C (Quick Inventory of Depressive Symptomatology by Clinician) for measurement of MDE symptoms by the clinician.
- For safety, the additional clinical and biological descriptive data.

Methodology:
National, multicentre, interventional, phase-IV open extension study, at variable doses (25 or 50 mg/day of Valdoxan®).
This study ensured the continuation of Valdoxan® treatment in patients who derived a therapeutic benefit during the acute phase of their Major Depressive Episode (MDE). The duration of Valdoxan® treatment was determined by the investigator for each patient. It covered the consolidation phase and, if necessary, the MDE-treatment maintenance phase according to the antidepressant prescription guidelines issued by AFSSAPS ("*Bon usage des médicaments antidépresseurs dans le traitement des troubles dépressifs et des troubles anxieux de l'adulte* [Proper usage of antidepressant medicinal products in the treatment of depressive disorders and anxiety disorders in adults] – October 2006") and the French National Authority for Health (HAS) ("*Prise en charge des complications évolutives d'un épisode dépressif caractérisé de l'adulte*" [Treatment of progressive complications of a major depressive episode in adults] – HAS – April 2007").
The investigator adjusted the frequency of consultations according to the clinical condition of the patient and to his/her usual practice taking into account the following four visits stipulated in the protocol:

- Inclusion visit **(V1)**, to be performed on the day of the final visit for the Valdoxan® D-Change or D-Rhythm study. After informing the patient and the signature of a new consent form, the Valdoxan® treatment (25 or 50 mg/day) was given to the patient.
- The **V2** visit enabled evaluation of the clinical effects of Valdoxan® after 12 to 14 weeks of treatment,
- The **V3** visit enabled evaluation of the clinical effects of Valdoxan® after 24 to 26 weeks of treatment,
- The End-of-study visit **(VEnd)** was performed at the end of treatment (normal end of MDE treatment or premature withdrawal) or at the marketing of Valdoxan® in France.

Valdoxan® dosage: at the V1, V2 and V3 consultations, the investigator was able to modify the prescribed dosage if he/she considered it clinically necessary.

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Number of patients:
Planned: 4480 patients (80% of patients expected in the Valdoxan D-Change and D-Rhythm studies).
Selected: 2815 (patients who completed normally D-Change or D-Rhythm study) - **Included**: 2044

Diagnosis and main criteria for inclusion:

Inclusion criteria

- Men or women, 18 years old or older, treated on an outpatient basis
- Having been included in the Valdoxan® D8Change study (protocol DM4-20098-108) or Valdoxan® D-Rhythm (protocol DM4-20098-107) in compliance with the inclusion and non-inclusion criteria.
- Having fully completed the Valdoxan® D-Change or D-Rhythm study.
- Having derived a therapeutic benefit, according to the investigator's assessment, from the Valdoxan® treatment.
- With laboratory test results at 6 weeks of Valdoxan® treatment compatible with its continuation.
- Wishing to continue the treatment.

Non-inclusion criteria

In general, patients for whom one of the non-inclusion criteria of the D-Change or D-Rhythm study would recently have been diagnosed.

- Patients presenting a psychiatric disorder associated with the MDE (bipolar disorders, schizoaffective disorders, acute psychosis, delusional state) or alcohol or drug-dependence, discovered after inclusion in the Valdoxan® D-Change or D-Rhythm study.
- Patients having presented hypersensitivity to agomelatine or to one of the excipients of Valdoxan® during the Valdoxan® D-Change or D-Rhythm study.
- Patients presenting a contraindication to agomelatine treatment, discovered after inclusion in Valdoxan® D-Change or D-Rhythm study:
  - Lactose intolerance (congenital galactosemia, lactase deficiency, glucose and lactose malabsorption syndrome),
  - Hepatic insufficiency (cirrhosis or ongoing hepatic disease).
- Patients requiring the administration of a forbidden treatment:
  - Other antidepressant treatment,
  - Other psychotropic treatment apart from an anxiolytic-hypnotic treatment,
  - Potent CYP1A2 inhibitors (fluvoxamine: Floxyfral®; ciprofloxacin: Ciflox®).
  - Unstable or severe somatic pathology which, according to the investigator's opinion, has a major impact on the patient's daily life and which may interfere with the patient's follow-up.
- General criteria:
  - Refusal to sign the informed consent form,
  - Pregnant or breast-feeding woman,
  - Woman of childbearing age without effective contraception (oral contraceptive agents, intrauterine device, contraceptive implant or condoms),
  - Patient unlikely to cooperate fully in the study and/or be compliant,
  - Patient having already been included in the study.

Study drug: agomelatine 25 mg tablet (Valdoxan): 1 or 2 tablets daily taken at bedtime.
Batch No. S01010 and S03008

Reference product: *not applicable*

Treatment duration: According to the investigator's assessment, at most until the marketing of Valdoxan® in France.

Criteria for evaluation:

Effectiveness criteria:

- CGI-I (Clinical Global Impression of Improvement) scale
- PGI-I (Patient Global Impression of Improvement) scale
- CGI-EI Efficacy Index, which is an assessment of the therapeutic effect and side effects of the treatment that enables the therapeutic effect/side effect ratio to be calculated.
- The QIDS-C (Quick Inventory of Depressive Symptomatology – Clinician-rated), which evaluates the intensity of the 9 symptoms listed in the DSM-IV-TR diagnostic criteria for MDE.

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Criteria for evaluation (cont'd)

Safety criteria:

The safety of Valdoxan® was assessed based on the adverse events reported, the evolution of the vital signs and hepatic biological parameters.

Statistical methods:

Efficacy criteria were analysed in the Full Analysis Set (all patients included in D-Change study (DM4-20098-108) or in D-Rhythm study (DM4-20098-107) having taken at least one dose of study treatment, and with at least one efficacy criterion available after inclusion visit).

Evolution of the CGI-I score during the W2-VEnd period was estimated using a mixed-effects repeated measured model (MMRM) with an unstructured covariance matrix, incorporating a coefficient for visit and a coefficient for first study (D-Change or D-Rhythm) and evolution of QIDS-C16 total score during W2-VEnd using the same model incorporating in addition a coefficient for baseline value. Analysis of other efficacy criteria was descriptive.

Efficacy criteria were also analysed in the FAS subgroups of age ("age ≥ 60 years", "age ≥ 65 years" and "age ≥ 75 years"), 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), "Very severe depression at inclusion" (QIDS-C16 total score ≥ 20), and, for CGI-I and PGI-I in 3 subgroups of therapeutic situation ("Treatment initiation": patients having received no antidepressant treatment during the two months preceding the first study drug intake, "Treatment change": patients having stopped their previous antidepressant treatment between 3 days before and 3 days after the first study drug intake date, "Wash-out": patients having received an antidepressant treatment during the two months preceding the first study drug intake).

Safety criteria were analysed in the Safety Set (all patients included in D-Change study (DM4-20098-108) or in D-Rhythm study (DM4-20098-107) having taken at least one dose of study treatment) and in the 3 subgroups of age.

SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients	**All patients**	**D-Change patients**	**D-Rhythm patients**
Selected	**3843**	**2943**	**900**
Included	**3836**	**2938**	**898**
Withdrawn [(1)] due to	**1021**	**769**	**252**
adverse event	527	431	96
consent withdrawal	253	176	77
lost to follow up	122	88	34
Investigator's decision	109	66	43
unknown reason [(1)]	10	8	2
Completed = Selected for D-Extension	**2815**	**2169**	**646**
Included in D-Extension	**2044**	**1655**	**389**
Withdrawn [(2)] due to	**600**	**528**	**72**
adverse event	148	130	18
consent withdrawal	118	103	15
lost to follow up	117	106	11
modification of antidepressant treatment	202	175	27
other reason	9	9	0
unknown reason [(2)]	6	5	1
Marketed Valdoxan® continued	**1124**	**845**	**279**
End of treatment of MDE	**320**	**282**	**38**
Safety Set	**3722**		
Full Analysis Set (FAS)	**3643**		

(1) Including patients with unknown status at the end of D-Change or D-Rhythm study.

(2) Including patients with unknown status at the end of D-Extension study.

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SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME (CONT'D)

Baseline characteristics		**Included Set** (N = 3836)
Age (years)	N	3830
	Mean ± Std dev	46.9 ± 12.5
	Median (Min ; Max)	47.0 (17 ; 90)
Age in classes		
< 25 years	n (%)	162 (4.2 %)
[25 ; 45 [years	n (%)	1438 (37.5 %)
[45 ; 60 [years	n (%)	1662 (43.4 %)
[60 ; 75 [years	n (%)	514 (13.4 %)
≥ 75 years	n (%)	54 (1.4 %)
Gender	N	3835
Female	n (%)	2628 (68.5 %)
Smoking habit	N	3835
Smoker	n (%)	1269 (33.1 %)
Has stopped smoking	n (%)	302 (7.9 %)
Alcohol habit	N	3834
Yes	n (%)	565 (14.7 %)
Has stopped	n (%)	169 (4.4 %)
History of previous MDE	N	3833
	n (%)	2671 (69.7 %)
Time since the first MDE (years)	N	3795
	Mean ± Std dev	9.61 ± 10.61
	Median (Min ; Max)	5.99 (0.0 ; 62.2)
Number of previous MDE	N	3649
	Mean ± Std dev	2.0 ± 3.0
	Median (Min ; Max)	1.0 (0 ; 50)
Current episode duration (months)	N	3823
	Mean ± Std dev	10.77 ± 25.87
	Median (Min ; Max)	3.94 (0.0 ; 564.7)
Current episode duration in classes		
< 3 months	n (%)	1594 (41.7 %)
[3 ; 6 [months	n (%)	805 (21.1 %)
[6 ; 12 [months	n (%)	652 (17.1 %)
[12 ; 24 [months	n (%)	416 (10.9 %)
≥ 24 months	n (%)	356 (9.3 %)
Psychotropic therapy (1) ongoing at inclusion	n (%)	2649 (69.1 %)
Any significant medical or surgical history	n (%)	1664 (43.4 %)
Other concomitant treatments (2) ongoing at inclusion	n (%)	2125 (55.4 %)

(1) Psychotherapy and drugs other than antidepressants (psychotherapy: 30.24 % of the IS patients).
(2) Concomitant treatments other than psychotropic drugs ongoing at inclusion.

No clinically significant difference was observed between the Included Set and the FAS for main baseline characteristics

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SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME (CONT'D)

Baseline values for efficacy criteria		Included Set (N = 3836)
CGI-Severity of illness score (1)	N	3834
	Mean ± Std dev	4.9 ± 0.6
	Median	5.0
	Min ; Max	3 ; 7
QIDS-C Total score (2)	N	3830
	Mean ± Std dev	18.9 ± 2.4
	Median	19.0
	Min ; Max	4 ; 27
Intensity of the depression according to QIDS-C total score	N	3830
Nil (score 0 to 5)	n (%)	1 (0.0 %)
Mild (score 6 to 10)	n (%)	4 (0.1 %)
Moderate (score 11 to 15)	n (%)	68 (1.8 %)
Severe (score 16 to 20)	n (%)	2320 (60.6 %)
Very severe (score 21 to 27)	n (%)	1437 (37.5 %)
Severity of sleep disorders according to QIDS-C (3)	N	3452
	n (%)	2568 (74.4 %)
SDS Work/studies (4)	N	2441
	Mean ± Std dev	6.9 ± 2.5
	Median	7.0
	Min ; Max	0 ; 10
SDS Social life (4)	N	3667
	Mean ± Std dev	7.4 ± 2.1
	Median	8.0
	Min ; Max	0 ; 10
SDS Family life and Home responsibilities (4)	N	3664
	Mean ± Std dev	7.1 ± 2.2
	Median	7.0
	Min ; Max	0 ; 10
Severe dysfunction according to SDS (5)	N	3638
	n (%)	1195 (32.8 %)

(1) CGI Severity score is from 1 (normal) through to 7 (extremely ill).

(2) The QIDS-C comprises 16 questions to rate the 9 symptoms included in the diagnostic criteria for an MDE in DSM-IV-TR. Each of the 16 items is rated from 0 (symptom absent) to 3 (maximum intensity/frequency). The total score is obtained by adding the highest score for the 4 items exploring sleep, the highest score for the 4 items exploring weight and appetite, the highest score for the 2 items exploring psychomotor agitation and the scores for the other 6 items (Mood, Concentration / Decision Making, Self image, Suicidal Ideation, Involvement in activities, Energy/fatigability). It varies from 0 to 27.

(3) Severity of sleep disorders: at least one score = 3 for item 1, 2 or 3.

(4) Each SDS score varies from 0 (no disruption) to 10 (extreme disruption).

(5) 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 for reasons unrelated to the depressive disorder.

No clinically significant difference was observed between the Included Set and the FAS for the baseline values of efficacy criteria

Study treatment

The study treatment duration, known for 3427 patients in the Included Set and for 3385 patients in the Safety Set, was similar in both populations: 111.0 ± 99 days (median: 71 days) in the IS and 112.3 ± 98.8 days (median: 75 days) in the Safety Set. Global compliance was similar in the Included Set and Safety Set. During the period W0-W6/W8, only 4.4 % of the 3582 patients with available observance in the Included Set and 3.3 % of the 3540 patients with available observance in the Safety Set took less than 70 % of the total dose they should have taken. During D-Extension period, 94.3 % of the patients with available observance took their treatment regularly at M3, 93.5% of them at M6 and 94.7% at VEnd.

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SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME (CONT'D)

Antidepressant therapy at the end of the study

At the end of the first study (D-Change or D-Rhythm), the rate of continuation of agomelatine (i.e. inclusion in D-Extension study or prescription of the commercial form when available) was 63.0 % of the patients in the Included Set and 63.9 % in the Safety Set. The rate of replacement of agomelatine by another antidepressant was the same in both populations: 22.5 % of the patients. And, the stop of any antidepressant was decided for 14.4 % of the patients in the Included Set and 13.7% in the Safety Set. At the end of D-Extension study, 66.3% of the patients included in D-Extension study continued agomelatine (i.e. prescription of the marketed form), when the stop of any antidepressant therapy was decided for 19.0% and the modification of the therapy occurred for 14.7% of the patients.

EFFICACY RESULTS

CGI-Improvement score (*)		**Full Analysis Set** (N = 3643)
At W2	N	3629
	Mean ± Std dev	3.1 ± 1.1
	Median (Min ; Max)	3.0 (1 ; 7)
At W6/W8	N	3164
	Mean ± Std dev	2.6 ± 1.2
	Median (Min ; Max)	2.0 (1 ; 7)
At M3	N	1924
	Mean ± Std dev	2.3 ± 1.1
	Median (Min ; Max)	2.0 (1 ; 7)
At M6	N	1424
	Mean ± Std dev	2.2 ± 1.1
	Median (Min ; Max)	2.0 (1 ; 7)
At VEnd	N	705
	Mean ± Std dev	2.0 ± 1.1
	Median (Min ; Max)	2.0 (1 ; 7)
At last value	N	3634
	Mean ± Std dev	2.8 ± 1.4
	Median (Min ; Max)	2.0 (1 ; 7)
Statistical analysis (1)	p-value : visit	**<0.001**
	p-value : 1st study	0.062

(*) CGI-I score varies from 1 = "considerably improved" to 7 = "considerably worse"

(1) p-values associated to the fixed effects: Visit and First study (D-Change / D-Rhythm) in a Mixed Model with Repeated Measures (unstructured covariance matrix) with visit and first study as covariates.

Clinical response according to CGI-Improvement score (*)		**Full Analysis Set** (N = 3643)
At W2	N	3629
	n (%)	1222 (33.7 %)
At W6/W8	N	3164
	n (%)	1886 (59.6 %)
At M3	N	1924
	n (%)	1394 (72.5 %)
At M6	N	1424
	n (%)	1103 (77.5 %)
At VEnd	N	705
	n (%)	564 (80.0 %)
At last value	N	3634
	n (%)	1895 (52.1 %)

(*) Clinical response: CGI-I score ≤ 2 = "considerably improved" or "obviously improved"

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EFFICACY RESULTS (CONT'D)

QIDS-C16 total score (*)		**Full Analysis Set** (N = 3643)
At W0	N	3642
	Mean ± Std dev	18.9 ± 2.4
	Median	19.0
	Min ; Max	4 ; 27
At W2	N	3561
	Mean ± Std dev	13.2 ± 5.0
	Median	14.0
	Min ; Max	0 ; 27
At W6/W8	N	3090
	Mean ± Std dev	9.6 ± 5.4
	Median	9.0
	Min ; Max	0 ; 27
At M3	N	131
	Mean ± Std dev	7.9 ± 6.0
	Median	6.0
	Min ; Max	0 ; 22
At M6	N	623
	Mean ± Std dev	6.6 ± 4.9
	Median	5.0
	Min ; Max	0 ; 24
At VEnd	N	299
	Mean ± Std dev	5.6 ± 4.6
	Median	4.0
	Min ; Max	0 ; 22
At last post-baseline value	N	3571
	Mean ± Std dev	10.0 ± 6.1
	Median	9.0
	Min ; Max	0 ; 27
Change from baseline	Mean ± Std dev	-8.8 ± 6.1
	Median	-9.0
	Min ; Max	-27 ; 12
Statistical analysis (1)	p-value: visit	**<0.001**
	p-value: 1st study	**0.003**
	p-value: baseline score	**<0.001**

(*) QIDS-C16 total score varies from 0 ("no depression") to 27

(1) p-values associated to the fixed effects: Visit, First study (D-Change / D-Rhythm) and Baseline score in a Mixed Model with Repeated Measures (unstructured covariance matrix) on the change from baseline at each post-baseline visit with visit, first study and baseline score as covariates.

Clinical response according to QIDS-C16 total score (*)		**Full Analysis Set** (N = 3643)
At W2	N (1)	3561
	n (%)	876 (24.6 %)
At W6/W8	N (1)	3090
	n (%)	1713 (55.4 %)
At M3	N	131
	n (%)	87 (66.4 %)
At M6	N	623
	n (%)	484 (77.7 %)
At VEnd	N	299
	n (%)	242 (80.9 %)
At last post-baseline value	N	3571
	n (%)	1872 (52.4 %)

(*) Clinical response: decrease ≥ 50 % in the QIDS-C16 total score

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EFFICACY RESULTS (CONT'D)

Evolutions of the mean PGI-I score and of the rate of clinical response according to PGI-I score, available during the whole study in D-Change patients and only during D-Extension period in D-Rhythm patients, were similar to those of the CGI-I score and CGI-I response rate. A decrease of the impact of the disease on daily activities was showed by the decrease of the mean SDS scores, available only during the first study, and the decreasing rate of patients with severe dysfunction (32.9% at W0, 19.7% at W2, 15.6% at W6/W8 and 17.6% at last post baseline value).

No clinically significant difference between the FAS overall and the two FAS subgroups "SDS severe dysfunction" and "Very Severe Depression" was observed for the evolution of efficacy criteria.

Efficacy results were slightly less good in the three subgroups of age than in the FAS (rate of CGI-I response at last value: 43.9%, 42.7% and 40.4% respectively in subgroups "age≥ 60 years" (n=544), "age≥ 65 years (n=255) and "age≥ 75 years" (n=52) - rate of QIDS-C response: 47.1% in subgroup "age ≥ 60 years", 42.2% in subgroup "age ≥ 65 years" and 32.0 % in subgroup "age ≥ 75 years").

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SAFETY RESULTS

Overall summary of safety results	**Safety set (N = 3722)**	
At least one	**n ***	**% ***
Adverse event emergent under treatment (1)	1703	45.75
Adverse event emergent under treatment (1) and treatment-related	1089	29.26
Adverse event emergent under treatment (1) leading to study drug withdrawal	679	18.24
Severe adverse event emergent under treatment (1)	520	13.97
Adverse event emergent after treatment (2)	47	1.26
Psychiatric disorders emergent under treatment (1)	597	16.04
Psychiatric disorders emergent under treatment (1) and treatment-related	333	8.95
Psychiatric disorders emergent under treatment (1) leading to study drug withdrawal	330	8.87
Gastrointestinal disorder emergent under treatment (1)	510	13.70
Gastrointestinal disorder emergent under treatment (1) and treatment-related	389	10.45
Gastrointestinal disorder emergent under treatment (1)leading to study drug withdrawal	171	4.59
Nervous system disorders emergent under treatment (1)	489	13.14
Nervous system disorders emergent under treatment (1) and treatment-related	359	9.65
Nervous system disorders emergent under treatment (1) leading to study drug withdrawal	145	3.90
Event Requiring Immediate Notification (ERIN) during the study	212	5.70
Emergent (3) ERIN	201	5.40
Emergent (3) fatal ERIN	3	0.08
Emergent (3) non-fatal ERIN	198	5.32
Emergent (3) psychiatric ERIN	116	3.12
Emergent (3) Suicidal event with acting out (4)	36	0.97
Emergent (3) Suicidal event with acting out treatment-related	0	0
Emergent (3) Suicidal event with acting out related to lack of efficacy	9	0.24
Emergent (3) aggravation of depression with hospitalisation	57	1.53
Emergent (3) aggravation of depression with hospitalisation treatment-related	1	0.03
Emergent (3) aggravation of depression with hospitalisation related to lack of efficacy	21	0.56
Hepatic disorder with transaminases increase (5)	66	1.77
Emergent (3) hepatic disorder with transaminases increase	52	1.40
Emergent (3) hepatic disorder with transaminases increase treatment-related	33	0.89

(*) n = number of patients with at least one AE - % = n/N

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

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

(3) Emergent adverse event: adverse event which occurred after the first study drug intake date or which occurred before the first study drug intake date and worsened or became serious after the first study drug intake date, without limit of time after the last study drug intake.

(4) emergent suicidal events with acting out: completed suicide (2 patients), suicide attempt (30 patients), intentional overdose (4 patients).

(5) MedDRA PT: hepatitis, hepatic steatosis, cytolytic hepatitis, hepatitis C, transaminases increased, alanine aminotransferase increased

SUMMARY - CONCLUSIONS

SAFETY RESULTS (CONT'D)

No clinically significant change in mean systolic and diastolic blood pressure, mean heart rate, mean weight and mean body mass index was observed during the study.

No clinically significant difference between the subgroups of age and the Safety Set overall was observed for adverse events emergent during treatment period, emergent adverse events treatment-related, emergent adverse events leading to study drug withdrawal, severe adverse events emergent during treatment period, adverse events emergent after treatment and the time to onset of the first emergent adverse event. The rate of serious adverse event emergent during the treatment period was slightly greater in the three subgroups of age (5.4 % for the subgroup "age ≥ 60 years", 6.1 % for the subgroup "age ≥ 65 years" and 7.6 % for the subgroup "age ≥ 75 years") than in the Safety Set overall (4.2 %), due to the occurrence of concomitant diseases or complications of concomitant illnesses.

Name of Company: ***LES LABORATOIRES SERVIER***	**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:**	

CONCLUSION

This study, of which the main objective was to evaluate the clinical long-term effects of Valdoxan® (25 or 50 mg/day), concerned the 3843 patients selected for the studies D-Change and D-Rhythm, among whom 3836 patients were included in one of these two short-term studies and 2044 patients in D-Extension study. The mean treatment duration was 16 weeks. Analyses of efficacy criteria showed a global improvement of the patient's status and a decrease of the intensity of depression and of the impact of the disease on daily activities as well as a good benefit/risk ratio during the whole study. Overall, efficacy results tended to be a little less good in elderly, but have not been influenced by the intensity of the depression or the impact of the disease on daily activities.

The nature and the frequency of emergent adverse events were in accordance with the safety profile of agomelatine. Most frequent emergent adverse events were psychiatric disorders (16.0 % of the patients), gastrointestinal disorders (13.7 % of the patients) and nervous system disorders (13.1 %). Emergent serious adverse events were reported in 5.4 % of the patients and emergent hepatic disorders with transaminases increase in 1.4 % of the patients. Most frequent emergent serious adverse events were psychiatric disorders (3.1 %), mainly hospitalisations for aggravation of depression (1.5 %), or anxiety (0.5 %), and suicidal events with acting out (1.0 % - 2 suicides, 30 suicide attempts, 4 intentional overdoses). In elderly, frequency of emergent adverse events was similar to that in the whole population; emergent serious adverse events were a little more frequent due to the occurrence of concomitant old-age diseases.

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