I.R.I.S.
INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Abbreviated clinical study report**
Study title	**Clinical efficacy of VALDOXAN in everyday practice conditions (efficiency) in depressed patients, on a treatment-naive or switch basis. Phase-IV, multicentre, open, interventional clinical study.** **VALDOXAN D-CHANGE Study**
Study drug	**agomelatine (S20098)** **Valdoxan®**
Studied indication	**Major depressive episode according to DSM-IV-TR criteria**
Development phase	**Phase IV**
Protocol code	**DM4-20098-108**
Study initiation date	**20 April 2009**
Study completion date	**04 August 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 30 September 2011**
Volume number	**No. 1/1**
	~~CONFIDENTIAL~~

2. SYNOPSIS

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Title of study: Clinical efficacy of VALDOXAN in everyday practice conditions (efficiency) in depressed patients, on a treatment-naive or switch basis. Phase-IV, multicentre, open, interventional clinical study. VALDOXAN D-CHANGE Study
Protocol No.: DM4-20098-108

National Coordinator: [redacted]

Study centre*(s)*
852 French hospital and community psychiatric centres – 620 centres having included at least one patient

Publication: Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 20 April 2009 Completion date: 04 August 2010	IV

Objectives:

The main objective of the study was to describe the efficiency of Valdoxan after 6 weeks of treatment, in different therapeutic situations (change of treatment (switch) or initiation of treatment) and in different patient sub-groups defined by the class of previous antidepressant (imipraminic, selective serotonin reuptake inhibitor, serotonin and noradrenaline reuptake inhibitor, mirtazapine/mianserine, other antidepressant), using a composite criterion of the clinical response, established on the basis of 4 assessment criteria: CGI-I (Clinical Global Impression-Improvement scale), PGI-I (Patient Global Impression-Improvement scale) (protocol appendix 3), LSEQ (Leeds Sleep Evaluation Questionnaire), and the patient's willingness to continue the study treatment.

The secondary objectives were

- To describe the efficiency of Valdoxan after 6 weeks of treatment, in the different sub-groups of therapeutic situations and previous treatment sub-groups, using this composite evaluation of the clinical response as a function of the following factors
  - the intensity of the depression at inclusion,
  - the intensity of sleep disorders at inclusion,
  - the Body Mass Index (BMI),
  - the number of previous episodes of major depression,
  - the extent of the impact of the disorder on daily activities,
  - the presence of undesirable side effects of the previous treatment at inclusion
  - the reason for stopping the previous antidepressant treatment.
- To describe the efficiency of Valdoxan after 6 weeks of treatment, in the different therapeutic situations and previous treatment sub-groups, analysing separately the four criteria that constitute the composite main criterion (CGI-I, PGI-I, LSEQ and the patient's willingness to continue the study treatment), as a function of the factors described above.
- To describe the effects of Valdoxan treatment on the impact of the illness on the patient's daily activities (work, social life - leisure activities, family life - domestic tasks) in the different sub-groups, using the SDS questionnaire (Sheehan Disability Scale).
- To describe the effects of Valdoxan treatment on the patient's mood in the different sub-groups, using the MAThyS scale (Multidimensional Assessment of Thymic State) and 2 visual analogue scales (one measuring the patient's mood, and the other how (s)he experiences any side effects of the treatment), as a function of the change in symptoms, assessed using the QIDS-C scale (Quick Inventory of Depressive Symptomatology - Clinician rating).
- To investigate the timing and the nature of the improvement obtained, using the CGI-EI (Clinical Global Impressions - Efficacy Index).
- To record the socioeconomic data: number of days of sick leave, number of days of hospitalisation, nature and duration of the concomitant psychotropic treatments (anxiolytics, hypnotics).

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Objectives (cont'd)

- To describe the safety of use and tolerance profile of Valdoxan from the adverse events reported, the change in the vital signs and the liver function parameters, the incidence of withdrawals due to adverse events and the CGI-EI - Efficacy Index.

Methodology:

National, multicentre, phase-IV, interventional study carried out as an open study with flexible doses (25 or 50 mg/day of Valdoxan).

Study carried out in depressed outpatients, corresponding to the DSM IV-TR criteria for a major depressive episode, who were either untreated on the day of inclusion (treatment initiation sub-group), or receiving antidepressant treatment that was either insufficiently effective and/or poorly tolerated (treatment switch sub-group), evaluated during 3 visits:

- W0: selection and inclusion visit - Treatment provided: in the treatment-initiation sub-group, Valdoxan (one 25 mg tablet/day) started on the evening of visit W0; in the switching-treatment sub-group, depending on the nature and dosage of the previous treatment and the Investigator's decision, Valdoxan (one 25 mg tablet/day) started, either the evening of visit W0, or after, at most, 3 days on the previous treatment at a lower dose.
- W2: performed 14 ± 2 days after starting the treatment with Valdoxan, during which the dose of Valdoxan was eventually increased to 50 mg/day, if there had been no improvement in the symptoms.
- W6: performed 42 ± 2 days after the beginning of treatment, end of study visit during which the main criterion of the study was evaluated.

At the end of visit W6, the patients, who, in the Investigator's opinion, had gained some therapeutic benefit from the six weeks of treatment (improvement in the symptoms, no adverse event), were proposed to take part in an extension study, if they wished to continue taking the treatment.

Number of patients:

Planned: **4000** – Selected: **2943** – Included**: 2938**

Diagnosis and main criteria for inclusion:

Inclusion criteria

- Man or woman, at least 18 years of age, followed up as an outpatient,
- Presenting with a major depressive episode:
  - according to DSM-IV-TR criteria:
    - single or recurrent episode,
    - 'devoid of melancholia', so modified by protocol amendment No. 1: 'with or without melancholic characteristics according to DSM-IV-TR criteria',
    - with no psychotic characteristic,
    - with no catatonic characteristic,
    - having started at least 2 weeks before inclusion.
  - moderate to severe, with a CGI-Severity score of ≥ 4 (at least "moderately ill") and a total QIDS-C score of ≥ 16.
- Requiring treatment with an antidepressant.
- Patient not taking any antidepressant treatment on the day of inclusion, i.e. who has not received any antidepressant treatment for the current episode and/or who has stopped the treatment prescribed for the previous episode since at least 2 months before the beginning of the current episode.

  Or patient taking antidepressant treatment on the day of inclusion, for the current episode or to prevent a recurrence of a previous episode, this treatment being either poorly tolerated, or insufficiently effective, according to the opinion of the Investigator and/or the patient.

Non-inclusion criteria

- Patients presenting with dysthymic disorder (with no concomitant MDE), bipolar disorder, schizoaffective disorder, acute or chronic psychosis, mental retardation, a delirious state or dementia.
- Patients dependent on alcohol or a drug (other than dependence on tobacco).
- Patients who have responded little or not at all to at least two antidepressant treatments prescribed for at least 4 weeks at an effective dose for the current episode.
- Patients who have not responded to a previous treatment with agomelatine.
- Patients with known hypersensitivity to agomelatine or to any of the excipient of Valdoxan.

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Non-inclusion criteria (cont'd)

- Patients with lactose intolerance (congenital galactosemia, lactase deficiency, glucose and lactose malabsorption syndrome).
- Patients with liver failure (cirrhosis or active hepatic disease).
- Treatment with a potent CYP1A2 inhibitor (fluvoxamine: Floxyfral®; ciprofloxacin: Ciflox®).
- Patients with a known unstable or severe somatic disorder that, in the Investigator's opinion, has a major impact on the patient's daily life, and could interfere with the patient's follow-up.
- Refusal to sign the informed consent form.
- Pregnant or lactating woman.
- Woman of childbearing potential and not using effective contraception (oral contraceptives, intra-uterine devices, contraceptive implant or condoms).
- Patient unlikely to cooperate fully in the study and/or to be compliant.
- Patient simultaneously taking part in another clinical trial, or who has taken part in a clinical trial within the 2 months preceding the inclusion visit or patient who has already been included in the study.
- Patient illiterate or incapable of understanding and completing the self-rating questionnaires him/herself.

Study drug:

agomelatine 25 mg tablet (Valdoxan): 1 tablet per day taken as an evening dose, with the possibility of increasing the dose to 50 mg per day (2 tablets as an evening dose), after two weeks of treatment if there is no improvement in the symptoms.

Batch No. R12007 and S02011

Reference product: *not applicable*

Duration of treatment: 6 weeks

Criteria for evaluation:

Effectiveness criteria:

The main criterion was a composite assessment of the clinical response after 6 weeks of treatment, established on the basis of 4 assessment criteria:

- CGI-I (Clinical Global Impression of Improvement),
- PGI-I (Patient Global Impression of Improvement),
- LSEQ (Leeds Sleep Evaluation Questionnaire),
- 100 mm VAS evaluating the patient's willingness to continue the study treatment.

The clinical response was defined as:

- A CGI-I score of ≤ 2 ("obviously improved" or "considerably improved")
- **And a** PGI-I score of ≤ 2 ("obviously improved" or "considerably improved")
- **And a** score of ≤ 40 mm for the assessment of sleep quality (items 2.a and 2.b on the LSEQ), score corresponding to the mean of the 2 individual scores, each of them being ≤ 40 mm, expressing an improvement of at least 10 mm, a threshold considered to be clinically pertinent.
- **And** an affirmative response to the question "If your doctor thinks it is necessary to continue the treatment, are you willing to do so", i.e. a score of ≥ 50 mm on the corresponding VAS.

The secondary criteria were scores based on:

- The SDS questionnaire (Sheehan Disability Scale), which assesses the impact of the illness on the patient's daily activities (work, social life - leisure activities, family life –domestic tasks).
- The MATHyS scale (Multidimensional Assessment of Thymic State), which assesses the thymic state of the patient.
- Two 100 mm VAS, one assessing the patient's mood, and, the other, the intensity of the side effects of the treatment as rated by the patient.
- The QIDS-C scale (Quick Inventory of Depressive Symptomatology - Clinician rating), which assesses the intensity of the 9 symptoms included in the diagnostic criteria of DSM-IV-TR for an MDE.
- The CGI-EI, which is an assessment of the therapeutic efficacy and the side effects of the treatment, which can be used to calculate a benefit/risk ratio.
- The socioeconomic data: number of days of sick leave, number of days of hospitalisation, nature and duration of the concomitant psychotropic treatments (anxiolytics, hypnotics).

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Criteria for evaluation (cont'd)

Safety criteria:

The safety criteria were the adverse events reported, the change in vital signs and liver function parameters, the incidence of unscheduled discontinuation due to the adverse events, and the CGI-EI.

Statistical methods:

Analyses were descriptive on the period W0-W6. The two-sided 95% confidence interval of the response rate at W6 and for last value was provided for response criteria.

Efficacy criteria were analysed 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) and in 3 subgroups of therapeutic situation ("Treatment initiation": patients who were not receiving any antidepressant treatment during the two months preceding the first study drug intake, "Treatment change": patients who stopped their previous antidepressant treatment between 3 days before and 3 days after the first study drug intake date, "Wash-out": patients who received an antidepressant treatment during the two months preceding the first study drug intake) and, among the subgroup Treatment Change, in 5 subgroups of previous antidepressant class (SSRI, SNRI, imipraminic, mirtazapin/mianserin, other).

Primary efficacy criteria were also analysed as a function of different factors (the intensity of the depression at inclusion based on the CGI-S, the intensity of sleep disorders at inclusion based on the QIDS-C sleep items, the Body Mass Index at inclusion, the number of previous major depressive episodes, the extent of the impact of the disorder on daily activities at inclusion visit based on the SDS, the reason for stopping the previous antidepressant treatment).

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients	
Selected	**2943**
Included	**2938**
Withdrawn	**770 ***
due to adverse event	432
due to consent withdrawal	176
due to lost to follow up	88
due to investigator's decision	66
due to unknown reason	8 *
Completed	**2168**
Safety Set	2852
Full Analysis Set (FAS)	2780

(*) Including 6 patients with unknown status at the end of the study

Demographic characteristics		**Included Set** (N = 2938)
Age (years)	N	2932
	Mean ± Std dev	46.9 ± 12.5
	Median (Min ; Max)	47.0 (17 ; 90)
< 25 years	n (%)	120 (4.1 %)
[25 ; 45 [years	n (%)	1122 (38.3 %)
[45 ; 60 [years	n (%)	1241 (42.3 %)
[60 ; 75 [years	n (%)	408 (13.9 %)
≥ 75 years	n (%)	41 (1.4 %)
Gender	N	2937
Female	n (%)	1966 (66.9 %)
Smoking habit	N	2937
Smoker	n (%)	934 (31.8 %)
Has stopped smoking	n (%)	229 (7.8 %)
Alcohol habit	N	2937
Yes	n (%)	412 (14.0 %)
Has stopped	n (%)	124 (4.2 %)

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME (CONT'D)

Main baseline characteristics		**Included Set** (N = 2938)
History of previous MDE	N	2935
	n (%)	2075 (70.7 %)
Time since the first MDE (years)	N	2905
	Mean ± Std dev	9.36 ± 10.50
	Median (Min ; Max)	5.69 (0.0 ; 62.2)
Number of previous MDE	N	2793
	Mean ± Std dev	2.0 ± 2.8
	Median (Min ; Max)	1.0 (0 ; 32)
Family history of psychiatric disorders	n (%)	1175 (40.0 %)
Current episode duration (months)	N	2927
	Mean ± Std dev	8.90 ± 16.52
	Median (Min ; Max)	3.94 (0.0 ; 241.1)
Sick leave due to the current episode	N	2931
	n (%)	936 (31.9 %)
Hospitalization due to the current episode	N	2936
	n (%)	228 (7.8 %)
Psychotropic therapy [1] ongoing at inclusion	n (%)	2011 (68.4 %)
Any significant medical or surgical history	n (%)	1190 (40.5 %)
Other concomitant treatments ongoing at inclusion [2]	n (%)	1589 (54.1 %)

(1) Drugs other than antidepressants or psychotherapy (psychotherapy: 33.6 % of the IS patients).

(2) Concomitant treatments other than psychotropic treatments ongoing at inclusion

Baseline values for CGI-S, SDS and MAThyS		**Included Set**(N = 2938)
CGI-Severity of illness score [1]	N	2936
	Mean ± Std dev	4.9 ± 0.6
	Median	5.0
	Min ; Max	3 ; 7
SDS Work/studies [2]	N	1859
	Mean ± Std dev	6.9 ± 2.5
	Median	7.0
	Min ; Max	0 ; 10
SDS Social life [2]	N	2793
	Mean ± Std dev	7.3 ± 2.1
	Median	8.0
	Min ; Max	0 ; 10
SDS Family life and Home responsibilities [2]	N	2792
	Mean ± Std dev	7.1 ± 2.2
	Median	7.0
	Min ; Max	0 ; 10
MAThyS Dimension total score [3]	N	2511
	Mean ± Std dev	81.62 ± 22.36
	Median	82.60
	Min ; Max	7.1 ; 170.3
MAThyS Emotional total score [4]	N	2743
	Mean ± Std dev	12.2 ± 3.7
	Median	12.0
	Min ; Max	1 ; 25

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

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

(3) The first part of the MAThyS scale comprises 20 visual analogical items related to scores from 0 (inhibition) to 10 (excitement). 5 sub-scores are calculated by adding the scores related to the measured dimension: Emotional reactivity (from 0 to 40), Thought processes (from 0 to 40), Psychomotor function (from 0 to 30), Motivation (from 0 to 40), Sensory perception (from 0 to 50). The dimension total score (from 0 to 200) is calculated as the sum of the 5 sub-scores.

(4) The second part of the MAThyS scale estimates 7 emotions (Sadness, Joy, Irritability, Panic, Anxiety, Anger, Exaltation). The emotion total score (from 0 to 28) is calculated as the sum of the 7 emotions coded from 0 (Never) to 4 (Constantly).

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STUDY POPULATION AND OUTCOME (CONT'D)

Baseline values for VAS of patient's mood and QIDS-C		**Included Set**(N = 2938)
Patient's mood score (mm) [5]	N	2709
	Mean ± Std dev	21.3 ± 17.5
	Median	17.0
	Min ; Max	0 ; 100
QIDS-C Total score [6]	N	2932
	Mean ± Std dev	18.8 ± 2.4
	Median	19.0
	Min ; Max	4 ; 27
Intensity of the depression according to QIDS-C total score	N	2932
Nil (score 0 to 5)	n (%)	1 (0.0 %)
Mild (score 6 to 10)	n (%)	3 (0.1 %)
Moderate (score 11 to 15)	n (%)	45 (1.5 %)
Severe (score 16 to 20)	n (%)	2187 (74.6 %)
Very severe (score 21 to 27)	n (%)	696 (23.7 %)

(5) The VAS evaluates the answer to the question 'How is your mood today?'. It varies from 0 (Low mood) to 100 mm (Good mood).

(6) 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.

Overall, **no clinically significant difference was observed between the Included Set and the FAS** for main baseline characteristics and baseline values of efficacy criteria.

Study treatment

The treatment duration, known for 2801 patients in the Included Set and for 2772 patients in the Safety Set, was similar in both populations: 37.0 ± 13.1 days (median: 42 days) in the IS and 37.4 ± 12.6 days (median: 42 days) in the SS. The treatment compliance was excellent and similar in the Included Set and Safety Set. Only 4.6 % of the 2753 patients with available observance in the Included Set and 3.6 % of the 2852 patients with available observance in the Safety Set took less than 70 % of the total dose they should have taken.

At the end of the study, 63.9 % of the patients in the Included Set and 64.8 % in the Safety Set continued agomelatine (i.e. inclusion in D-Extension study or prescription of the commercial form when available). Agomelatine was replaced by another antidepressant for 22.5 % of the patients in the Included Set and 22.4 % in the Safety Set, and the stop of any antidepressant was decided for 13.5 % of the patients in the Included Set and 12.8 % in the Safety Set.

EFFICACY RESULTS

Primary efficacy criterion in the FAS

Clinical response (composite evaluation)		**Full Analysis Set** (N = 2780)
W6	N	2265
	n (%)	634 (28.0 %)
Statistical analysis	Clinical response rate	**28.0**
	95% CI *	**[26.1; 29.8] %**
Last value	N	2726
	n (%)	665 (24.4 %)
Statistical analysis	Clinical response rate	**24.4**
	95% CI *	**[22.8; 26.0] %**

(*) 95% confidence interval of the rate of clinical response (asymptotic method)

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EFFICACY RESULTS (CONT'D)

Primary efficacy criterion in the FAS subgroups of therapeutic situations

Clinical response (composite evaluation)		**FAS subgroup Treatment initiation** (N = 1123)	**FAS subgroup Treatment change** (N = 1363)	**FAS subgroup Wash out** (N = 252)
W6	N	931	1106	194
	n (%)	307 (33.0 %)	270 (24.4 %)	51 (26.3 %)
Statistical analysis	Clinical response rate	**33.0**	**24.4**	**26.3**
	95% CI *	**[30.0; 36.0] %**	**[21.9; 26.9] %**	**[20.1; 32.5] %**
Last value	N	1094	1346	244
	N (%)	321 (29.3 %)	284 (21.1 %)	54 (22.1 %)
Statistical analysis	Clinical response rate	**29.3**	**21.1**	**22.1**
	95% CI *	**[26.6; 32.0] %**	**[18.9; 23.3] %**	**[16.9; 27.3] %**

(*) 95% confidence interval of the rate of clinical response (asymptotic method)

Primary efficacy criterion in FAS subgroup "Treatment Change" according to previous antidepressant classes

Clinical response (composite evaluation)		**FAS subgroup SNRI** (N = 396)	**FAS subgroup SSRI** (N = 646)	**FAS subgroup imipraminic antidepressant** (N = 93)	**FAS subgroup mirzatapine / mianserin** (N = 130)	**FAS subgroup other antidepressant** (N = 169)
W6	N	304	540	71	105	143
	n (%)	82 (27.0 %)	123 (22.8 %)	9 (12.7 %)	25 (23.8 %)	44 (30.8 %)
Statistical analysis	Clinical response rate	**27.0**	**22.8**	**12.7**	**23.8**	**30.8**
	95% CI *	**[22.0; 32.0] %**	**[19.2; 26.3] %**	**[4.9; 20.4] %**	**[15.7; 32.0] %**	**[23.2; 38.3] %**
Last value	N	392	636	93	129	167
	n (%)	85 (21.7 %)	131 (20.6 %)	9 (9.7 %)	28 (21.7 %)	44 (26.3 %)
Statistical analysis	Clinical response rate	**21.7**	**20.6**	**9.7**	**21.7**	**26.3**
	95% CI *	**[17.6; 25.8] %**	**[17.5; 23.7] %**	**[3.7; 15.7] %**	**[14.6; 28.8] %**	**[19.7; 33.0] %**

(*) 95% confidence interval of the rate of clinical response (asymptotic method)

Secondary analyses showed no impact of the majority of the studied factors on the clinical response rate at W2, W6 and last evaluation. An impact has been observed for only two factors: the rate of clinical response at W6 and last evaluation was higher in the obese patients in the FAS overall and in the subgroup "Treatment change", and higher in the patients with no previous MDE in the subgroup "Treatment initiation"

Secondary efficacy criteria

- Clinical response according each of the four criteria defining main criterion

CGI-I response (Score <= 2)		**Full Analysis Set** (N = 2780)
W6	N	2412
	n (%)	1424 (59.0 %)
Statistical analysis	Rate of response - 95% CI *	**59.0 % [57.1; 61.0]**
Last value	N	2773
	n (%)	1468 (52.9 %)
Statistical analysis	Rate of response - 95% CI *	**52.9 % [51.1; 54.8]**

(*) 95% confidence interval of the rate of clinical response (asymptotic method)

PGI-I response (Score <= 2)		**Full Analysis Set** (N = 2780)
W6	N	2107
	n (%)	1197 (56.8 %)
Statistical analysis	Rate of response - 95% CI *	**56.8 % [54.7; 58.9]**
Last value	N	2496
	n (%)	1289 (51.6 %)
Statistical analysis	Rate of response - 95% CI *	**51.6 % [49.7; 53.6]**

(*) 95% confidence interval of the rate of clinical response (asymptotic method)

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EFFICACY RESULTS (CONT'D)

- Clinical response according each of the four criteria defining main criterion (cont'd)

LSEQ Quality of sleep response (items 2.a and 2.b ≤ 40mm)		**Full Analysis Set** (N = 2780)
W6	N	2095
	n (%)	1049 (50.1 %)
Statistical analysis	Rate of response - 95% CI *	**50.1 % [47.9; 52.2]**
Last value	N	2495
	n (%)	1170 (46.9 %)
Statistical analysis	Rate of response - 95% CI *	**46.9 % [44.9; 48.9]**

(*) 95% confidence interval of the rate of clinical response (asymptotic method)

Patient's willingness to continue the study treatment (VAS >=50)		**Full Analysis Set** (N = 2780)
W6	N	2137
	n (%)	1688 (79.0 %)
Statistical analysis	Rate of response - 95% CI *	**79.0 % [77.3; 80.7]**
Last value	N	2546
	n (%)	1925 (75.6 %)
Statistical analysis	Rate of response - 95% CI *	**75.6 % [73.9; 77.3]**

(*) 95% confidence interval of the rate of clinical response (asymptotic method)

The same differences in the response rate that were showed between the subgroups of therapeutic situations (**higher in the subgroup "Treatment initiation**") and between the "Treatment Change" subgroups of previous antidepressant classes (**lower in the subgroup "imipraminics**") for the primary criterion were observed for the **CGI-I response rate, PGI-I response rate and LSEQ Quality of sleep response rate**, while **no difference between subgroups** of therapeutic situations or previous antidepressant classes was observed for the **rate of patients wishing to continue the study treatment.**

- Analysis of other secondary efficacy criteria showed:

- a **global improvement of patients' status** (decrease of the CGI-S score, CGI-Improvement, PGI-Improvement and increase of CGI-Efficacy Index score),
- an **improvement of depressive symptoms** (increase of VAS measuring the patient's mood, decrease of QIDS-C total score)
- an **improvement of sleep disorders** (Getting off to sleep score, Quality of sleep score, Sleep awakening score and Integrity of behaviour score less than 50),
- a **decrease of the impact of the disease on daily activities** (decrease of SDS Work/Studies score, Social life score and Family life and Home responsibilities score),
- a **normalisation of thymic state** (increase of MAThyS Dimension total score from "inhibition" to normal status),
- a stability of the **willingness to continue the treatment** for the majority of the patients during the study (mean VAS superior to 65 at each time-point).

For the majority of these criteria, no clinically significant difference was observed between subgroups of therapeutic situations or between subgroups of previous antidepressant classes.
Differences most often observed were **better results** in the subgroup **"Treatment initiation**" (for decrease of CGI-S score, CGI-I score, PGI-I score, increase of CGI-EI, decrease of SDS Work/Studies score and QIDS-C total score) and **less good results** in the Treatment Change subgroup **"imipraminics"** (for decrease of CGI-S score, CGI-I score, PGI-I score, increase of CGI-EI, decrease of SDS Work/Studies score, QIDS-C total score, LSEQ-Quality of sleep score and patient's willingness to continue the treatment).

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SUMMARY - CONCLUSIONS

SAFETY RESULTS

Overall summary of safety results	**Safety set (N = 2852)**	
At least one	**n ***	**% ***
Adverse event emergent under treatment[1]	1170	41.02 %
Adverse event emergent under treatment[1] treatment-related	800	28.05 %
Adverse event emergent under treatment[1] leading to study drug withdrawal	434	15.22 %
Severe emergent adverse event under treatment[1]	351	12.31 %
Adverse event emergent after treatment [2]	29	1.02 %
Gastrointestinal disorder emergent under treatment[1]	385	13.50 %
Gastrointestinal disorder emergent under treatment[1] and treatment-related	300	10.52 %
Gastrointestinal disorder emergent under treatment[1] leading to study drug withdrawal	138	4.84 %
Psychiatric disorders emergent under treatment[1]	380	13.32 %
Psychiatric disorders emergent under treatment[1] and treatment-related	241	8.45 %
Psychiatric disorders emergent under treatment[1] leading to study drug withdrawal	203	7.12 %
Nervous system disorders emergent under treatment[1]	332	11.64 %
Nervous system disorders emergent under treatment[1] and treatment-related	257	9.01 %
Nervous system disorders emergent under treatment[1] leading to study drug withdrawal	96	3.37 %
Serious Adverse Event during the study	85	2.98 %
Emergent[3] Serious Adverse Event	80	2.80%
Emergent[3] fatal Serious Adverse Event	1	0.03 %
Emergent[3] non-fatal Serious Adverse Event	79	2.77 %
Emergent[3] psychiatric Serious Adverse Event	56	1.96 %
Emergent[3] Suicidal event with acting out [4]	10	0.35 %
Emergent[3] Suicidal event with acting out treatment-related	0	0 %
Emergent[3] Suicidal event with acting out related to lack of efficacy	3	0.11 %
Emergent[3] aggravation of depression with hospitalisation	30	1.05 %
Emergent[3] aggravation of depression with hospitalisation treatment-related	0	0 %
Emergent[3] aggravation of depression with hospitalisation related to lack of efficacy	13	0.46 %
Emergent[3] other ERIN [5]	12	0.42 %
Hepatic disorder with transaminases increase [6]	27	0.95 %
Emergent[3] hepatic disorder with transaminases increase	21	0.74 %
Emergent[3] hepatic disorder with transaminases increase treatment-related	12	0.42 %

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

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

(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 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 and worsened or became serious after the first study drug intake, without limit of time after the last study drug intake.

(4) suicidal events with acting out: completed suicide (1 patient), suicide attempt (7 patients), intentional overdose (2 patients).

(5) emergent other ERIN: increase of transaminases ≥ 3 ULN at two successive determinations (10 patients), pregnancy (1 patient) and overdose (1 patient).

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

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

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CONCLUSION

In this study, of which the main objective was to describe the efficiency of Valdoxan after 6 weeks of treatment under different therapeutic situations, and in different sub-groups of patients defined by the class of antidepressant used previously, the clinical response rate (composite criterion) was 14.4 % of the patients at W2, 28.0 % (CI $_{95\,\%}$ [26.1 ; 29.8]) at W6 and 24.4 % (CI $_{95\,\%}$ [22.8 ; 26.0]) at the last post-baseline evaluation. The response rates according each of the four criteria defining main criterion were at W6 and at last post-baseline evaluation about 50 % for the CGI-I response, PGI-I response and LSEQ Quality of sleep response, and at least 75 % for the response rate for patient's willingness to continue the study treatment. Analysis of secondary efficacy criteria showed a global improvement of patients' status, an improvement of depressive symptoms and sleep disorders, a decrease of the impact of the disease on daily activities, a normalisation of thymic state, and a stability of the patients' willingness to continue the treatment during all the study. Overall, efficacy results tended to be better in the subgroup of patients who had not taken antidepressant for the two months preceding the study and less good in the subgroup of patients previously treated with imipraminics.

The nature and the frequency of emergent adverse events were in accordance with the safety profile of agomelatine. Most frequent emergent adverse events were gastrointestinal disorders (13.5 % of the patients), psychiatric disorders (13.3 %) and nervous system disorders (11.6 %). Emergent serious adverse events were reported in 2.8 % of the patient and emergent hepatic disorders with transaminases increase in 0.7 % of the patients. Most frequent serious adverse events were psychiatric disorders (2.0 %), mainly hospitalisations for aggravation of depression (1.1 %), or anxiety (0.5 %), and suicidal events with acting out (0.4 % - 1 suicide, 7 suicide attempts, 2 intentional overdoses).

Date of the report: 30 September 2011