Document title	**Clinical Study Report Synopsis**
Study title	**Initiation of agomelatine after antidepressant treatment by SSRI or SNRI in outpatients suffering Major Depressive Disorder.** **A 3-week, randomised, double then single-blind, controlled, parallel groups, international, multicentre safety study with a 5-week open extension period.**
Study drug	**S 20098**
Studied indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-073**
Study initiation date	**09 November 2010**
Study completion date	**21 December 2011**
Main coordinator	[redacted] **- FRANCE**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes cedex - FRANCE**
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 1 October 2012**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: Initiation of agomelatine after antidepressant treatment by SSRI or SNRI in outpatients suffering Major Depressive Disorder.
A 3-week, randomised, double then single-blind, controlled, parallel groups, international, multicentre safety study with a 5-week open extension period.
Protocol No.: CL3-20098-073

Scientific advisor: [redacted], France)
National coordinators: [redacted], Brazil), [redacted], France), [redacted], Germany), [redacted] Hungary), [redacted], Portugal), [redacted], Italy), [redacted], Spain).

Study centres:
Overall, 47 located in 8 countries included at least one patient: Belgium (2 centres – 10 included patients), Brazil (7 centres – 36 included patients), France (7 centres – 39 included patients), Germany (7 centres – 92 included patients), Hungary (9 centres – 44 included patients), Portugal (3 centres – 23 included patients), Italy (5 centres – 28 included patients), Spain (7 centres – 44 included patients).

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 09 November 2010 Completion date: 21 December 2011	III

Objectives:
Primary objective: to compare 3 different ways to initiate agomelatine after antidepressant treatment by SSRI or SNRI, using the Discontinuation-Emergent Signs and Symptoms check-list: either by immediate substitution or by initiation of agomelatine with 2 different taperings of the previous drug, in depressed out-patients requiring a change in their antidepressant treatment due to an insufficient treatment efficacy (associated or not with poor acceptability).

Secondary objectives:

- To document general safety.
- To describe the early effects on subjective sleep and daytime sleepiness.
- To describe the global clinical benefit.
- To provide information on emotional effects.

in the context of those different ways to initiate agomelatine.

Methodology:
International, multicenter, double- then single-blind, controlled, phase III safety study with a 5-week open extension period, performed in outpatients suffering from Major Depressive Disorder and requiring a change in their previous antidepressant (AD) treatment. The patients received:
Group 1: agomelatine 25 mg o.d. and previous antidepressant at therapeutic dose o.d (20 mg for paroxetine, 75 mg for venlafaxine) on the 1st week then at half therapeutic dose on the 2nd week, then placebo on the 3rd week (*Long tapering*)
Group ½: agomelatine 25 mg o.d. and previous antidepressant at half therapeutic dose o.d. (10 mg for paroxetine, 35.5mg for venlafaxine) on the 1st week, then placebo on the 2nd and 3rd week (*Short tapering*)
Group 0: agomelatine 25 mg o.d. on the 3 first weeks (*Immediate substitution*).
The group was assigned at inclusion by a balanced (non-adaptive) randomisation, with stratification on the previous antidepressant (paroxetine or venlafaxine) and on the centre.

Number of patients:
Planned: 300 (100 in each group)
Included: 316 (107 in the group 1, 102 in the group ½ and 107 in the group 0)

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Diagnosis and main criteria for inclusion:
Male or female outpatients, aged between 18 and 65 years (inclusive), fulfilling DSM-IV-TR criteria for Major Depressive Episode of moderate or severe intensity, treated with either paroxetine or venlafaxine, at therapeutic doses (20 mg/d for paroxetine and 75 mg/d for venlafaxine) or above, continuously for at least 6 weeks at selection and requiring a change in antidepressant treatment due to an insufficient treatment efficacy as assessed by a Clinical Global Impression item1 severity of illness ≥ 4 (= from moderately ill) associated or not with poor acceptability.

Study drugs:
Agomelatine 25mg tablet: 1 tablet in a yellow capsule once a day, *p.o.* at bedtime. Batch No. L0034326 and L0034411.
Paroxetine 20 mg tablet: 1 or one half tablet masked in a red capsule once a day, *p.o.* in the morning.
Venlafaxine 75 mg capsule: 1 capsule masked in a red capsule once a day, *p.o.* in the morning.
Venlafaxine 37.5 mg capsule: 1 capsule masked in a red capsule once a day, *p.o.* in the morning.
Placebo: 1 red capsule once a day, *p.o.* in the morning.

Reference product: Not applicable.

Duration of treatment:
3 to 10 days selection period (from selection to inclusion (W0) visits): ongoing AD treatment (paroxetine 20 mg/d or venlafaxine 75 mg/d).
2-week double-blind treatment period (from W0 to W2): agomelatine 25 mg and AD (paroxetine 20 or 10 mg/d or venlafaxine 75 or 37.5 mg/d or placebo).
1**-week single-blind treatment period** (from W2 to W3): agomelatine 25 mg and placebo.
5-week open extension treatment period (from W3 to W8): agomelatine 25 mg.

Criteria for evaluation:
Safety measurements:
Primary criterion: total number of discontinuation emergent symptoms according to the Discontinuation-Emergent Signs and Symptoms check-list (DESS) (*i.e.* symptoms rated as "new" or "worsening"). DESS was evaluated at W0, W1, W2 and W3.
Secondary criteria:
- Adverse events recorded at each visit.
- Physical examination: blood pressure, heart rate and body weight at selection, inclusion, W3 and W8 visits.
- Haematology and biochemistry parameters at selection and W3 visits, (and W8 for liver parameters only).

Efficacy measurements:
Global clinical benefit assessed using Clinical Global Impression (CGI): severity of illness (at each visit), global improvement and efficacy index scores (at W1, W2, W3 and W8).

Subjective sleep and daytime sleepiness assessed using two self-rating visual analogue scales:
- Leeds Sleep Evaluation Questionnaire (LSEQ): getting off to sleep, quality of sleep and sleep awakening scores (W1, W2, W3 and W8).
- VAS on Daytime sleepiness: daytime sleepiness and feeling good scores (W0, W1, W2, W3 and W8).

Emotional effects (initially planned as safety criteria then considered as efficacy criteria) using a Visual analogue scale at each visit from inclusion to W8 visit.

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Statistical methods:

Safety analysis:

Primary criterion

The 3 different ways to initiate agomelatine after antidepressant treatment by SSRI or SNRI were compared two by two on the total number of discontinuation emergent symptoms in the DESS Set (all patients of the Safety Set having at least one value of total number of DESS at W1, W2 or W3), using a single Negative Binomial regression with group and previous antidepressant treatment (paroxetine or venlafaxine) as explanatory variables, at the following times:

- W1, W2 and W3.
- W2 and W3 in terms of cumulative value.
- One week after previous antidepressant treatment stop, *i.e.* at W3 in group 1, at W2 in group ½ and at W1 in group 0.

A comparison was also performed at the end of the week with previous antidepressant treatment at half therapeutic dose, *i.e.* at W2 in group 1 and at W1 in group ½.

The same comparisons were performed according to the type of previous antidepressant treatment, using a Negative Binomial regression with group as explanatory variable.

As no pre-defined hypothesis could be stated in this study, all statistical analyses were performed at the (two-sided) significance level of 5%.

Secondary safety criteria

Descriptive statistics were provided by group in the Safety Set (all included patients having taken at least one dose of agomelatine) for emergent adverse events during the 3-week and 8-week treatment periods and after the treatment period, and for serious adverse events on the whole study.

In addition, for emergent adverse events on the 3-week treatment period, descriptive statistics were also provided according to the previous antidepressant treatment but all groups pooled.

Descriptive statistics were also provided for other safety criteria.

Analysis of total number of discontinuation emergent symptoms was performed in term of patients with at least one discontinuation emergent symptom and mean number of symptoms in patients with at least one discontinuation emergent symptom (unplanned). Analysis of each type of symptom in the DESS check list was performed globally and according to previous AD treatment (unplanned).

Efficacy analysis:

For each analytical approach, descriptive statistics were provided on the W0-W3 and W0-W8 periods in the patients of the FAS (all patients of the RS having taken at least one dose of agomelatine and having at least one post-baseline efficacy assessment), in the DESS Set for CGI scores, and in the FAS subgroup of patients blunted at baseline for VAS on emotional effects.

In addition, for CGI scores and VAS on emotional effects, descriptive statistics were provided by previous antidepressant treatment on the W0-W3 period (respectively in the FAS and DESS Set, and in the whole FAS).

SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME

The distribution of the treatment groups was well balanced (see Table). Of the 316 included patients, 136 (43.0%) were previously treated with paroxetine and 180 (57.0%) with venlafaxine without relevant difference between groups.

The main reason for withdrawal was adverse events (16 patients, 5.1%) with a trend to greater frequency from the group 1 to the group 0: 4 patients in the group 1 (3.7%), 5 in the group ½ (4.9%) and 7 in the group 0 (6.5%). Withdrawals for protocol deviations were more frequent in the group 1 (4 patients, 3.7%) than in the groups ½ (1 patient, 1.0%) and 0 (none patient).

Overall, 49 patients (15.5%) withdrew on the W0-W8 period with a slightly lower rate in the group ½ (12.7%) than in the groups 1 and 0 (17.8% and 15.9%, respectively), mainly due to adverse events (8.4%, 5.9% and 8.4% in the groups 1, ½ and 0, respectively) and protocol deviations (4.7%, 1.0% and none in the groups 1, ½ and 0, respectively).

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SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME (Cont'd)

Disposition of patients

Status		Group 1	Group ½	Group 0	All
Included (randomised)	n	**107**	**102**	**107**	**316**
Lost to follow-up	n	**-**	**-**	**-**	**-**
Withdrawn on the W0-W3 period due to	n	**11**	**9**	**10**	**30**
Adverse event	n	4	5	7	16
Lack of efficacy	n	1	1	2	4
Cure, remission or improvement	n	1	-	-	1
Non-medical reason	n	1	2	1	4
Protocol deviation	n	4	1	-	5
Completed the W0-W3 period	n	**96**	**93**	**97**	**286**
Ongoing in the extension period	n	**90**	**88**	**93**	**271***
Withdrawn on the extension period	n	**8**	**4**	**7**	**19**
Adverse event	n	5	1	2	8
Lack of efficacy	n	2	3	3	8
Cure, remission or improvement	n	-	-	-	-
Non-medical reason	n	-	-	2	2
Protocol deviation	n	1	-	-	1
Lost to follow up	n	-	-	-	-
Completed the W0-W8 period	n	**82**	**84**	**86**	**252**
Full Analysis Set (FAS)	n (%)	106 (99.1)	102 (100)	105 (98.1)	313 (99.1)
Safety Set (SS)	n (%)	107 (100)	102 (100)	106 (99.1)	315 (99.7)
DESS Set	n (%)	106 (99.1)	102 (100)	104 (97.2)	312 (98.7)

% % of the Randomised Set

** 15 patients did not entered the optional extension period*

At selection, the mean ± SD age was 47.4 ± 11.3 years in the RS. Most patients were female (66.1%). No relevant difference between groups was observed regarding demographic data, vital signs, BMI, risk factors, medical and surgical history and psychiatric disorders other than MDD, non-psychotic concomitant treatments and TSH levels at baseline.

In the RS, 78.8% of the patients (76.6%, 75.5% and 84.1% in the groups 1, ½ and 0, respectively) were diagnosed as recurrent MDD according to the DSM-IV-TR criteria; 73.1% had a moderate MDD and 26.9% had a severe MDD without psychotic feature. Melancholic features were observed in half of patients (48.4%). Seasonal pattern was observed in 3 patients. No relevant difference between groups was observed for diagnostic criteria.

MDD has lasted on average for 8.7 ± 8.8 years, median = 5.8 years, with a mean number of depressive episodes including the current one of 3.5 ± 2.9. The duration of the MDD was slightly lower in the group 1 (on average 8.3 ± 8.9 years, median = 5.1 years) and group ½ (8.5 ± 9.6 years, median = 4.7 years) than in the group 0 (9.1 ± 7.9 years, median = 8.1 years). Mean duration of current MDE was 6.7 ± 5.6 months (median = 4.7 months).

At inclusion, 42.7% of the patients were on psychotropic treatments; mainly psycholeptics (42.1%) with anxiolytics (37.3%) slightly less frequent in the groups 1 and ½ (33.6% and 34.3% respectively) than in the group 0 (43.9%), which was maintained during the treatment period.

In all, 29 patients (9.2%) had a lifetime history of suicide attempts with slightly less patients in the groups 1 and ½ (8 patients, 7.5% and 8 patients, 7.8% respectively) than in the group 0 (13 patients, 12.2%).

At inclusion, the mean HAD score was 13.6 ± 4.3 for depression and 10.0 ± 4.0 for anxiety without relevant difference between groups. Overall, 80.1% of the patients had a depression score ≥ 11 indicating that most of patients felt markedly depressed with a slightly lower rate in the group 1 (72.0%) than in the groups ½ (85.3%) and 0 (83.2%). For 43.7% of the patients the anxiety score was ≥ 11 without relevant difference between groups.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

The mean *CGI severity of illness score* was 4.4 ± 0.6 corresponding to patients moderately ill, the mean *VAS daytime sleepiness score* was 50.2 ± 28.4 mm (corresponding to the middle between "not at all" and "a lot") without relevant difference between groups. The mean *VAS feeling good score* was 31.0 ± 22.9 mm (corresponding to a score near "not in form at all") with higher value in the group 1 (34.6 ± 26.0 mm) than in the groups ½ (31.6 ± 21.2 mm) and 0 (26.8 ± 20.7 mm). Regarding *emotional effects* (with 0 = "fully disagree" and 100 mm = "fully agree"), few differences were observed for spectator feeling (ranging from 57.0 ± 29.2 mm in the group 1 to 61.2 ± 26.7 mm in the group 0), numbed emotions (ranging from 65.9 ± 25.1 mm in the group 1 to 70.0 ± 24.3 mm in the group ½) and things not important (ranging from 61.5 ± 28.1 mm in the group 1 to 66.0 ± 23.1 mm in the group ½); in addition, mean toned down values were similar in all groups (from 57.0 ± 27.8 mm to 57.7 ± 25.2 mm) with however median lower in the group 1 (57.0 mm) than in the group ½ (64.0 mm).

Mean number of present symptoms on DESS checklist at baseline in the DESS Set was 12.2 ± 6.2 without relevant difference between groups.

The demographic data and other baseline characteristics in the FAS and in the DESS Set were similar to those described in the RS.

In the Randomised Set, the mean treatment duration was 20.5 ± 4.1 days over W0-W3 period and 48.9 ± 16.0 days over W0-W8 period with similar results in the FAS, the SS and the DESS Set. Compliance was good over both periods: on average 96.7 ± 11.4% over W0-W3 and 99.3 ± 11.3% over W0-W8. No relevant difference was observed between groups.

MAIN SAFETY CRITERION AND EFFICACY RESULTS

MAIN SAFETY CRITERION: **Total number of discontinuation emergent symptoms**

At each visit, the mean total number of discontinuation emergent symptoms was higher in the group for which the previous AD has been stopped one week before (group 0 at W1, group ½ at W2 and group 1 at W3).

At each visit, the difference between groups in term of mean total number of discontinuation emergent symptoms was statistically significant in disfavor of the group for which the previous AD was stopped one week before:

- At W1: the estimated ratio was 0.63 ($p = 0.010$) between groups ½ and 0 and 0.41 ($p < 0.0001$) between groups 1 and 0.
- At W2: the estimated ratio was 0.45 ($p < 0.001$) between groups 1 and ½ and 2.69 ($p < 0.0001$) between groups ½ and 0.
- At W3: the estimated ratio was 3.03 ($p < 0.0001$) between groups 1 and ½ and 2.89 ($p < 0.001$) between groups 1 and 0.

Total number of discontinuation emergent symptoms at each visit - DESS Set

		Group 1 (N = 106)	Group ½ (N = 102)	Group 0 (N = 104)
W1	n	105	102	104
	Mean ± SD	2.1 ± 3.3	3.2 ± 4.6	5.1 ± 4.7
	Median	1.0	2.0	4.0
	Min ; Max	0 ; 20	0 ; 22	0 ; 22
W2	n	102	99	99
	Mean ± SD	1.7 ± 3.2	3.9 ± 5.2	1.5 ± 2.5
	Median	0.0	2.0	0.0
	Min ; Max	0 ; 17	0 ; 22	0 ; 12
W3	n	98	95	96
	Mean ± SD	2.9 ± 4.6	0.9 ± 2.1	1.0 ± 1.8
	Median	1.0	0.0	0.0
	Min ; Max	0 ; 23	0 ; 14	0 ; 7

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SUMMARY – CONCLUSIONS (Cont'd)

MAIN SAFETY CRITERION AND EFFICACY RESULTS (Cont'd)

MAIN SAFETY CRITERION: **Total number of discontinuation emergent symptoms**

Within each group, the mean total number of discontinuation emergent symptoms was also higher one week after the previous antidepressant stop (W3 in the group 1, W2 in the group ½ and W1 in the group 0).

So, whatever the switch strategy, a withdrawal syndrome was observed one week after stopping SSRI/SNRI treatment.

Psychic symptoms were the most frequently reported (nervousness/anxiety, agitation, increased dreaming/nightmares, bouts of crying, sudden worsening of mood, trouble sleeping/insomnia).

Somatic symptoms were quite few except dizziness, fatigue/tiredness and in a less extent nausea.

One week after previous antidepressant stop, mean total number of discontinuation emergent symptoms was lower in the group 1 (long tapering) than in the group ½ (short tapering) and lower in the group ½ than in the group 0 (immediate substitution). A statistically significant difference was observed between group 1 and group 0 with an estimated ratio of 0.57 (p-value = 0.004) meaning that with long tapering, the total number of discontinuation symptoms was 43% less than with immediate substitution.

The percentage of patients with at least one discontinuation emergent symptom one week after the treatment stop (unplanned analysis) was lower in the group 1 (56.1% at W3) than in the group ½ (62.6 % at W2) and lower in the group ½ than in the group 0 (79.8% at W0). However, in these patients, between-group differences regarding the number of discontinuation emergent symptoms were slight: on average 5.1 ± 5.2 in the group 1, 6.3 ±5.3 in the group ½ and 6.3 ± 4.4 in the group 0.

At the end of the week with previous antidepressant at half therapeutic dose, the mean total number of discontinuation emergent symptoms was lower in the group 1 (long tapering) than in the group ½ (short tapering): 1.7 ± 3.2 at W2 and 3.2 ± 4.6 at W1, respectively. The between-group difference was statistically significant with an estimated ratio of 0.53 (p = 0.006) meaning that with long tapering, the total number of discontinuation symptoms was 47% less than with short tapering.

The percentage of patients with at least one discontinuation emergent symptom at the end of the week with previous antidepressant at half therapeutic (unplanned analysis) dose was lower in the group 1 (44.1% at W2) than in the group ½ (63.7% at W1). However, in these patients, between-group differences regarding the number of discontinuation emergent symptoms were moderate: on average 3.9 ± 3.9 in the group 1 and 5.0 ± 5.0 in the group 0.

As the whole, the greater the length of time of the tapering, the lower the number of discontinuation emergent symptoms there was one week after the treatment stop and at the end of the week with previous antidepressant at half therapeutic dose. This was mainly due to the lower rate of patients reporting withdrawal symptoms in the group with the longest tapering than in other groups and to a less extent, to the reduction of the number of emergent symptoms in affected patients.

Regarding data according to previous antidepressant treatment (paroxetine or venlafaxine), results on discontinuation emergent symptoms were close to those observed for both previous antidepressant pooled.

EFFICACY RESULTS

CGI

In the FAS, the mean CGI *severity of illness* and *global improvement* scores decreased from baseline to W3 and W8 in all groups indicating that patient's condition improved under agomelatine treatment. At each visit, CGI severity of illness score and CGI global improvement score were both higher (*i.e.* patients less improved on average) in the group for which the AD was stopped one week before *i.e.* at the visit with the highest number of discontinuation symptoms: at W1 in the group 0, at W2 in the group ½ and at W3 in the group 1.

Regarding severity of illness score within each group, the improvement from the previous visit was less marked one week after the previous antidepressant stop than at the other visits (see Table).

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

CGI – Severity of illness score and global improvement score

		Group 1 (N = 106)	Group ½ (n = 102)	Group 0 (N = 105)
Severity of illness score				
Baseline	n	106	102	105
	Mean ± SD	4.3 ± 0.5	4.4 ± 0.6	4.4 ± 0.6
	Median	4.0	4.0	4.0
	Min ; Max	4 ; 6	4 ; 6	4 ; 6
W1	n	106	102	105
	Mean ± SD	4.0 ± 0.7	4.1 ± 0.8	4 3 ± 0.7
	Median	4.0	4.0	4.0
	Min ; Max	2 ; 6	2 ; 6	2 ; 6
W2	n	103	99	99
	Mean ± SD	3.6 ± 1.0	3.9 ± 0.9	3.6 ± 0.9
	Median	4.0	4.0	4.0
	Min ; Max	1 ; 6	1 ; 6	1 ; 6
W3	n	99	95	96
	Mean ± SD	3.4 ± 1.0	3.3 ± 1.0	3 1 ± 1.0
	Median	3.0	3.0	3.0
	Min ; Max	1 ; 5	1 ; 6	1 ; 6
Last post baseline value on W0-W8	n	106	102	105
	Mean ± SD	3.0 ± 1.3	3.0 ± 1.3	3.0 ± 1.3
	Median	3.0	3.0	3.0
	Min ; Max	1 ; 6	1 ; 6	1 ; 6
Global improvement score				
W1	n	106	102	105
	Mean ± SD	3.5 ± 0.8	3.6 ± 0.9	4.0 ± 1.0
	Median	4.0	4.0	4.0
	Min ; Max	1 ; 5	1 ; 6	2 ; 6
W2	n	103	99	99
	Mean ± SD	3.1 ± 1.0	3.4 ± 1.1	3 1 ± 1.0
	Median	3.0	3.0	3.0
	Min ; Max	1 ; 6	1 ; 6	1 ; 6
W3	n	99	95	96
	Mean ± SD	3.0 ± 1.2	2.9 ± 1.2	2.6 ± 1.0
	Median	3.0	3.0	3.0
	Min ; Max	1 ; 7	1 ; 7	1 ; 6
Last value on W0-W8	n	106	102	105
	Mean ± SD	2.7 ± 1.4	2.7 ± 1.5	2.6 ± 1.4
	Median	2.0	2.0	2.0
	Min ; Max	1 ; 7	1 ; 7	1 ; 6

In the FAS, the *rate of responders* (defined according to CGI global improvement score: 1 or 2) increased from W1 to W3 and W8. At each visit, except W3, the rate of responders was slightly lower in the group for which the previous antidepressant was stopped one week before *i.e.* at the visit with the highest number of discontinuation symptoms: at W1, 10.4%, 8.8% and 5.7% and at W2, 27.2%, 18.2% and 26.3%, in the groups 1, ½ and 0, respectively. At W3, the rate of responders was slightly lower in the groups ½ and 1 (40.0% and 41.4%, respectively) than in the group 0 (47.9%).

Mean *CGI efficacy index* increased in all groups from W1 to W3 and W8 reflecting an improvement of patients condition. At each visit, the CGI efficacy index was found lower (*i.e.* patients less improved) in the group for which the previous antidepressant was stopped one week before *i.e.* at the visit with the highest number of discontinuation symptoms: at W1, 1.22 ± 0.79 in the group 0, at W2, 1.70 ± 0.96 in the group ½ and at W3, 2.04 ± 1.14 in the group 1.

Clinically, those results suggested a direct impact of withdrawal symptoms on efficacy as judged by the physician (CGI).

Regarding last value on W0-W8, no relevant difference was observed between groups for severity of illness score and CGI efficacy index; the rate of responders was slightly higher in the group 0 (58.1%) than in the other groups (52.8% and 55.9% in the groups 1 and ½) without clinically relevance.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

LSEQ

In the FAS, *LSEQ scores* decreased in all groups from W1 to W3 and W8 indicating that getting off to sleep, quality of sleep and sleep awakening were improved under agomelatine treatment.

At each visit, the *quality of sleep score* was higher (*i.e.* patients less improved) in the group for which the previous antidepressant was stopped one week before *i.e.* at the visit with the highest number of discontinuation symptoms: at W1, 52.2 ± 24.3 in the group 0, at W2, 45.1 ± 22.4 in the group ½ and at W3, 40.1 ± 24.6 in the group 1. As regards to *getting off to sleep* and *sleep awakening* score, no obvious relationship was observed with the previous AD stop even if a trend could be retained. These data suggested an impact of withdrawal symptoms on the sleep. Regarding last value on W0-W8, the mean getting off to sleep score was slightly lower in the group 1 (37.6 ± 20.9 mm, median 35.7) than in the group 0 (40.9 ± 18.6 mm, median 37.3) without relevant difference regarding medians; no relevant difference was observed between groups for quality of sleep and sleep awakening score.

VAS on Daytime sleepiness

In the FAS, a decrease in *daytime sleepiness* was observed in all groups from baseline to W3 and W8 indicating that patients felt less drowsy during the day under agomelatine treatment. At W2 and W3, the decrease from baseline in daytime sleepiness score was lower or slightly lower (*i.e.* patients less improved) in the group for which the previous antidepressant was stopped one week before (*i.e.* when the number of discontinuation of emergent symptoms was the highest): at W2, -4.8 ± 29.5 in the group ½ and at W3, -11.7 ± 29.8 in the group 1. Within each group, the improvement was less marked one week after the previous antidepressant stop, than at the other visits.

In the FAS, an increase in *feeling good* was observed in all groups from baseline to W3 and W8 indicating that patients felt better under agomelatine treatment. At each visit, except W1, the mean increase from baseline in feeling good score was lower (*i.e.* patients less improved) in the group for which the previous antidepressant was stopped one week before *i.e.* at the visit with the highest number of discontinuation symptoms: at W2, 7.2 ± 29.8 in the group ½ and at W3, 7.5 ± 28.1 in the group 1.

These data suggested an impact of withdrawal symptoms on the daytime sleepiness.

Regarding last post-baseline value on W0-W8 for *daytime sleepiness*, the mean decrease from baseline was slightly greater (*i.e.* patients more improved) in the group 1 (-15.7 ± 35.6 mm, median = -11.0) than in the others (-12.8 ± 31.4 mm with median = -11.0 and -12.7 ± 31.8 mm with median = -9.0 in the groups ½ and 0, respectively) with however no relevant difference regarding medians.

Regarding last post-baseline value on W0-W8 for *feeling good*, the mean increase from baseline in *feeling good* was higher (*i.e.* patients more improved) in the group 0 (-20.3 ± 29.0 mm) than in the others (12.1 ± 34.0 mm and 12.1 ± 34.8 mm, in the groups ½ and 0, respectively).

VAS on emotional effects

In the FAS, mean values of "toned down" emotions, "spectator" feeling, "numbed" emotions and "things not important" feeling decreased from baseline to W3 and W8 indicating that emotional blunting improved under agomelatine treatment. Except possibly for "things not important", improvement did not show obvious relationship with the previous antidepressant stop:

- Toned down: the mean decrease from baseline to W3 was lower (*i.e.* patients less improved) in the group 1 (-8.2 ± 30.7 mm) than in the groups ½ and 0 (-14.6 ± 29.7 mm and -17.9 ± 32.9, respectively). Regarding last post-baseline value on W0-W8, the decrease from baseline was greater in the group 0 (-20.3 ± 34.8 mm) than in the group ½ (-16.2 ± 37.2 mm).
- Spectator: the mean decrease from baseline to W3 was lower in the group 1 (-11.9 ± 30.5 mm) than in the groups ½ and 0 (-18.5 ± 26.5 mm and -18.9 ± 33.6 mm, respectively). Regarding last post-baseline value on W0-W8, the decrease from baseline was greater in the group 0 (-20.6 ± 35.1 mm) than in the others (-18.2 ± 35.5 mm and -17.6 ± 31.4 mm, in the groups 1 and ½, respectively).
- Numbed: the mean decrease from baseline to W3 was lower in the group 1 (-19.9 ± 31.1 mm) than in the groups ½ and 0 (-27.7 ± 27.8 mm and -25.4 ± 31.4, respectively). No relevant difference between groups was observed regarding decrease from baseline to last post-baseline value on W0-W8 period.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

VAS on emotional effects (Cont'd)

- Things not important: at each visit, except W2, the mean decrease in "things not important" feeling was lower in the group for which the AD was stopped one week before *i.e.* at the visit with the highest number of discontinuation symptoms: at W1, -6.2 ± 24.7 mm in the group 0 and at W3, -10.8 ± 28.3 mm in the group 1. These data suggested an impact of withdrawal symptoms. No relevant difference between groups was observed regarding mean decrease from baseline to last post-baseline value on W0-W8 period; regarding median, the decrease was greater in the groups ½ and 0 (-20.0) than in the group 1 (-15.0).

Globally, results on discontinuation emergent symptoms and efficacy according to previous AD showed similar trends as those observed in the FAS.

Results in the DESS (99.7% of the FAS) were similar to those observed in the FAS.

GENERAL SAFETY RESULTS

Overall summary of safety results

		Group 1 (N = 107)	Group 1/2 (N = 102)	Group 0 (N = 106)
W0-W3 period				
Patients having reported				
at least one emergent adverse event	n (%)	27 (25.2)	33 (32.4)	41 (38.7)
at least one treatment-related emergent adverse event	n (%)	11 (10.3)	12 (11.8)	10 (9.4)
Patients having experienced				
at least one serious adverse event*	n (%)	1 (0.9)	2 (2.0)	2 (1.9)
at least one treatment-related serious adverse event	n (%)	-	-	-
Patients withdrawn				
due to an emergent adverse event	n (%)	6 (5.6)	5 (4.9)	8 (7.5)
due to a serious emergent adverse event	n (%)	-	2 (2.0)	2 (1.9)
due a treatment-related emergent adverse event	n (%)	3 (2.8)	2 (2.0)	2 (1.9)
During the study				
Patients having reported				
at least one emergent adverse event	n (%)	32 (29.9)	37 (36.3)	49 (46.2)
at least one treatment-related emergent adverse event	n (%)	14 (13.1)	13 (12.7)	11 (10.4)
Patients having experienced				
at least one serious adverse event	n (%)	2** (1.9)	2 (2.0)	5 (4.7)
at least one serious emergent adverse event	n (%)	1 (0.9)	2 (2.0)	5 (4.7)
at least one treatment-related serious adverse event	n (%)	-	-	-
Patients withdrawn				
due to an emergent adverse event	n (%)	9 (8.4)	6 (5.9)	10 (9.4)
due to a serious emergent adverse event	n (%)	-	2 (2.0)	3 (2.8)
due a treatment-related emergent adverse event	n (%)	4 (3.7)	2 (2.0)	2 (1.9)
Patients who died	n (%)	-	-	-

**All serious adverse events on the W0-W3 period were emergent*

*** One patient experienced a spontaneous abortion 28 days after the study withdrawal (not emergent)*

During the 3-week treatment period, the percentage of patients with at least one emergent adverse event (EAE) became increasingly higher from the group 1 (long tapering) to the group 0 (immediate substitution): 25.2%, 32.4% and 38.7% in the groups 1, ½ (short tapering) and 0, respectively. The greater the length of time of the tapering, the lower the number of emergent adverse events there was.

Similar trend was observed during the 8-week treatment period: 29.9%, 36.3% and 46.2% in the groups 1, ½ and 0, respectively.

As all patients received the same new treatment (agomelatine 25 mg/d), between-group differences were likely to be related to the discontinuation of the previous AD. Safety results regarding adverse events were congruent with withdrawal symptoms evidenced with the DESS.

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SUMMARY – CONCLUSIONS (Cont'd)

GENERAL SAFETY RESULTS (Cont'd)

The most frequently affected system organ classes in all groups (in more than 8.0% of the patients in any group) during the 3-week treatment period were nervous system disorders with greater frequency from the group 1 to the group 0 (8.4%, 12.7% and 15.1% in groups 1, ½ and 0, respectively), gastrointestinal disorders less frequent in the groups 1 and ½ than in the group 0 (9.3% and 8.8% *versus* 14.2%, respectively) and psychiatric disorders reported in each group without relevant difference (8.4%, 10.8% and 9.4% in groups 1, ½ and 0, respectively).

Overall, the most frequently (at least 5.0% of the patients in any group) reported emergent adverse events were headache, nausea, dizziness and insomnia: all of them, except insomnia, were less frequent in the group 1 than in the groups ½ and/or 0:

- Headache: less frequent in the groups 1 and ½ than in the group 0 (4.7% and 4.9% *versus* 9.4%, respectively).
- Nausea with a trend to be more and more frequent from the group 1 to the group 0 (3.7%, 5.9% and 6.6%, in the groups 1, ½ and 0, respectively).
- Dizziness: less frequent in the group 1 than in the group ½ and 0 (1.9% *versus* 6.9% and 5.7%, respectively).
- Insomnia: more frequent in the groups 1 and ½ than in the group 0 (5.6% and 4.9% *versus* 1.9%, respectively).

Results on the 8-week treatment period were close to those on the 3-week treatment period.

Regarding EAE according to previous antidepressant (paroxetine and venlafaxine) on the 3-week treatment period, no relevant difference was observed between paroxetine and venlafaxine groups: 32.4% and 31.8% of the patients, respectively. Regarding the most frequently affected system organ classes, gastrointestinal disorders were less frequent in the paroxetine group (8.8%) than in the venlafaxine group (12.3%). Regarding the most frequent emergent adverse events in any group, nausea (6.6% *versus* 4.5%), dizziness (5.9% *versus* 3.9%) and insomnia (5.1% *versus* 3.4%) were slightly more frequent in the paroxetine group than in the venlafaxine group; headache was similarly reported in both paroxetine and venlafaxine groups (6.6% *versus* 6.1%, respectively).

On the 3-week treatment period, no relevant difference between groups was observed regarding patients who reported at least one severe EAE: 4 patients (3.7%) in the group 1, 2 patients (2.0%) in the group ½ and 4 patients (3.8%) in the group 0. Severe EAEs were most frequently related to nervous system disorders (with a trend to greater frequency from the group 1 to the group 0: none, 1 patient and 3 patients in the groups 1, ½ and 0, respectively) mainly due to headache (none patient in the groups 1 and ½ *versus* 2 patients in the group 0), gastrointestinal disorders and psychiatric disorders without relevant difference between groups in term of patients affected (none to 2 patients for both).

Results on the 8-week treatment period were close to those on the 3-week treatment period.

During the 3-week treatment period, 10.5% of the patients experienced at least one EAE considered as treatment-related according to the investigator without relevant difference between groups: 10.3%, 11.8% and 9.4% in the groups 1, ½ and 0.

During the 8-week treatment period, 5 additional patients reported treatment-related EAEs: among them, alanine aminotransferase increased was reported by 2 patients in the group 1 and 1 patient in the group ½.

The percentage of patients with an EAE leading to study drug withdrawal was slightly lower in the group ½ than in the group 0 on the 3-week treatment period (5.6%, 4.9% and 7.5% in the groups 1, ½ and 0, respectively) and slightly lower in the group ½ than in the groups 1 and 0 (5.9% *versus* 8.4% and 9.4%, respectively) on the 8-week treatment period.

During the 3-week treatment period, 5 patients reported 31 serious emergent adverse events (SEAEs) without relevant difference between groups: 1 patient (0.9%) in the group 1, 2 patients (2.0%) in the group ½ and 2 patients (1.9%) in the group 0. They were mostly related to psychiatric disorders (2 patients in both groups ½ and 0, respectively) and general disorders and administration site conditions (2 patients in both groups ½ and 0, respectively).

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SUMMARY – CONCLUSIONS (Cont'd)

GENERAL SAFETY RESULTS (Cont'd)

During the 8-week treatment period, 3 additional patients reported 12 SEAEs: SEAEs were less frequently reported in the group 1 than in the group 0 (1 patient, 0.9% *versus* 5 patients, 4.7%, respectively) and similarly reported in both groups 1 and ½ (1 patient, 0.9% and 2 patients, 2.0%, respectively). The most frequent SEAEs were related to psychiatric disorders: 2 patients (11 SEAEs) in the group ½ and 3 patients (15 SEAEs) in the group 0. All serious adverse events recovered; none was considered as related to the study treatment and 12 as due to lack of efficacy.

Neither clinically relevant changes nor differences between groups over time were detected in the Safety Set during the ASSE-W3 period regarding biochemistry and haematology parameters. High emergent potentially clinically significant abnormal (PCSA) values were sparse in all groups except for triglycerides: 6 patients in the group 1, 4 in the group ½ and 8 in the group 0 (most of them were not assessed in fasting conditions).
Overall, 2 emergent PCSA haematological values were reported by one patient in the group 0 (high haemoglobin and haematocrit): those parameters normalised 2 weeks later on treatment.
Regarding liver acceptability, during both periods, neither clinically relevant changes nor differences between groups over time were detected in the Safety Set. On the ASSE-W3 period, 5 emergent PCSA values of liver parameters were reported: GGT > 3 ULN (3 patients in the group 1), total bilirubin and free bilirubin > 3 ULN (1 patient in the group ½). On the ASSE-W8 period, 2 additional emergent PCSA values were observed for ALAT > 3 ULN: one patient in the group ½ and 1 patient in the group 0. Both values normalised after treatment stop.

Neither relevant change over time nor relevant difference between groups was observed in the Safety Set regarding weight, sitting blood pressure and heart rate during the W0-W8 period.

CONCLUSION

This international, controlled, phase III study conducted in outpatients suffering from major depressive disorder and with insufficient antidepressant treatment efficacy showed that whatever the switch strategy (long tapering, short tapering or immediate substitution), discontinuation symptoms occurred after the previous antidepressant treatment stop: however, discontinuation symptoms were less frequent with long tapering than with short tapering and immediate substitution. This was mainly due to the lower number of patients affected (complementary analysis). Psychic symptoms were the most frequently reported (nervousness/anxiety, agitation, increased dreaming/nightmares, bouts of crying, sudden worsening of mood, trouble sleeping/insomnia).
Whatever the switch strategy, patients were markedly improved over time after intake of agomelatine 25 mg, with a high rate of responders despite failure of the previous antidepressant treatment by SSRI or SNRI. Efficacy was similar in all groups after 8 weeks of treatment even if for few criteria (feeling good and some emotions) improvement was found slightly better in patients with immediate substitution than in patients with tapering of the previous AD.
For most of efficacy criteria, improvement was clearly less marked when discontinuations symptoms were more frequent. This study thus suggested a direct impact of discontinuations symptoms on efficacy as judged by the physician (CGI), sleep, daytime sleepiness and in a less extent on emotions.
Emergent adverse events were less frequent in patients with long tapering than in patients with short tapering and immediate substitution. This likely reflected the differences in withdrawal symptoms evidenced with the DESS. Globally, the greater the length of time of the tapering, the lower the number of emergent adverse events there was. Regarding biology and other safety criteria, no relevant difference was observed according to the switch strategy.

Date of the report : 1 October 2012