Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy and safety of 3 doses (0.25, 0.5 and 1 mg/day) of agomelatine sublingual administration over an 8-week treatment period, in out-patients with Major Depressive Disorder.** **An 8-week randomised, double-blind, fixed dose, international multicentre, placebo-controlled study with parallel groups, followed by an extension double-blind treatment period of 16 weeks.**
Study drug	**S 90098**
Studied indication	**Major Depressive Disorder**
Development phase	**Phase II**
Protocol code	**CL2-90098-009**
Study initiation date	**22 February 2010**
Study completion date	**04 May 2011 (last W8/Wend visit)** **01 September 2011 (last W24/Wend visit)**
Main coordinator	[redacted] **- Canada**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Servier Canada, Inc.** **235, Armand-Frappier Boulevard** **Laval, Quebec, H7V 4A7 - Canada**
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 04 September 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:
Efficacy and safety of 3 doses (0.25, 0.5 and 1 mg/day) of agomelatine sublingual administration over an 8-week treatment period, in out-patients with Major Depressive Disorder.
An 8-week randomised, double-blind, fixed dose, international multicentre, placebo-controlled study with parallel groups, followed by an extension double-blind treatment period of 16 weeks.
Protocol No.: CL2-90098-009

Coordinators:
International coordinator: [redacted] (Toronto, Canada) who was also national coordinator in Canada.
National coordinators: [redacted] (Praha, Czech Republic) [redacted] (Tallinn, Estonia), [redacted] (Marseille, France), [redacted] (Helsinki, Finland), [redacted] (Monterrey, Mexico), [redacted] (Moscow, Russia), [redacted] (Stockholm, Sweden).

Study centres:
In all, 56 centres located in 8 countries were opened and 54 included at least one patient: Canada (58 included patients in 5 centres), Czech Republic (56 included patients in 4 centres), Estonia (30 included patients in 4 centres), Finland (127 included patients in 7 centres), France (63 included patients in 11 centres), Mexico (73 included patients in 7 centres), Russian Federation (80 included patients in 7 centres), Sweden (70 included patients in 9 centres).

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:** II
Initiation date: 22 February 2010 Completion date: 04 May 2011 *(last W8/Wend visit)* 01 September 2011 *(last W24/Wend visit)*	

Objectives:
The primary objective of this study was to assess the antidepressant efficacy of 3 doses (0.25, 0.5 and 1 mg/day) of S 90098 compared to placebo in out-patients suffering from Major Depressive Disorder, after 8 weeks of treatment, using the Hamilton Depression Scale 17 items total score (HAM-D 17-item; Hamilton, 1967).
The secondary objectives were to provide short-term and long-term safety data, to provide long-term antidepressant efficacy data, and to provide pharmacokinetic data in patients after sublingual administration of S 90098 at 0.25, 0.5 and 1 mg/day.
A pharmacogenetic substudy was described in a separate study protocol. The aims were to evaluate:
- Associations between polymorphisms in candidate genes and response to treatment.
- Associations between polymorphisms in candidate genes and safety profile.

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Methodology:
International multicentre, double-blind, placebo-controlled, phase II, randomised study with 4 parallel groups comparing 3 fixed doses, 0.25 mg, 0.50 mg and 1 mg of S 90098 *versus* placebo after 8 weeks of treatment in out-patients suffering from Major Depressive Disorder. At W8, according to investigator opinion and patient agreement, patients could continue in the 16-week extension double-blind treatment period with the same treatment. At W12 visit, only the patients having CGI item 2 ≤ 2 were allowed to continue in the extension period.
Randomisation was balanced, non-adaptive, with stratification on the raters (psychiatrist in charge of the scales administration in the centre *i.e.* investigator or co-investigator). Treatment randomisation and allocation were centralised with an Interactive Response System (IRS).
The analysis intended to respond at the primary objective of the study was performed before the end of the study on the data collected up to W8. Although the blind was broken before the end of the study, neither the investigators, nor the patients, nor the monitors were informed of the study treatment taken during the treatment period.
The results of the W8 analysis as well as those of the whole study were the subject for the present report.

Considering sublingual agomelatine (S 90098) was simultaneously developed in Europe and in USA, this dose-ranging study was to be included into the registration dossiers submitted to EMA and FDA. In this purpose, the main analysis was planned to be analysed using different statistical methods in order to fulfil the requirements for each Agency. This report focused on results of analyses for non-US submissions, analyses for US submission being considered as sensitivity analyses.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 540 patients (135 by treatment group)
Included: 557 patients (142 in the S 90098 0.25 mg group, 135 in the S 90098 0.50 mg group, 137 in the S 90098 1 mg group, and 143 patients in the placebo group).

Diagnosis and main criteria for inclusion:
Male or female out-patients, aged between 18 (or legal age of majority in the country) and 70 years (inclusive), and fulfilling DSM-IV TR criteria for Major Depressive Disorder. At selection, HAM-D 17 items total score was to be ≥ 22, HAD depression score ≥ 11, and CGI severity of illness was to be ≥ 4. At inclusion, HAM-D 17 items total score was still to be ≥ 22 and no more than a 20% of decrease in HAM-D total score between selection and inclusion, and CGI severity of illness was still to be ≥ 4.

Study drug:
Agomelatine: sublingual tablet containing 0.25 mg, or 0.50 mg or 1 mg, taken sublingually once a day at bedtime, preferably before 11 p.m.
Batch No. L0030798, L0031224, L0031226, L0034320, L0034360, L0034398

Reference product:
Placebo: sublingual tablet, taken sublingually once a day at bedtime, preferably before 11 p m.

Duration of treatment:
- 3 to 7-day run-in period without study treatment from selection to inclusion (W0) visits.
- 8-week acute double-blind treatment period (from W0 to W8).
- 16-week extension double-blind treatment period (from W8 to W24).
- 7-day follow-up period without treatment at the end of the acute double-blind period for patients not continuing the extension period or at the end of the extension double-blind period, or in case of premature withdrawal.

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Criteria for evalua2tion:

Efficacy measurements:

HAM-D 17-item scale: rated by the investigator at each visit from selection to W24 visits, or in case of premature withdrawal. The primary efficacy criterion was the HAM-D 17-item total score.

Clinical Global Impression scale (CGI): severity of illness score and global improvement score rated by the investigator at each visit from selection (severity of illness) or W2 (global improvement) to W24 visits, or in case of premature withdrawal.

Sheehan Disability Scale (SDS): self-assessed by the patient at selection, and W8, or in case of premature withdrawal between W0 and W8.

Safety measurements:

Adverse events: recording at each visit from selection to the follow-up visit.

Laboratory tests: prescribed at selection in order to have the results at W0, and at W8 and W24 or in case of premature withdrawal. Tests had to be done within 3 days after the visit. For liver function parameters only, additional tests were prescribed at W4 and W12.

Clinical examination: blood pressure and heart rate (in sitting position after 5 minutes rest), and weight were measured at selection, inclusion, W8, and W24 visits, or in case of premature withdrawal. Height was measured at selection. In addition, for patients who agreed to have pharmacokinetic samplings between W8 and W12, sitting blood pressure and heart rate were measured before study drug administration and 2 hours after study drug administration.

12-lead electrocardiogram: available at inclusion, and W24 visit, or at Wend in case of premature withdrawal.

Pharmacokinetic measurements:

After W8 visit, 4 blood samples were taken in patients followed in centres performing such measurements and who agreed to participate. Samples were collected 15 min, 30 min, 1 hour and 2 hours after drug administration (around 8 p m.).

Statistical methods:

Efficacy analyses

Primary criterion

Main analysis

In the context of non-US submissions, the superiority of each dose of S 90098 as compared to placebo was studied in the FAS on the change from baseline to W8 in HAM-D total score, using a single two-way analysis of covariance (ANCOVA) model on factors treatment and rater (random effect), with baseline as covariate and no interaction.

Missing data were imputed using a Last Observation Carried Forward (LOCF) approach.

The step-down Dunnett procedure was used to control the familywise error rate in the context of multiple comparisons *versus* placebo.

Sensitivity analyses

Some sensitivity analyses to the main analysis for non-US submissions were performed:

- Sensitivity analyses to the method of handling missing data:
  - MMRM: a MMRM on the change from baseline to each post-baseline visit until W8, including terms for effects of treatment, baseline HAM-D total score, rater (random effect), visit and an interaction term for treatment and visit was used for the comparison of each S 90098 dose *versus* placebo at W8, in the FAS. The step-down Dunnett procedure was used to deal with multiplicity issues.
  - Observed Cases analysis: the same ANCOVA model as main analysis was performed on the change from baseline to W8 considering only patients of the FAS having a value at W8. The step-down Dunnett procedure for multiplicity was a post-hoc adjustment.

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Statistical methods: (Cont'd)
Efficacy analyses (Cont'd)
Sensitivity analyses (Cont'd)

- Sensitivity analyses to the adjustment for covariates:
  - Unadjusted analysis: a single one-way analysis of variance model on factor treatment was performed in the FAS on the value at W8, missing data being imputed using an LOCF approach. The step-down Dunnett procedure for multiplicity was a post-hoc adjustment.

Some descriptive statistics in the FAS were provided for all analytical approaches of the primary criterion, overall and by country on the W0-W8 period (except for remission), and overall on the W0-W24 period, with and without imputation using an LOCF approach.

Secondary analyses

Information on the dose-response profile were provided in the FAS, considering the change from baseline to W8, missing data being imputed using an LOCF approach.
Besides, the difference between each dose of S 90098 and placebo was also studied in the FAS on the response to treatment at W8 (missing data being imputed using an LOCF approach) using a Chi-Square test.

Secondary criteria

For all analytical approaches of secondary criteria, descriptive statistics were provided in the FAS on the W0-W8 period (except for remission based on CGI-I), and the W0-W24 period, with and without imputation using an LOCF approach.
In addition for CGI scale, the difference between each S 90098 dose and placebo was studied in the FAS, on value at W8 with an LOCF approach to impute missing data:

- For Severity of illness and Global improvement scores, using a two-sided Student's t-test for independent samples and a Mann-Whitney test.
- On the response to treatment based on CGI-I using a Chi-Square test.

Safety analysis

Descriptive statistics were provided in the Safety Set by treatment group over the ASSE-W8/Wend and ASSE-W24/Wend periods for serious and emergent adverse events, and laboratory parameters, and over the W0-W8/Wend and W0-W24/Wend periods for physical examination, and ECG.

Pharmacokinetic analysis

A previous population PK model was developed using all available S 90098 PK information at the time of the analysis (Gaynor, NP30033, 2010). It took into account the statistical (but not clinical) impact of age and smoking habits on clearance and of BMI on the distribution volume. This model was used to analyse the pharmacokinetic data of the present study. Thus, the individual PK parameters of each patient were estimated using a Bayesian feedback approach. This approach takes into account the population distributions (through the population PK model and the corresponding parameter estimates) together with the observed data. This Bayesian feedback was performed using the Bayesian post-hoc conditional estimate option implemented in NONMEM. The individual primary PK parameter estimates were then used to compute the following secondary parameters: the area under the concentration-time curve (AUC), the terminal half-life ($t_{1/2,Z}$), the maximal concentration (C_{max}) and the corresponding time (t_{max}).

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

		S 90098 0.25 mg (N = 142)	**S 90098 0.50 mg (N = 135)**	**S 90098 1 mg (N = 137)**	**Placebo (N = 143)**	**ALL (N = 557)**
Included (Randomised)	N	**142**	**135**	**137**	**143**	**557**
W0-W8 period						
Lost to follow-up	n (%)	**-**	**-**	**3 (2.2)**	**1 (0.7)**	**4 (0.7)**
Withdrawn due to	n (%)	**26 (18.3)**	**18 (13.3)**	**30 (21.9)**	**29 (20.3)**	**103 (18.5)**
Lack of efficacy	n (%)	15 (10.6)	12 (8.9)	17 (12.4)	20 (14.0)	64 (11.5)
Non-medical reason	n (%)	3 (2.1)	1 (0.7)	10 (7.3)	5 (3.5)	19 (3.4)
Adverse event	n (%)	6 (4.2)	4 (3.0)	3 (2.2)	4 (2.8)	17 (3.1)
Protocol deviation	n (%)	1 (0.7)	1 (0.7)	-	-	2 (0.4)
Recovery, improvement	n (%)	1 (0.7)	-	-	-	1 (0.2)
Completed the W0-W8 period	n (%)	**116 (81.7)**	**117 (86.7)**	**104 (75.9)**	**113 (79.0)**	**450 (80.8)**
W8-W24 period						
Ongoing in the extension period	n (%)	**103 (72.5)**	**104 (77.0)**	**91 (66.4)**	**93 (65.0)**	**391 (70.2)**
Lost to follow-up	**n (%)**	**1 (0.7)**	**1 (0.7)**	**-**	**-**	**2 (0.4)**
Withdrawn due to	**n (%)**	**14 (9.9)**	**20 (14.8)**	**14 (10.2)**	**21 (14.7)**	**69 (12.4)**
Lack of efficacy	n (%)	10 (7.0)	12 (8.9)	6 (4.4)	14 (9.8)	42 (7.5)
Non-medical reason	n (%)	2 (1.4)	3 (2.2)	4 (2.9)	3 (2.1)	12 (2.2)
Adverse event	n (%)	1 (0.7)	4 (3.0)	4 (2.9)	2 (1.4)	11 (2.0)
Protocol deviation	n (%)	-	1 (0.7)	-	1 (0.7)	2 (0.4)
Recovery, improvement	n (%)	1 (0.7)	-	-	1 (0.7)	2 (0.4)
Completed at W24	**n (%)**	**88 (62.0)**	**83 (61.5)**	**77 (56.2)**	**72 (50.3)**	**320 (57.5)**
Performed the follow-up visit	n (%)	*122 (86.0)*	*128 (94.8)*	*117 (85.4)*	*132 (92.3)*	*499 (89.6)*
Analysis Sets						
Randomised Set (RS)	n	142	135	137	143	557
Full Analysis Set (FAS)	n (%)	141 (99.3)	134 (99.3)	135 (98.5)	142 (99.3)	552 (99.1)
Safety Set (SS)	n (%)	142 (100.0)	135 (100.0)	136 (99.3)	143 (100.0)	556 (99.8)
Pharmacokinetic Set	n (%)	41 (28.9)	41 (30.4)	39 (28.5)	NA	121 (21.7)

% according to randomised patients ; NA not applicable

A total of 686 patients were selected of whom 557 were included and randomised: 142 in the S 90098 0.25 mg group, 135 in the S 90098 0.50 mg group, 137 in the S 90098 1 mg group and 143 in the placebo group. Among them, 450 (80.8%) completed the acute double-blind treatment period (W0-W8). Among the patients who completed the acute treatment period, patients entering in the extension period (391 in total, 86.9%) were more numerous in each of the S 90098 dose groups (88.8% in the 0.25 mg group, 88.9% in the 0.50 mg group and 87.5% in the 1 mg group) than in the placebo group (82.3%). A total of 320 randomised patients (57.5%) completed the study at W24.

During the W0-W24 period, 6 patients (1.1%) were lost to follow-up. Among them, 4 were responders to treatment at the last visit attended, and 2 did not attend the W2 visit.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Overall, excluding these 6 patients, 172 patients (30.9%) were prematurely withdrawn during the W0-W24 period: 40 (28.2%) in the S 90098 0.25 mg group, 38 (28.1%) in the S 90098 0.50 mg group, 44 (32.1%) in the S 90098 1 mg group, and 50 (35.0%) in the placebo group. The highest rate of withdrawals was reported in the placebo group. The main reason for premature withdrawal was lack of efficacy in 106 patients (19.0%) with a lower frequency in the 3 active treatment groups than in the placebo group: 25 patients (17.6%) in the S 90098 0.25 mg group, 24 patients (17.8%) in the S 90098 0.50 mg group, 23 patients (16.8%) in the S 90098 1 mg group *versus* 34 patients (23.8%) in the placebo group.

In all but one treatment group (S 90098 0.50 mg group), the withdrawals occurred more frequently during the W0-W8 period than during the W8-W24 period.

During the W0-W8 period, the highest rate of withdrawals was reported in the S 90098 1 mg group (18.3% of patients in the S 90098 0.25 mg group, 13.3% in the S 90098 0.50 mg group, 21.9% in the S 90098 1 mg group, and 20.3% in the placebo group), mainly because of the most frequent withdrawals for non-medical reasons (2.1% in the S 90098 0.25 mg group, 0.7% in the S 90098 0.50 mg group, 7.3% in the S 90098 1 mg group, and 3.5% in the placebo group).

In the RS, patients had a mean age of 45.3 ± 13.0 years, and approximately 2 thirds were women (63.9%) with a higher percentage of females in each of the S 90098 dose groups (62.7% in the 0.25 mg group, 68.9% in the 0.50 mg group and 65.7% in the 1 mg group) than in the placebo group (58.7%). All patients were diagnosed with major depressive disorder (MDD) according to the DSM-IV-TR for a mean duration of 8.4 ± 9.0 years (median 5.3 years with a longer median duration in the S 90098 0.25 mg group, 6.4 years than in the other groups: 5.1 years in the S 90098 0.50 mg group and 5.2 years in the S 90098 1 mg and placebo groups). Recurrent episode was observed in most patients (76.5% overall: 74.7% in the S 90098 0.25 mg group, 78.5% in the S 90098 0.50 mg group, 77.4% in the S 90098 1 mg group, 75.5% in the placebo group). The current episode was of 5.8 ± 4.4 months duration in average (median 4.4 months).

Most patients (64.3%) had a moderate MDD and 35.7% had a severe MDD, without psychotic feature. Melancholic features were observed in 77.7% of the patients (78.9% in the S 90098 0.25 mg group, 77.0% in the S 90098 0.50 mg group, 78.1% in the S 90098 1 mg group and 76.9% in the placebo group).

Regarding **depression scales**, *HAM-D 17-item total score* at inclusion ranged from 22 to 35 (mean ± SD = 26.1 ± 2.7). *CGI severity of illness score* ranged from 4 (moderately ill) to 6 (severely ill), with mean ± SD = 4.7 ± 0.6. At selection, mean *HAD depression score* was 15.3 ± 2.6, ranging from 11 to 21, and mean *HAD anxiety score* was 11.2 ± 4.0 (range from 2 to 21). Lastly, mean respective *SDS scores* for work, social life and family and home responsibilities at selection were 7.4 ± 1.7, 7.5 ± 1.5 and 7.3 ± 1.6, indicating a marked disruption of these activities induced by the symptoms of depression. There was no relevant difference between groups for any of these criteria except for the percentage of anxious patients (anxiety score ≥ 11) which was higher in the S 90098 0.25 mg and 0.50 mg groups than in the other groups (57.0% in the S 90098 0.25 mg and 0.50 mg groups *versus* 47.5% in the S 90098 1 mg group and 51.8% in the placebo group).

Baseline characteristics in the FAS (N = 552, 99.1% of the Randomised Set) were similar to those in the RS.

In the Randomised Set, the mean treatment duration over the acute treatment period was of 52.5 ± 9.8 days, *i.e.* approximately 7.5 weeks (median = 56 days) without relevant difference between groups.

During the W0-W24 treatment period, treatment duration ranged between 5 and 197 days, with a mean ± SD of 123.2 ± 57.4 days, *i.e.* approximately 18 weeks (median = 166 days) with a longer duration in the 3 S 90098 groups than in the placebo group.

Global compliance was satisfactory in all treatment groups during both periods (mean ± SD = 97.6 ± 7.8% during the W0-W8 period). Similar results were observed over the W0-W24 period.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

The results summarized hereafter are those corresponding to analyses over the W0-W8 period.

Primary assessment criterion: HAM-D total score

In the FAS, the mean HAM-D total score decreased from baseline to W8 (LOCF) in the four treatment groups. The mean decrease was higher in the 3 S 90098 groups than in the placebo group:

- –13.7 ± 7.9 in the S 90098 0.25 mg group.
- –13.9 ± 7.4 in the S 90098 0.50 mg group.
- –13.1 ± 8.4 in the S 90098 1 mg.
- –11.8 ± 7.7 in the placebo group.

No statistically significant difference were observed between any of the S 90098 dose groups and the placebo group for the change from baseline to W8 LOCF (main analysis: covariance analysis adjusted for baseline HAM-D total score and rater using step-down Dunnett adjustment for multiplicity):

- S 90098 0.25 mg group *versus* placebo group: E (SE) = 1.83 (0.84), 95% CI = [0.17 ; 3.49], p = 0.074.
- S 90098 0.50 mg group *versus* placebo group: E (SE) = 1.88 (0.86), 95% CI = [0.20 ; 3.56], p = 0.074.
- S 90098 1 mg group *versus* placebo group: E (SE) = 1.14 (0.85), 95% CI = [-0.53, 2.82], p = 0.181.

The results of the main analysis were confirmed by the sensitivity analyses using post-hoc step-down Dunnett adjustment for multiplicity (see Table below): unadjusted analysis for value at W8 (LOCF), and MMRM on the change from baseline to W8. Observed cases analysis at W8 adjusted for baseline HAM-D total score and rater also confirmed this result for the change from baseline to W8 in the S 90098 0.50 mg group, and showed a statistically significant difference between S 90098 0.25 and 1 mg groups compared to the placebo group in favour of S 90098.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Summary of statistical results of the change from baseline in HAM-D 17-item total score to W8 and W8 (LOCF) over the W0-W8 period in the FAS (main analysis and sensitivity analyses results)

		S 90098 0.25 mg (N = 141)	**S 90098 0.50 mg (N = 134)**	**S 90098 1 mg (N = 135)**	**Placebo (N = 142)**
Baseline	n	141	134	135	142
	Mean ± SD	26.1 ± 2.7	26.1 ± 2.6	26.3 ± 2.8	26.0 ± 2.7
W8	n	124	123	107	123
	Mean ± SD	10.9 ± 6.7	11.6 ± 7.0	10.7 ± 6.5	12.7 ± 7.0
W8 (LOCF)	n	141	134	135	142
	Mean ± SD	12.4 ± 7.9	12.3 ± 7.4	13.2 ± 8.0	14.2 ± 7.7
Change from baseline to W8	n	124	123	107	123
	Mean ± SD	-15.2 ± 6.8	-14.6 ± 6.8	-15.6 ± 7.0	-13.4 ± 6.9
Change from baseline to W8 (LOCF)	n	141	134	135	142
	Mean ± SD	-13.7 ± 7.9	-13.9 ± 7.4	-13.1 ± 8.4	-11.8 ± 7.7
Statistical analysis					
Main analysis #	E (SE) (1)	1.83 (0.84)	1.88 (0.86)	1.14 (0.85)	
(on change from baseline to W8 (LOCF))	95% CI (2)	[0.17 ; 3.49]	[0.20 ; 3.56]	[-0.53 ; 2.82]	
	p-value (3)	0.074	0.074	0.181	
Sensitivity analyses					
Unadjusted analysis ##	E (SE) (1)	1.80 (0.92)	1.91 (0.93)	1.05 (0.93)	
(on W8 LOCF)	95% CI (2)	[-0.01 ; 3.61]	[0.08 ; 3.74]	[-0.78 ; 2.88]	
	p-value (3)*	0.104	0.104	0.260	
MMRM###	E (SE) (1)	1.64 (0.81)	1.60 (0.81)	1.67 (0.83	
(on change from baseline to W8)	95% CI (2)	[0.05 ; 3.23]	[0.01 ; 3.20]	[0.03 ; 3.30]	
	p-value (3)	0.110	0.110	0.110	
Observed Cases #	E (SE) (1)	1.78 (0.77)	1.27 (0.77)	2.16 (0.80)	
(on change from baseline to W8)	95% CI (2)	[0.26 ; 3.29]	[-0.25 ; 2.78]	[0.59 ; 3.74]	
	p-value (3)*	0.040	0.100	0.020	

 # Analysis of covariance model on factor treatment with baseline HAM-D total score and rater (random effect) as covariates
Analysis of variance model on factor treatment
Mixed-effects Model with Repeated Measures including terms for effects of Treatment, Visit, Treatment x Visit, baseline HAM-D total score and rater (random effect)
(1) Estimate (Standard Error) of the difference between adjusted or not treatment group means Placebo minus S 90098 dose
(2) Two-sided 95% Confidence Interval of the estimate
(3) Two-sided p-value taking into account step-down Dunnett's adjustment (to be compared to 0.05)
** Step-down Dunnett's adjustment not planned in the statistical analysis plan*

In the FAS, the percentage of responders (decrease in HAM-D total score of at least 50% from baseline) at W8 (LOCF) in each S 90098 dose groups (60.3% with 0.25 mg, 60.5% with 0.50 mg and 58.5% with 1 mg) was higher than in the placebo group (49.3%) without reaching statistically significant difference.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Secondary assessment criteria

- Clinical Global Impression (CGI)

Severity of illness score:

In the FAS, the mean CGI severity of illness score decreased over the W0-W8 period in all treatment groups. At W8 (LOCF), there was no statistically significant difference between any of the S 90098 dose groups and the placebo group (see Table below).

Global improvement score

In the FAS, the mean CGI global improvement score decreased over the W0-W8 period in all treatment groups. At W8 (LOCF), it was statistically significantly lower in the 0.50 mg group than in the placebo group, and showed no statistically significant difference with the other S 90098 doses (see Table below).

In the FAS, the percentage of responders according to CGI global improvement (score = 1 or 2) increased over the W0-W8 period in all treatment groups. At W8 (LOCF), it was statistically significantly higher in the S 90098 0.25 and 0.50 mg groups than in the placebo group, and showed no statistically significant difference between the S 90098 1 mg group and the placebo group (see Table below).

Summary of statistical results of both CGI scores at W8 (LOCF) in the FAS

		S 90098 0.25 mg (N = 141)	S 90098 0.50 mg (N = 134)	S 90098 1 mg (N = 135)	Placebo (N = 142)
Severity of illness score					
Value at W8 (LOCF)	n	141	134	135	142
	Mean ± SD	2.9 ± 1.4	2.9 ± 1.3	3.0 ± 1.3	3.2 ± 1.3
	Median	3.0	3.0	3.0	3.0
Statistical analysis					
	E (SE) (1)	0.24 (0.16)	0.27 (0.16)	0.20 (0.16)	
	95% CI (2)	[-0.07 ; 0.55]	[-0.04 ; 0.57]	[-0.11 ; 0.51]	
	p-value (3)	0.133	0.088	0.202	
	p-value (4)	0.095	0.050	0.173	
Global Improvement score					
Value at W8 (LOCF)	n	141	134	135	142
	Mean ± SD	2.2 ± 1.2	2.1 ± 1.1	2.3 ± 1.3	2.4 ± 1.2
	Median	2.0	2.0	2.0	2.0
Statistical analysis					
	E (SE) (1)	0.27 (0.14)	0.33 (0.14)	0.09 (0.15)	
	95% CI (2)	[0.00 ; 0.55]	[0.06 ; 0.60]	[-0.20 ; 0.38]	
	p-value (3)	0.050	0.017	0.549	
	p-value (4)	0.040	0.014	0.361	
Response at W8 (LOCF)	n (%)	95 (67.4)	98 (73.1)	88 (65.2)	79 (55.6)
Statistical analysis					
	E (SE) (1)	-11.74 (5.74)	-17.50 (5.66)	-9.55 (5.85)	
	95% CI (2)	[-23.00 ; -0.49]	[-28.60 ; -6.41]	[-21.01 ; 1.91]	
	p-value (5)	0.042	0.002	0.104	

(1) Estimate (Standard Error) of the difference between treatment group means or percentages Placebo minus S 90098 dose; (2) Two-sided 95% Confidence Interval of the estimate; (3) Two-sided Student's T-test for independent samples p-value; (4) Mann-Whitney test p-value; (5) Chi-Square test p-value

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- Sheehan Disability Scale (SDS)

In the FAS, the 3 mean SDS score decreased between the baseline and W8 (LOCF) in all treatment groups. The 3 mean decreases were higher in any of the S 90098 dose groups than in the placebo group as follows:

- Work: -3.3 ± 2.8 in the S 90098 0.25 mg group, -3.0 ± 2.8 in the S 90098 0.50 mg group and –3.0 ± 3.1 in the S 90098 1 mg group *versus* –2.3 ± 2.9 in the placebo group.
- Social life: -3.5 ± 2.9, -3.1 ± 2.8, -3.0 ± 3.0 *versus* – 2.5 ± 2.7, respectively.
- Family life and home responsibilities: - 3.3 ± 2.9, -3.0 ± 2.5, -3.0 ± 3.1 *versus* –2.6 ± 3.1, respectively.

SAFETY RESULTS

Main safety results

		S 90098 0.25 mg (N = 142)	**S 90098 0.50 mg (N = 135)**	**S 90098 1 mg (N = 136)**	**Placebo (N = 143)**
8-week treatment period					
Patients having reported					
at least one emergent adverse event	n (%)	67 (47.2)	62 (45.9)	61 (44.9)	66 (46.2)
at least one treatment-related emergent adverse event	n (%)	42 (29.6)	37 (27.4)	37 (27.2)	31 (21.7)
24-week treatment period					
Patients having reported					
at least one emergent adverse event	n (%)	79 (55.6)	74 (54.8)	72 (52.9)	73 (51.0)
at least one treatment-related emergent adverse event	n (%)	45 (31.7)	39 (28.9)	38 (27.9)	35 (24.5)
During the study					
Patients having experienced					
at least one serious adverse event (excluding death)	n (%)	2 (1.4)	2 (1.5)	3 (2.2)	3 (2.1)
at least one emergent serious adverse event	n (%)	1 (0.7)	2 (1.5)	1 (0.7)	3 (2.1)
at least one emergent treatment-related serious adverse event	n (%)	-	-	-	1 (0.7)
Patients withdrawn					
due to an emergent adverse event (excluding death)	n (%)	8 (5.6)**	7 (5.2)	7 (5.1)	7 (4.9)**
due to an emergent serious adverse event	n (%)	1 (0.7)	1 (0.7)	-	2 (1.4)
due a treatment-related adverse event	n (%)	4 (2.8)	4 (3.0)	5 (3.7)	5 (3.5)
due a treatment-related serious adverse event	n (%)	-	-	-	1 (0.7)
Patients who died	n (%)	-	1* (0.7)	-	-

** 59-year-old male patient (No. 009 250 0505 09463) died of unknown cause after 174 days on S 90098 0.50 mg. The death was considered as not related to the study drug by the investigator.*

*** Including one patient withdrawn from the study due to lack of efficacy.*

In the Safety Set, the percentage of patients with at least one emergent adverse event during the 8-week treatment period showed no relevant differences between treatment groups (47.2% in the S 90098 0.25 mg group, 45.9% in the S 90098 0.50 mg group, 44.9% in the S 90098 1 mg group, and 46.2% in the placebo group).

During this period, the most frequently affected system organ classes (at least 15% of patients) were nervous system disorders and gastrointestinal disorders in all treatment groups. Nervous system disorders were reported in 17.6% of the patients in the S 90098 0.25 mg group, 17.8% in the S 90098 0.50 mg group, 22.1% in the S 90098 1 mg group and 16.1% in the placebo group with a higher frequency in the S 90098 1 mg group than in the placebo group. Frequency of gastrointestinal disorders showed no relevant differences between treatment groups (between 14.7% in the placebo group and 16.9% in the S 90098 0.25 mg group).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

During the 8-week treatment period, the most frequent emergent adverse event was headache in all treatment groups without relevant difference between the 3 S 90098 groups and the placebo group (13.4% in the S 90098 0.25 mg group, 12.6% in the S 90098 0.50 mg group, 11.0% in the S 90098 1 mg group, and 11.9% in the placebo group). Among the other most frequent emergent adverse events (reported in at least 4% of patients), the following ones had a higher frequency (*i.e.* with a difference of at least 3 patients) in one of the S 90098 groups than in the placebo group:

- Dizziness in the 3 S 90098 groups: 6 patients (4.2%) in the S 90098 0.25 mg group, 6 patients (4.4%) in the S 90098 0.50 mg group, and 13 patients (9.6%) in the S 90098 1 mg group *versus* 3 patients (2.1%) in the placebo group.
- Nausea in the 1 mg group: 4, 4, and 7 patients *i.e.* 2.8%, 3.0%, 5.1% in the 0.25 mg, 0.50 mg, and 1 mg groups, respectively *versus* 3 patients, 2.1% in the placebo group.
- Dry mouth in the 1 mg group: 5, 5 and 6 patients *i.e.* 3.5%, 3.7%, and 4.4% in the 0.25 mg, 0.50 mg, and 1 mg groups, respectively *versus* 3 patients, 2.1% in the placebo group.
- Nasopharyngitis in the 0.50 mg group: 4, 7 and 4 patients *i.e*. 2.8%, 5.2%, and 2.9% in the 0.25 mg, 0.50 mg, and 1 mg groups, respectively *versus* 3 patients, 2.1% in the placebo group.

No dose effect was observed.

The percentage of patients who experienced at least one severe emergent adverse event was lower in the 3 S 90098 groups than in the placebo group (7.9% in the S 90098 0.25 mg group, 4.4% in the S 90098 0.50 mg group, 5.0% in the S 90098 1 mg group *versus* 10.1% in the placebo group).

During the 8-week treatment period, the percentage of patients with at least one emergent adverse event considered by the investigator to be related to the study treatment, was higher in each of the S 90098 dose groups than in the placebo group (29.6% in the S 90098 0.25 mg group, 27.4% in the S 90098 0.50 mg group, 27.2% in the S 90098 1 mg group versus 21.7% in the placebo group).

During the 24-week treatment period in the Safety Set as during the 8-week treatment period, the percentage of patients with at least one emergent adverse event showed no relevant differences between treatment groups (55.6% in the S 90098 0.25 mg group, 54.8% in the S 90098 0.50 mg group, 52.9% in the S 90098 1 mg group, and 51.0% in the placebo group). Results obtained during the 24-week treatment period were in the same line as those during the 8-week treatment period.

During the study, one 59-year-old male patient (No. 009 250 0505 09463) died of unknown cause after 174 days on S 90098 0.50 mg. The death was considered as not related to the study drug by the investigator.

In addition, 7 patients experienced at least one non-fatal serious emergent adverse event during the 24-week treatment period without relevant difference between the treatment groups (1 patient (0.7%) in the S 90098 0.25 mg, 2 patients (1.5%) in the S 90098 0.50 mg group, 1 patient (0.7%) in the S 90098 1 mg group, and 3 patients (2.1%) in the placebo group).

No serious emergent adverse event was considered as treatment related by the investigator in the 3 S 90098 groups, and one was reported in the placebo group (mania).

All serious emergent adverse events resolved in the 3 S 90098 groups. In the placebo group, one cholelithiasis was recovering at the end of the study.

Non-fatal serious emergent adverse events led to study treatment discontinuation in 1 patient in the S 90098 0.25 mg group for an acute pyelonephritis, 1 patient in the S 90098 0.50 mg group for suicidal ideation, and 2 patients in the placebo group, one for a worsening of major depression, and the other for a mania.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

In addition, non-serious emergent adverse events were responsible for premature treatment withdrawal in 7 patients (4.9%) in the S 90098 0.25 mg group, 6 patients (4.4%) in the S 90098 0.50 mg group, 7 patients (5.1%) in the S 90098 1 mg group and 5 patients (3.5%) in the placebo group.

- **Laboratory evaluation**
  - No relevant difference between groups was detected on mean evolution over time of laboratory parameters over the ASSE-W24 period.
  - Over the ASSE-W24 period, emergent PCSA values were related to potassium, glucose, total cholesterol and triglycerides, chloride, urea, creatinine, and creatinine clearance. Emergent PCSA values were mainly reported for high total cholesterol (only reported in the S 90098 0.50 mg group (2 patients, 1.5%) and 1 mg group (3 patients, 2.5%)), and high triglycerides (4 patients (3.0%) in the S 90098 0.25 mg group, 8 patients (6.2%) in the S 90098 0.50 mg group, 7 patients (5.8%) in the S 90098 1 mg group and 3 patients (2.2%) in the placebo group).
  - Regarding liver parameters, emergent PCSA values were observed during the ASSE-W24 period in 4 patients (2.8%) in the S 90098 0.25 mg group, 5 (3.7%) in the S 90098 0.50 mg group, 3 (2.2%) in the S 90098 1 mg group and 7 (4.9%) in the placebo group.
    Among them, emergent PCSA values of ALAT and/or ASAT were reported in 2 patients (1.4%) in the S 90098 0.25 mg group, 3 (2.2%) in the S 90098 0.50 mg group, 1 (0.7%) in the S 90098 1 mg group and 2 (1.4%) in the placebo group. All patients recovered except one patient in the S 90098 1 mg group who was recovering at the end of the study. PCSA values are described below:
    - In the S 90098 0.25 mg group: 2 patients had emergent PCSA values of ASAT (18.1 ULN and 9.2 ULN) and ALAT (5.7 ULN and 15.6 ULN). These values were associated with emergent abnormal values of bilirubin (total, free and conjugated) without reaching PCSA limit in one patient, and with PCSA value of GGT (5.7 ULN) and a moderate increase in conjugated bilirubin and ALP in the other patient.
    - In the S 90098 0.50 mg group:
      - 2 patients had emergent PCSA values of ASAT (5 ULN and 3.1 ULN). In one patient, this value was associated with a moderate increase of ALAT and bilirubin (total, free and conjugated) under the PCSA limit.
      - 1 patient had emergent PCSA ALAT (maximum value 6.7 ULN). This value was associated with emergent abnormal ASAT and ALP without reaching the PCSA limit, and PCSA value of GGT (maximum value 6.7 ULN).
    - In the S 90098 1 mg group: 1 patient had emergent PCSA value of ALAT (3.1 ULN). This value was associated with a slight increase of ASAT, GGT and ALP under the PCSA limit.
    - In the placebo group:
      - 1 patient had emergent PCSA of ALAT (4.1 ULN) associated with a slight increase of ASAT above the normal range and emergent PCSA value of GGT (5.2 ULN).
      - 1 patient had emergent PCSA of ASAT (4 ULN) associated with a slight increase of ALAT above the normal range.
  - Regarding haematology, emergent PCSA values were reported for low haemoglobin, and haematocrit, low and high white blood cells, low neutrophils and high eosinophils. Emergent PCSA values were mainly reported for low white blood cells (3 patients *i.e.* 2.3% in the S 90098 0.25 mg group, 3 patients *i.e.* 2.3% in the S 90098 0.50 mg group, 1 patient *i.e.* 0.8% in the S 90098 1 mg group and 4 patients *i.e*. 3.0% in the placebo group) and low neutrophils (respectively 3 patients *i.e.* 2.3%, 3 patients *i.e.* 2.3%, 1 patient *i.e.* 0.8% and 3 patients *i.e*. 2.2%).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Clinical examination**

  Clinical examination (weight, BMI, sitting blood pressure and heart rate) did not show any clinically relevant changes over time nor between-group difference over the W0-W24 period.

- **Electrocardiogram abnormalities**

  Emergent ECG abnormalities under treatment over the W0-W24 period were reported in 11/103 patients (10.7%) in the S 90098 0.25 mg group, 15/102 patients (14.7%) in the S 90098 0.50 mg group, 11/94 patients (11.7%) in the S 90098 1 mg group, and 20/113 patients (17.7%) in the placebo group. All emergent ECG abnormalities were considered as not clinically significant by the investigator.

PHARMACOKINETIC RESULTS

Descriptive statistics of the agomelatine pharmacokinetic parameters in plasma per dose

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

[1] *mean ± SD (median)*
[2] *median (min ; max)*
[3] *patients with only BLQ data were not taken into account in the analysis*
N number of patients

The median AUC values were [redacted] and [redacted] ng/mL.h for the agomelatine doses of 0.25, 0.50 and 1 mg, respectively. The median C_{max} values were [redacted] and [redacted] ng/mL.h for the agomelatine doses of 0.25, 0.50 and 1 mg, respectively.

Few patients had all or some samples below the lower limit of quantification (BLQ). Four patients (3.3% of the PK set) had all samples BLQ and 5 patients (4.1% of the PK set) had 1, 2 or 3 samples BLQ. These agomelatine BLQ levels can be due to an incorrect drug intake by swallowing despite the controlled conditions at the investigator site. It gives an indication of potentially low drug palatability in current clinical condition.

CONCLUSION

This international double-blind, randomised placebo-controlled study in patients suffering from Major Depressive Disorder failed to show a statistically significant effect of sublingual agomelatine (S 90098) at 0.25, 0.50 or 1 mg/day as compared to placebo on the HAM-D total score reduction over an 8-week treatment period (primary efficacy criterion). An inadequate intake of the study drug as well as the high rate of placebo responders (49%) probably explained the failure to demonstrate a statistically significant difference as compared to placebo.

The short-term and long-term safety of the three doses of sublingual agomelatine was satisfactory. No unexpected adverse event was observed.

Date of the report: 04 September 2012