Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy and safety of 2 doses of S 90098 (1 and 2 mg/day), sublingual formulation for 8 weeks 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 for 16 weeks.**
Study drug	**S 90098 - Agomelatine orodispersible**
Studied indication	**Major Depressive Disorder**
Development phase	**Phase II**
Protocol code	**CL2-90098-005**
Study initiation date	**25 February 2008**
Study completion date	**24 April 2009**
Main coordinator	[redacted] **France**
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 04 December 2009**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

Title of study:
Efficacy and safety of 2 doses of S 90098 (1 and 2 mg/day), sublingual formulation for 8 weeks 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 for 16 weeks.
Protocol No.: CL2-90098-005

Coordinators:
International coordinator: [redacted] France [redacted] was also national coordinator for France.
National coordinators: [redacted] Czech Republic; [redacted] Estonia; [redacted] Lithuania; [redacted] Finland.

Study centres:
In all, 26 centres located in 5 countries were opened and 25 included at least one patient: Czech Republic (50 included patients in 4 centres), Estonia (35 included patients in 4 centres), Finland (101 included patients in 7 centres), France (46 included patients in 6 centres / 7 centres opened), Lithuania (35 included patients in 4 centres).

Publication (reference): Not applicable

Studied period: Initiation date: 25 February 2008 Completion date: 24 April 2009	**Phase of development of the study:** II

Objectives:
Primary objective: to assess the antidepressant efficacy of 2 doses of S 90098 compared to placebo after 8 weeks of treatment, in out-patients suffering from Major Depressive Disorder (MDD), using the Hamilton Depression Rating Scale 17-item (HAM-D) total score.
Secondary objectives: to provide short-term and long-term safety data, to study the effects of S 90098 on subjective sleep and daytime sleepiness, to provide long-term efficacy data, and to provide pharmacokinetic data after 12 weeks of treatment.

Methodology:
International, multicentre, randomised, phase II study with therapeutic benefit conducted in double-blind with 3 parallel groups, comparing two fixed doses, 1 and 2 mg of S 90098 *versus* placebo after 8 weeks of treatment in patients with moderate to severe MDD. At W8, patients well-improved according to investigator's opinion could continue in the 16-week extension double-blind treatment period with the same treatment. According to Amendment No. 3, in Czech Republic, patients well-improved at W8 were defined as patients with CGI global improvement score (CGI-I) ≤ 2. All investigators were psychiatrists.
Randomisation was balanced, non adaptive, with stratification on the centre.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 240 patients (80 by group)
Included: 267 patients (86 in the S 90098 1 mg group, 89 in the S 90098 2 mg group, 92 in the placebo group)

Diagnosis and main criteria for inclusion:
Male or female, out-patients, aged from 18 (or legal age of majority in the country) to 70 years (inclusive), fulfilling DSM-IV TR criteria for Major Depressive Disorder of moderate or severe intensity, with a single or recurrent episode which lasted from at least 4 weeks. At selection and inclusion, HAM-D 17-item total score was to be ≥ 22 (with decrease between selection and inclusion, if any, ≤ 20%), CGI severity of illness score (CGI-S) ≥ 4 (in Czech Republic centres, CGI-S ≥ 4 and ≤ 6 according to Amendment No. 3). At selection, HAD depression sub-score was to be ≥ 11.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

Study drug:
Agomelatine: sublingual tablet containing 1 or 2 mg, taken sublingually once a day at bedtime, preferably before 11 p m.
Batch No.: L0020761 (1 mg); L0020759 (2 mg)

Reference product:
Placebo: sublingual tablet, taken sublingually once a day at bedtime, preferably before 11 p.m.
Batch No.: L0020894

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 or at the end of the extension double-blind period, or in case of premature withdrawal.

Criteria for evaluation:

EFFICACY MEASUREMENTS:

DEPRESSION:

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.

Hospital Anxiety and Depression scale (HAD): self-assessed by the patient at selection, at W8, and at W24 for patients ongoing in the extension period (added by Amendment No. 1), or in case of premature withdrawal.

Sheehan Disability Scale (SDS): self-assessed by the patient at selection, at W8, and at W24 for patients ongoing in the extension period (added by Amendment No. 1), or in case of premature withdrawal.

SLEEP:

Leeds Sleep Evaluation Questionnaire (LSEQ): self-assessed at each visit from W2 to W8, or in case of premature withdrawal during the W0-W8 period.

Daytime sleepiness visual analogue scales (VAS): rated by the patient at each visit from W0 to W8, or in case of premature withdrawal during the W0-W8 period. Due to a printing error in the case report form (CRF), the VAS used had not the usual length (100 mm) and was different between France (about 85 mm) and the other countries (about 90 mm). The results are thus not presented in the synopsis.

SAFETY MEASUREMENTS:

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

Laboratory tests: results available at inclusion, W8 and W24 visits, and at the follow-up visit (WEND) in case of premature withdrawal.

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 at W12, sitting blood pressure and heart rate were measured before study drug administration and 1 and 3 hours after study drug administration.

12-lead electrocardiogram: available at inclusion, W8 and W24 visit, or in case of premature withdrawal.

PHARMACOKINETIC MEASUREMENTS:

At W12, 5 blood and saliva samples were taken in patients followed in centres performing such measurements and who agreed to participate. Samples were collected in the evening of W12 after clinical assessments 30 minutes prior to drug administration, then, 15 min, 30 min, 1 hour and 3 hours post-dose. The pharmacokinetic analysis is described in a separate report.

Name of Company: I.R.I.S. 6 place des Pleiades 92415 Courbevoie - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

Statistical methods:

Since the main analysis was set up over the acute treatment period (W0-W8), the blind was broken once all data of the W0-W8 period were available and validated, in order to perform this analysis. However, although the blind was broken before the end of the study, neither investigators, nor patients, nor monitors were informed of the study treatment taken during the treatment period, and the analysis of the whole study period (W0-W24) was performed subsequently.

EFFICACY ANALYSES

- **Primary efficacy criterion: HAM-D 17-item total score**

Main analysis

The superiority of each dose of S 90098 on placebo was studied in the Full Analysis Set (FAS) on the change from baseline to last post-baseline value of HAM-D-17-item total score over the W0-W8 period, using a single two-way analysis of covariance on factors treatment and centre (random effect), with baseline as covariate and no interaction. The Hochberg's procedure was used in order to take into account the multiplicity of comparisons *versus* placebo.

Sensitivity analysis

The same analysis strategy without adjustment for centre and baseline was repeated on the last post-baseline value over the W0-W8 period, using a single one-way analysis of variance on factor treatment.

Secondary analyses

The difference between each dose of S 90098 and placebo was also studied in the FAS on the response to treatment (defined as a decrease from baseline in total score ≥ 50%) taking into account the last post-baseline value over the W0-W8 period, using a Chi-Square test at the 5% level.

All previous analyses were also performed at W8 in the Observed Cases W8 Set (OCW8S defined as patients of the FAS having a value for the primary efficacy criterion at W8), and over the W0-W24 period in the FAS.

Moreover, the difference between each dose of S 90098 and placebo was also estimated in the FAS (giving the 95% confidence interval of the difference) on the remission (defined as a total score ≤ 7) taking into account the last post-baseline value over the W0-W24 period.

- **Secondary efficacy criteria**
  - *CGI scores*

The difference between each S 90098 dose and placebo was studied in the FAS:

On the last (post-baseline) value for severity of illness and global improvement scores over the W0-W8 period, using a two-sided Student's t-test for independent samples and a Mann-Whitney test at the 5% level.

On the response to treatment (defined as a CGI-I score = 1 or 2) considering the last value over the W0-W8 period, using a Chi-Square test at the 5% level.

The previous analyses were also performed over the W0-W24 period.

The difference between each dose of S 90098 and placebo was also assessed in the FAS (giving the 95% confidence interval of the difference) on the remission (defined as a CGI-I score = 1) taking into account the last value over the W0-W24 period.

  - *Other secondary criteria*

For other efficacy criteria on depression (HAD and SDS scores), and on sleep (LSEQ scores), descriptive statistics were provided in the FAS over the W0-W8 and W0-W24 (for HAD and SDS) periods.

As complementary analyses, the difference between each dose of S 90098 and placebo was also studied in the FAS on the last value over the W0-W8 period for the LSEQ getting off to sleep and quality of sleep scores, using a two-sided Student's t-test at the 5% level.

SAFETY ANALYSES

Descriptive statistics were provided in the Safety Set for the 3 treatment groups over the W0-W8 and W0-W24 periods.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

		S 90098 1 mg	S 90098 2 mg	Placebo	All
Acute double-blind treatment period (W0-W8)					
Included (Randomised)	**N**	**86**	**89**	**92**	**267**
Withdrawn due to	**n (%)**	**11 (12.8)**	**16 (18.0)**	**14 (15.2)**	**41 (15.4)**
Lack of efficacy	n (%)	7 (8.1)	6 (6.7)	5 (5.4)	18 (6.7)
Adverse event	n (%)	1 (1.2)	4 (4.5)	5 (5.4)	10 (3.7)
Protocol deviation	n (%)	-	6 (6.7)	2 (2.2)	8 (3.0)
Non medical reason	n (%)	3 (3.5)	-	2 (2.2)	5 (1.9)
Completed the W0-W8 period	**n (%)**	**75 (87.2)**	**73 (82.0)**	**78 (84.8)**	**226 (84.6)**
Extension double-blind treatment period (W8-W24)					
Ongoing in the W8-W24 extension period	**N' (%)**	**67 (77.9)**	**56 (62.9)**	**56 (60.9)**	**179 (67.0)**
Withdrawn due to	**n (%')**	**9 (13.4)**	**5 (8.9)**	**7 (12.5)**	**21 (11.7)**
Lack of efficacy	n (%')	4 (6.0)	2 (3.6)	1 (1.8)	7 (3.9)
Adverse event	n (%')	4 (6.0)	1 (1.8)	2 (3.6)	7 (3.9)
Non medical reason	n (%')	1 (1.5)	2 (3.6)	3 (5.4)	6 (3.4)
Protocol deviation	n (%')	-	-	1 (1.8)	1 (0.6)
Completed the W8-W24 period	n (%')	**58 (86.6)**	**51 (91.1)**	**49 (87.5)**	**158 (88.3)**
Completed the W0-W24 period	**n (%)**	**58 (67.4)**	**51 (57.3)**	**49 (53.3)**	**158 (59.2)**
Analysis sets					
Randomised Set (RS)	n	86	89	92	267
Full Analysis Set (FAS)	n (%)	86 (100)	87 (97.8)	91 (98.9)	264 (98.9)
Observed Cases W8 Set (OCW8S)	n (%)	75 (87.2)	75 (84.3)	77 (83.7)	227 (85.0)
Safety Set (SS)	n (%)	86 (100)	87 (97.8)	92 (100)	265 (99.3)

% = (n/N) x 100 (percentage of patients from the RS); *%' = (n/N') x 100 (percentage of patients ongoing in the extension period)*

A total of 267 patients were included and randomised: 86 in the S 90098 1 mg group, 89 in the S 90098 2 mg group, and 92 in the placebo group. Among them, respectively 75 (87.2%), 73 (82.0%), and 78 (84.8%) completed the **acute treatment period (W0-W8)**, while 11 (12.8%), 16 (18.0%), and 14 (15.2%) were prematurely withdrawn during this period. The main reason for withdrawal was lack of efficacy: 7 patients (8.1%) in the S 90098 1 mg group, 6 patients (6.7%) in the S 90098 2 mg group, and 5 patients (5.4%) in the placebo group. Ten patients were withdrawn for adverse event: 1 (1.2%) in the S 90098 1 mg group, 4 (4.5%) in the S 90098 2 mg group, and 5 (5.4%) in the placebo group. More patients from the S 90098 1 mg group (77.9%) entered the **extension treatment period (W8-W24)** than from the S 90098 2 mg group (62.9%) and the placebo group (60.9%). Among them, overall, 158 patients (88.3%) completed the extension treatment period (W8-W24), and 21 (11.7%) of the patients were prematurely withdrawn during the W8-W24 period: 9 patients (13.4%) in the S 90098 1 mg group, 5 patients (8.9%) in the S 90098 2 mg group, and 7 patients (12.5%) in the placebo group, mainly for lack of efficacy and adverse event. No patient was lost to follow-up during the study. A total of 158 patients (59.2% of the RS) completed the study at W24.

In the RS, patients had a mean age of 47.0 ± 12.9 years, and approximately 2 thirds were women (68.2%).
All patients were diagnosed with major depressive disorder (MDD) according to the DSM-IV-TR criteria, for a mean duration of 9.0 ± 9.5 years (median 6.6 years with a longer median duration in the S 90098 1 and 2 mg groups, 7.3 and 7.9 years, respectively than in the placebo group, 4.6 years). Recurrent episode was observed in most patients (81.7% overall: 84.9% in the 1 mg group and 83.2% in the 2 mg group, and 77.2% in the placebo group). The current episode was of 5.5 ± 5.0 months duration in average (median 3.6 months).

Name of Company: I.R.I.S. 6 place des Pleiades 92415 Courbevoie - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Most patients (61.8%) had a moderate MDD, and 38.2% had a severe MDD, without psychotic feature. The latter were more numerous in the S 90098 1 mg group (44.2%) than in the S 90098 2 mg group (34.8%) and the placebo group (35.9%). Melancholic features were observed in 79.0% of the patients (respectively 80.2%, 75.3%, and 81.5%). More than half of the patients (59.2%) had received a previous psychotropic treatment, mainly selective serotonin reuptake inhibitors (33.7%).

No relevant difference between groups was detected for these characteristics except for duration of the disease, severity, and melancholic feature.

Regarding **depression scales**, *HAM-D 17-item total score* at inclusion ranged from 22 to 37 (mean ± SD = 26.5 ± 2.8). *CGI severity of illness score* ranged from 4 (moderately ill) to 6 (severely ill), with mean ± SD = 4.9 ± 0.6. At selection, mean *HAD depression score* was 14.9 ± 2.9, ranging from 8 to 21 (2 patients were deviant as they had a score < 11), and mean *HAD anxiety score* was 11.5 ± 3.6, ranging from 2 to 21. Lastly, mean respective *SDS scores* for work / school, social life, and family and home responsibilities at selection were 7.0 ± 1.9, 7.4 ± 1.5, and 7.1 ± 1.7, 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.

As concerns **sleep criteria**, on *screening of sleep and circadian rhythm disorders (Cirscreen)*, more than 60% of the patients had often or very often experienced, during the 7 days before inclusion, repeated awakening (71.5%), early morning awakening with difficulties falling asleep again (61.8%), and/or difficulties falling asleep at night or becoming wide awake in the morning (60.7% each); 71.2% had felt more depressed at particular times of the day, and 60.7% had often or very often felt sleepy during the daytime. No relevant difference between groups was detected.

Baseline characteristics in the FAS (N = 264) and the OCW8S (N = 227) were similar to those in the RS.

Mean **treatment duration** over the W0-W8 treatment period was 52.1 ± 11.6 days, *i.e.* approximately 7.4 weeks (median = 56 days), with no relevant difference between groups. Over the W0-W24 treatment period, mean treatment duration was 123.3 ± 58.8 days overall, *i.e.* approximately 17.6 weeks (median = 167 days), and was longer in the S 90098 1 mg group (136.0 ± 53.1 days) than in the S 90098 2 mg group (118.8 ± 61.4 days) and in the placebo group (115.7 ± 60.0 days), but with similar median values between groups.

Global compliance over the W0-W8 treatment period was satisfactory (mean ± SD = 96.7 ± 11.9%), and with no relevant difference between groups. Results were similar over the W0-W24 period.

EFFICACY

EFFICACY ON DEPRESSION

- **Primary efficacy criterion: HAM-D 17-item total score**

Change from baseline to last post-baseline value (main analytical approach)

Over the W0-W8 period in the FAS (main analysis), mean HAM-D total score decreased from W0 to last post-baseline value in all treatment groups (See Table on following page). This decrease was higher in the S 90098 1 mg group (mean change = -15.0 ± 7.3) than in the placebo group (-13.2 ± 7.8), without statistically significant difference (E (SE) = 1.81 (1.09), 95% CI = [-0.33 ; 3.95], p = 0.097).

The mean decrease from baseline in the S 90098 2 mg group (-13.9 ± 8.0) and the placebo group showed no relevant difference (E (SE) = 0.84 (1.09), 95% CI = [-1.30 ; 2.97], p = 0.443).

These results were confirmed by the unadjusted sensitivity analysis on the last post-baseline value.

In FAS patients with HAM-D total score at W8 (OCW8S), similar results were observed as the mean decrease in HAM-D 17-item total score from W0 to W8 was higher in the S 90098 1 mg group (-16.5 ± 6.1) than in the placebo group (-14.7 ± 7.1), but with no statistically significant difference. The mean decrease from baseline in the S 90098 2 mg group (-15.7 ± 6.8) and the placebo group showed no relevant difference.

Name of Company: I.R.I.S. 6 place des Pleiades 92415 Courbevoie - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)
EFFICACY ON DEPRESSION (Cont'd)

HAM-D 17-item total score over the W0-W8 period - FAS

		S 90098 1 mg (N = 86)	S 90098 2 mg (N = 87)	Placebo (N = 91)
	n	86	87	91
W0	Mean ± SD	26.5 ± 2.5	26.3 ± 2.8	26.6 ± 3.2
	Min - Max	22 - 35	22 - 35	22 - 37
Last post-baseline value	Mean ± SD	11.5 ± 7.2	12.4 ± 8.0	13.4 ± 7.7
	Min - Max	0 - 34	0 - 31	1 - 33
Change from W0 to last post-baseline value	Mean ± SD	-15.0 ± 7.3	-13.9 ± 8.0	-13.2 ± 7.8
	Min - Max	-30 - 2	-33 - 4	-26 - 3
Statistical analysis (main analysis) #	E (SE) (1)	1.81 (1.09)	0.84 (1.09)	
	95% CI (2)	[-0.33 ; 3.95]	[-1.30 ; 2.97]	
	p-value (3)	0.097 **	0.443 *	

 # Main analysis single two-way analysis of covariance on factors treatment and centre (random effect) and with baseline as covariate
(1) Estimate (Standard Error) of the difference between (adjusted) treatment group means Placebo minus S 90098 1 mg and Placebo minus S 90098 2 mg
(2) Two-sided 95% confidence interval of the estimate
(3) Two-sided p-value of treatment effect - Adjustment for multiplicity using Hochberg procedure
**p-value to be compared to 0.050 ** p-value to be compared to 0.050/2 (0.025) if p-value (*) > 0.050*

Over the W0-W24 period in the FAS, the mean decrease from baseline to last post-baseline value in HAM-D total score was more pronounced than over the W0-W8 period. Besides, it was higher in the S 90098 1 mg group (-16.3 ± 8.4) than in the placebo group (-14.5 ± 8.5), but with no statistically significant difference. The mean decrease from baseline in the S 90098 2 mg group (-15.4 ± 9.0) and the placebo group showed no relevant difference.

Response to treatment (defined as a decrease from baseline in HAM-D total score of at least 50%)
Over the W0-W8 period in the FAS, the rate of responders at last post-baseline assessment (See Table below) was the highest in the S 90098 1 mg group (68.6%), with a statistically significant and clinically relevant difference as compared to the placebo group (51.7%): E (SE) = -16.96% (7.24), 95% CI = [-31.16 ; -2.76], **p = 0.021**. In a lesser extent, the rate of response in the S 90098 2 mg group (58.6%) was higher than in the placebo group, but with no statistically significant difference.
Similar results were observed in the OCW8S: the rate of responders was significantly higher at W8 in the S 90098 1 mg group (76.0%) than in the placebo group (59.7%), with E (SE) = -16.26% (7.45), 95% CI = [-30.87 ; -1.65], **p = 0.032**. There was no statistically significant difference between the S 90098 2 mg group (66.7%) and the placebo group.

HAM-D 17-item: Response to treatment over the W0-W8 period - FAS

			S 90098 1 mg (N = 86)	S 90098 2 mg (N = 87)	Placebo (N = 91)
Last post-baseline assessment	**Yes**	**n (%)**	**59 (68.60)**	**51 (58.62)**	**47 (51.65)**
	No	n (%)	27 (31.40)	36 (41.38)	44 (48.35)
Statistical analysis		E (SE) (1)	-16.96 (7.24)	-6.97 (7.44)	
		95% CI (2)	[-31.16 ; -2.76]	[-21.55 ; 7.61]	
		p-value (3)	**0.021**	0.350	

% = (n/N)x100
(1) Estimate (Standard Error) of the difference between treatment group percentages of responders Placebo minus S 90098 1 mg and Placebo minus S 90098 2 mg
(2) Two-sided 95% Confidence Interval of the estimate
(3) Two-sided p-value of treatment effect (Chi-Square test), to be compared to 0.05

Name of Company: I.R.I.S. 6 place des Pleiades 92415 Courbevoie - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY ON DEPRESSION (Cont'd)

Over the W0-W24 period in the FAS, the rate of responders at last post-baseline assessment was higher in the S 90098 1 mg (65.1%) and 2 mg (63.2%) groups than in the placebo group (57.1%), but with no statistically significant difference.

Remission (defined as an HAM-D total score ≤ 7)

At last post-baseline assessment over the W0-W24 period in the FAS, the rate of remitters was higher in both S 90098 dose groups (48.8% with 1 mg and 48.3% with 2 mg) than in the placebo group (37.4%), without significant difference.

- **Secondary efficacy criteria on depression**
  - CGI scale

CGI scores

Over the W0-W8 period in the FAS, mean CGI severity of illness score was comparable between groups at baseline (4.9 ± 0.6 in average, *i.e.* patients "markedly ill"), and progressively decreased in the 3 treatment groups, to reach at last post-baseline assessment 2.8 ± 1.3 in the S 90098 1 mg group, 3.0 ± 1.4 in the S 90098 2 mg group, and 3.1 ± 1.3 in the placebo group (*i.e.* patients "borderline mentally ill" to "mildly ill").

Mean CGI global improvement score at last assessment was 2.0 ± 1.1 in the S 90098 1 mg group, 2.2 ± 1.3 in the S 90098 2 mg group, and 2.2 ± 1.1 in the placebo group, showing that patients were "much improved" on average.

For both scores, no statistically significant difference between any of the S 90098 dose groups and the placebo group was detected.

Over the W0-W24 period in the FAS, comparable results were observed.

Response to treatment (defined as a CGI global improvement score of 1 "very much improved" or 2 "much improved")

Over the W0-W8 period in the FAS, at last assessment, the rate of responders was higher in the S 90098 1 mg group (75.6%) than in the placebo group (60.4%), with a statistically significant and clinically relevant difference: E (SE) = -15.14% (6.91), 95% CI = [-28.68 ; -1.60], **p = 0.031**. The rate of responders was also higher in the S 90098 2 mg group (67.8%) than in the placebo group, but with no statistically significant difference.

Over the W0-W24 period in the FAS, the rate of responders was higher in the S 90098 1 mg group (72.1%) and in a lesser extent in the S 90098 2 mg group (67.8%) than in the placebo group (60.4%), but with no statistically significant difference.

Remission (defined as a CGI global improvement score of 1 "very much improved")

At last assessment over the W0-W24 period in the FAS, the rate of remitters was higher in the S 90098 1 mg group (52.3%) and in a lesser extent in the S 90098 2 mg group (48.3%) than in the placebo group (45.1%), without significant difference.

- **Hospital anxiety and depression (HAD) scale**

Over the selection - W8 period in the FAS, HAD depression score decreased from baseline to last post-baseline assessment in the 3 treatment groups (-7.2 ± 5.3 in the S 90098 1 mg group, -7.4 ± 5.3 in the S 90098 2 mg group, and -7.1 ± 5.6 in the placebo group), with no relevant difference between groups.

A decrease in HAD anxiety score was also observed in the 3 treatment groups, with no relevant difference between groups (-3.9 ± 4.1 in the 1 mg group, -3.9 ± 4.2 in the 2 mg group, -3.4 ± 4.2 in the placebo group).

Over the selection - W24 period in the FAS, comparable results were observed.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY ON DEPRESSION (Cont'd)

- **Sheehan disability scale (SDS)**

Over the selection - W8 period in the FAS, disability scores, indicative of a marked disruption of all activities at baseline, decreased in all treatment groups, with a moderate disruption at last post-baseline assessment.
Mean changes from baseline to last post-baseline value in the S 90098 1 mg, S 90098 2 mg, and placebo groups were, respectively:

- Work / school disability score: -2.8 ± 2.8 ; -2.9 ± 3.0 ; -3.0 ± 2.9.
- Social life: -3.1 ± 2.8 ; -3.3 ± 3.1 ; -3.2 ± 2.6.
- Family life / Home responsibilities: -3.0 ± 3.0 ; -3.2 ± 3.0 ; -3.0 ± 2.8.

No relevant difference between groups was observed.

Over the selection - W24 period, more pronounced decreases were observed than over the acute double-blind treatment period, with no relevant difference between groups.

EFFICACY ON SLEEP

- **Leeds sleep evaluation questionnaire (LSEQ)**

In the FAS, **over the W0-W8 period**, mean scores at last assessment in the S 90098 1 mg, S 90098 2 mg, and placebo groups, were, respectively:

- Getting off to sleep score: 30.7 ± 19.1 mm; 33.6 ± 19.0 mm; 37.4 ± 16.6 mm.
- Quality of sleep score: 29.5 ± 22.7 mm; 31.7 ± 21.0 mm; 37.7 ± 20.9 mm.
- Sleep awakening score: 35.0 ± 21.1 mm; 40.5 ± 22.2 mm; 39.3 ± 21.5 mm.
- Integrity of behaviour score: 38.7 ± 20.5 mm; 42.2 ± 20.6 mm; 42.9 ± 20.3 mm.

All scores were more improved in the S 90098 1 mg group than in the placebo group, as shown by the lower mean scores in the S 90098 1 mg group, with a statistically significant difference for getting off to sleep (E (SE) = 6.64 mm (2.69), 95% CI = [1.33 ; 11.95], **p = 0.015**), and for quality of sleep (E (SE) = 8.25 mm (3.28), 95% CI = [1.77 ; 14.73], **p = 0.013**) (unplanned analyses).
Getting off to sleep and quality of sleep were also more improved in the S 90098 2 mg group than in the placebo group, but with no significant difference.

SAFETY RESULTS

- **Adverse events**

Main safety results

	S 90098 1 mg (N = 86)			**S 90098 2 mg (N = 87)**			**Placebo (N = 92)**		
	NAE	n	%	NAE	n	%	NAE	n	%
W0-W8/WEND period									
at least one EAE	55	35	40.7	61	37	42.5	56	35	38.0
at least one treatment-related EAE	30	20	23.3	44	27	31.0	35	22	23.9
W0-W24/WEND period									
at least one EAE	77	43	50.0	81	45	51.7	81	42	45.7
at least one treatment-related EAE	36	21	24.4	47	28	32.2	45	22	23.9
During the whole study period									
at least one serious AE	2	2	2.3	-	-	-	-	-	-
at least one non-serious EAE leading to treatment discontinuation	5	5	5.8	5	5	5.7	7	7	7.6

N number of exposed patients in the considered treatment group
n number of affected patients
EAE emergent adverse events
NAE number of adverse events
% n/N x 100

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

During the W0-W8/WEND period, the percentage of patients with an emergent adverse event was comparable between groups: 40.7% in the S 90098 1 mg group, 42.5% in the S 90098 2 mg group, and 38.0% in the placebo group.

During this period, the **most frequently affected system organ class** overall was Nervous system disorders, reported in 9.3% of the patients in the S 90098 1 mg group, 18.4% in the S 90098 2 mg group, and 16.3% in the placebo group.

System organ classes more frequently reported in one of the S 90098 dose groups as compared to the placebo group were:

- More frequent in the 2 mg group: Gastrointestinal disorders, in 9.3% in the 1 mg group, 13.8% in the 2 mg group, and 8.7% in the placebo group.
- More frequent in the 1 mg group: Infections and infestations, in respectively 16.3%, 2.3% and 8.7%, and Skin and subcutaneous tissue disorders, in respectively 7.0%, 2.3% and 1.1%.

Other system organ classes were similarly or less frequently reported in the S 90098 groups as compared to the placebo group.

The **most frequent emergent adverse event** overall during the W0-W8/WEND period was headache, reported in 5 patients (5.8%) in the S 90098 1 mg group, 7 patients (8.0%) in the S 90098 2 mg group, and 8 patients (8.7%) in the placebo group. The other most frequent emergent adverse events, reported in at least 3 patients in one of the S 90098 groups, were:

- With a higher frequency in the S 90098 2 mg group than in the placebo group (*i.e.* with a difference of at least 3 patients): nausea, in 1 patient (1.2%) in the 1 mg group, 5 patients (5.7%) in the 2 mg group, and in 1 patient (1.1%) in the placebo group.
- With no relevant difference between the S 90098 groups and the placebo group: dizziness (in respectively 2, 5, and 3 patients, *i.e.* 2.3%, 5.7%, and 3.3%), somnolence (in 1, 4, and 3 patients, *i.e.* 1.2%, 4.6%, and 3.3%), dry mouth (in 1, 3, and 1 patients, *i.e.* 1.2%, 3.4%, and 1.1%), and nasopharyngitis (in 5, none, and 4 patients, *i.e.* 5.8%, 0%, and 4.3%).

Treatment-related emergent adverse events during the W0-W8/WEND were reported in 23.3% of the patients in the S 90098 1 mg group, 31.0% in the S 90098 2 mg group, and 23.9% in the placebo group, and were mainly those already described as most frequent.

During the W0-W24/WEND period, the incidence of patients with an emergent adverse event was 50.0% in the S 90098 1 mg group, 51.7% in the S 90098 2 mg group, and 45.7% in the placebo group.

Similar trends as over the W0-W8/WEND period were observed as concerns the most frequently reported emergent adverse events and treatment-related emergent adverse events.

During the W0-W24/WEND period, most emergent adverse events (225/239) were rated by the investigator as mild or moderate. Eleven **severe emergent adverse events** were observed in 10 patients: 4 patients (4.7%) in the S 90098 1 mg group, 2 (2.3%) in the S 90098 2 mg group, and 4 (4.3%) in the placebo group.

Most emergent adverse events (229/239) recovered or were recovering during the treatment period or after its end. A total of 9 patients (10 emergent adverse events) had not recovered at the end of the study: 1 patient (1.2%) in the S 90098 1 mg group, 5 (5.7%) in the S 90098 2 mg group, and 3 (3.3%) in the placebo group.

No patient died during the study. Two patients had a **serious adverse event** with hospitalisation during the W0-W24/WEND period, both in the S 90098 1 mg group (2.3%), for a worsening of their depression: one during the treatment period, which led to study drug withdrawal, and the other one 4 days after the last drug intake. None was related to the study drug according to the investigator and both patients recovered.

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Non-serious emergent adverse events led to treatment discontinuation in 17 patients overall (6.4%) during the W0-W24/WEND period, without relevant difference between treatment groups:

- In the S 90098 1 mg group: 5 patients (5.8%), including 2 (2.3%) with treatment-related adverse event.
- In the S 90098 2 mg group: 5 patients (5.7%), including 4 (4.6%) with treatment-related adverse event.
- In the placebo group: 7 patients (7.6%), including 4 (4.3%) with treatment-related adverse event.

They belonged mainly to the SOC Psychiatric disorders in each treatment group: 2 patients (2.3%) in the S 90098 1 mg group, 2 (2.3%) in the S 90098 2 mg group, and 3 (3.3%) in the placebo group.

- **Clinical laboratory evaluation**

No relevant difference between groups was detected on mean evolution over time of laboratory parameters, whatever the period.

Over the W0-W24/WEND period, emergent PCSA (potentially clinically significant abnormal) biochemical values (except liver parameters) were mainly reported for high triglycerides (4 patients, *i.e.* 4.8% in the S 90098 1 mg group, 2 patients, *i.e.* 2.6% in the S 90098 2 mg group, and 4 patients, *i.e.* 4.6% in the placebo group, including 1.2%, 1.3% and 2.3% with not fasting values), high total cholesterol (respectively 2 patients, *i.e.* 2.4%, 1 patient, *i.e.* 1.3%, and none), and high urea (respectively none, 2.6%, and 1.1%). No relevant difference between groups was observed.

Emergent PCSA values of hepatic parameters were observed in 5 patients overall:

- In the S 90098 1 mg group, 1 patient (1.2%), a 18 year-old woman with medical history of non alcoholic steatohepatitis, had elevated ALAT and ASAT at baseline (2.6 ULN and 2.0 ULN, with ULN = upper limit of normal values), which worsened under treatment and reached at their maximum 3.9 ULN and 3.1 ULN (110 days after the first study drug intake). These elevated values were related to steatohepatitis according to the investigator and were not associated with elevated values of total bilirubin or ALP. The patient was withdrawn and ALAT and ASAT decreased below 3 ULN (2.9 ULN and 1.9 ULN, at last sampling performed, 246 days after last treatment intake).
- In the S 90098 2 mg group, 2 patients (2.6%) with normal hepatic parameters at baseline had emergent PCSA values of ALAT, both with associated emergent abnormal ASAT (between 1 and 3 ULN).
  For the first one, a 18 year-old man, ALAT first increased to 3.1 ULN (59 days after the first study drug intake), then fluctuated and reached a maximum PCSA value under treatment of 5.8 ULN (2 days after the last intake of a 170-day treatment period). According to the investigator, this significant increase was related to weight gain. ALAT reached 8.3 ULN 24 days after the last treatment intake of the W0-W24 treatment period, and finally returned to normal 90 days after the last treatment intake.
  The other one, a 52 year-old woman, had emergent PCSA values of ALAT and GGT, which reached respectively 3.1 ULN and 3.2 ULN at W8 under treatment. According to the investigator, this significant increase was related to consumption of alcohol. All values returned to normal within two weeks, while the patient was still under treatment.
  For both patients, PCSA transaminases were never associated with abnormal total bilirubin or ALP.
- In the placebo group, 2 patients (2.3%) had emergent PCSA values of GGT (3.3 ULN and 3.5 ULN). For both it was a worsening of an abnormal value at baseline, and one had associated emergent abnormal values of ALAT (1.9 ULN) and ASAT (2.6 ULN). No further test was available for any of them.

Regarding haematology, emergent PCSA values were observed in 2 patients (2.4%) in the S 90098 1 mg group (low WBC), 1 patient (1.3%) in the S 90098 2 mg group (low platelets, reported as a non-related adverse event [Thrombocytopenia] which resolved), and 1 patient (1.1%) in the placebo group (low haematocrit).

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: S 90098 (Sublingual agomelatine)	**Page:**	

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, whatever the period.

- **Electrocardiogram abnormalities**

Over the W0-W24/WEND period, one patient in the S 90098 2 mg group with no abnormality at baseline had an abnormality at W8 (PR prolongation), which was judged clinically significant by the investigator and reported as a possibly treatment-related emergent adverse event (recovered under treatment). Other ECG abnormalities reported post-baseline were not considered as clinically significant by the investigator.

CONCLUSION

This double-blind, randomised placebo-controlled study in patients suffering from Major Depressive Disorder showed a beneficial effect of sublingual agomelatine (S 90098) at 1 mg/day as compared to placebo on HAM-D total score reduction over an 8-week treatment period (primary efficacy criterion), without reaching statistical significance. The unusually high placebo responders rate (52%) may have contributed to the failure to demonstrate a statistically significant difference. Nevertheless, a statistically significant and clinically relevant effect of the S 90098 1 mg daily dose as compared to placebo was observed on the rate of responders according to HAM-D and CGI global improvement, and on subjective sleep (getting off to sleep, and quality of sleep) over the 8-week treatment period. S 90098 at 2 mg/day did not discriminate from placebo on any criteria.

The safety of both doses of S 90098 was satisfactory and similar to placebo.

Date of the report: 04 December 2009