Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy of agomelatine (25mg/day with potential adjustment to 50 mg) given orally on rest/activity circadian rhythms in outpatients with Major Depressive Disorder.** **A randomised, double-blind international study with parallel groups *versus* sertraline (50 mg/day with potential adjustment to 100 mg).** **Six-week treatment plus optional continuation for 18 weeks.**
Study drug	**Agomelatine - S 20098**
Indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-046**
Study initiation date	**04 May 2005**
Study completion date	**12 March 2007**
Main coordinator	[redacted] [redacted]**Paris**[redacted]**- France**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **924284 Suresnes Cedex - France** **Laboratorios Servier, S.L.** **Avenida de los Madronos, 33** **28043 Madrid - Spain**
Responsible medical officer	[redacted]**(I.R.I.S.)**
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 16 July 2008**

~~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: Agomelatine (S 20098)	**Page:**	

Title of study: Efficacy of agomelatine (25 mg/day with potential adjustment to 50 mg) given orally on rest/activity circadian rhythms in outpatients with Major Depressive Disorder.
A randomised, double-blind international study with parallel groups *versus* sertraline (50 mg/day with potential adjustment to 100 mg).
Six-week treatment plus optional continuation for 18 weeks.
Protocol No.: CL3-20098-046

Main International Coordinator: [redacted] – France)
National Coordinators: [redacted] Italy), [redacted] – Spain), [redacted] Germany), [redacted] – Austria), [redacted] Poland), [redacted] – The Netherlands)
Scientific advisor: [redacted] Switzerland).

Study centres:
45 centres located in 7 countries were opened and 37 centres located in 6 countries were active: Austria – 2 centres (38 included patients), France – 12 centres (112 included patients), Germany – 7 centres (73 included patients), Italy – 5 centres (31 included patients), Poland – 2 centres (17 included patients) and Spain – 9 centres (43 included patients).

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 04 May 2005 *(date of first visit)* Completion date: 12 March 2007 *(date of last visit)*	Phase III study

Objectives:
Main objective: to demonstrate that agomelatine (25/50 mg) improves rest/activity circadian rhythms faster than sertraline in outpatients suffering from Major Depressive Disorder (MDD).
Secondary objective: to study circadian rhythms' evolution and to provide additional antidepressant efficacy and safety data on agomelatine in this population.

Methodology:
International, multicentric, randomised, double-blind, phase III study with parallel groups (agomelatine *versus* sertraline) using a flexible dosage in patients suffering from Major Depressive Disorder and requiring antidepressant treatment.
The study consisted of the following periods:
- Run-in period of 5 to 7 days (ASSE - W0).
- Double-blind treatment period of 6 weeks (W0-W6): patients received randomly agomelatine 25 mg daily or sertraline 50 mg daily from W0 to W2. At W2, if the improvement of the patient's depressive condition was considered insufficient, the dosage was increased to 50 mg daily for agomelatine and 100 mg daily for sertraline, in blinded conditions for the investigator and patients.
- Double-blind treatment extension period of 18 weeks (W6-W24) for patients much improved at W6 (CGI-global improvement score = 1 or 2): patients received the same treatment and the same dose as during W2-W6 period.
- Follow-up period of 1 week after treatment discontinuation

The criteria for adaptation of the dose at W2 was determined by the Sponsor prior to the study start and kept in blind. The randomisation was balanced (non-adaptive) with stratification on the centre. Treatment allocation and dose adjustment were done centrally using Interactive Voice Response System (IVRS).

Number of patients:
Planned: 300 patients randomised (150 by group).
Selected: 367 patients / Included: 314 patients / Randomised: 313 patients, *i.e.* 154 patients in the agomelatine group and 159 patients in the sertraline group.

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: Agomelatine (S 20098)	**Page:**	

Diagnosis and main criteria for inclusion:

Male or female outpatients, aged between 18 and 60 years inclusive, fulfilling DSM-IV-TR criteria for MDD, single or recurrent episode of moderate or severe intensity, with or without melancholic features, without seasonal pattern, without psychotic features, without post partum onset for the current episode, without catatonic features and with current episode ≥ 4 weeks.

The diagnosis was to be documented using the brief structured M.I.N.I interview.

Patients were included if the following criteria were fulfilled:

- HAM-D 17-items total score ≥ 22.
- HAM-D item 3 (suicide) ≤ 2.
- HAM-D decrease (if any) between ASSE and W0 ≤ 20%.
- Sum of HAM-D items 5+6 (insomnia) ≥ 3.
- Sum of items H1 + H2 + H5 + H6 + H7 + H8 + H10 + H13 (core of depression + items 5 and 6) of HAM-D 17-items scale ≥ 55% of HAM-D 17-items total score.
- CGI item 1 “severity of illness” ≥ 4 (moderately to severely ill).

Study drug:

Agomelatine, tablets of 25 mg, masked in capsule, 1 or 2 tablets per day, single administration, around 8 p.m, with a glass of water.

Patients received 25 mg/day (1 agomelatine capsule 25 mg + 1 placebo capsule) from W0 with possible increase to 50 mg/day (1 agomelatine capsule 50 mg [2 tablets of 25 mg] + 1 placebo capsule) from W2, in case of insufficient improvement. During the optional period (W6-W24), patients received the same dose as during W2-W6 period.

Batch No.: L0005264, L0005421.

Reference product:

- Sertraline, capsules of 50 mg, 1 or 2 capsules per day, single administration, around 8 p.m, with a glass of water.

  Patients received 50 mg/day (1 sertraline capsule 50 mg + 1 placebo capsule) from W0 with possible increase to 100 mg/day (2 sertraline capsules 50 mg) from W2. During the optional period (W6-W24), patients received the same dose as during W2-W6 period.
- Placebo, tablets masked in capsule, 1 capsule per day for patients who received agomelatine 25 or 50 mg/day or sertraline 50 mg/day, single administration, around 8 p.m, with a glass of water.

Duration of treatment:

- Period from selection (ASSE) to inclusion without treatment (between 5 and 7 days).
- Double-blind treatment period of 6 weeks (from W0 to W6).
- Double-blind treatment extension period of 18 weeks (from W6 to W24).
- Follow-up period of 1 week without treatment.

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: Agomelatine (S 20098)	**Page:**	

Criteria for evaluation:

Efficacy measurements:

- **Primary efficacy criterion:** Relative amplitude of the rest/activity cycle

Efficacy on rest/activity circadian rhythms, *evaluated by actigraphy recording:*

The actigraphy data were recorded daily, from ASSE until W6 visit (or withdrawal visit in case of premature study discontinuation), using activity monitor worn by the patient on his/her non-dominant wrist for continuous measurements of the intensity and duration of all movements over 0.05 g. The parameters were assessed on periods of around 7 days (D0, D7, D14, D21, D28, D35, and D42) from "average day" profiles of activity derived from these periods. There was a reading and analysis of the actigraphy recordings by a team of 3 experts (Amendment No.3), following standardized procedures.

The primary efficacy criterion was the relative amplitude (RA) of the rest/activity cycle, defined as the difference between M10 (average activity level during the 10 most active hours) and L5 (average activity level during the 5 least active hours), *i.e.* amplitude of the cycle, divided by the sum of M10 and L5.

$$RA = \frac{M10 - L5}{M10 + L5}$$

- **Secondary efficacy criteria:**

Efficacy on rest/activity circadian rhythms:

- Actimetry parameters: L5 onset time, M10 onset time, interdaily stability, intradaily variability, L5 (counts), M10 (counts), cosine acrophase time (addition of these 3 last criteria by Amendment No. 3), sleep efficiency (%), actual sleep (%), actual sleep time (min), assumed sleep time (min), sleep start time, sleep stop time, sleep latency (min), wake bouts number, average of mean wake bout time (min) and actual wake time (min).
- Sleep-wake diary: data about bed and wake-up time, duration of naps, … were recorded daily by patient from ASSE until W6 visits (or withdrawal visit). Data from diary were used to help reading of actigraphy recordings.

Efficacy on depression, *evaluated by:*

- The HAM-D-17 item scale: at each visit (ASSE, W0, W2, W4, W6, W10, W14, W18, W22 and W24).
- The CGI scale (item 1: severity of illness; item 2: global improvement): at each visit from W0 (only item 1 at W0).
- The HAM-A scale: at W0 and W6.

Efficacy on sleep *evaluated by self-rating questionnaires (subjective evaluation):*

- The Leeds Sleep Evaluation Questionnaire (LSEQ): at W2, W4 and W6.
- The Epworth Sleepiness Scale (ESS): at W0, W2, W4 and W6.

Efficacy on rest/activity circadian rhythms (subjective evaluation):

- The Composite Scale of Morningness (CSM): at W0 and W6.
- The Screening of sleep and circadian rhythms disorder questionnaire: at W0 and W6.

Safety measurements:

- Adverse events reported at each visit during the study (from ASSE to W24/WEND).
- Laboratory tests: between selection (ASSE) and W0 visit (results available for the inclusion visit), between W4 and W6 visits (results available at W6), between W22 and W24 visits (results available at W24) and between the withdrawal visit if applicable and the follow-up visit (results available for the follow-up visit).
- Vital signs (blood pressure, heart rate and body weight) at selection, W0, W6, W24 and at the follow-up visit (only blood pressure and heart rate).
- 12-lead electrocardiogram (ECG) between selection and W0 (results available for the inclusion), between W22 and W24 (results available for W24) and between the last visit and the follow-up visit in case of premature withdrawal at W6 or at any visit before W22.

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: Agomelatine (S 20098)	**Page:**	

Statistical methods:

The main analysis sets were:

- Randomised Set (RS): all included and randomised (according to IVRS) patients.
- Full Analysis Set (FAS): all included and randomised (according to IVRS) patients, having taken at least one dose of study treatment and having at least one post-baseline efficacy assessment (other than relative to actigraphy and sleep-wake diary) over the W0-W6 period.
- Actigraphy Analysis Set (AAS): all included and randomised (according to IVRS) patients, having taken at last one dose of study treatment and having one reliable baseline value and at least one reliable post-baseline value for the relative amplitude.
- Safety Set: all included patients having taken at least one dose of study treatment.

Efficacy analyses:

Primary criterion: Relative Amplitude (RA)

Main analysis:

Agomelatine and sertraline groups were compared in the AAS using a Mixed-effects Model with Repeated Measures (MMRM) including factors Treatment, Time and Treatment*Time interaction as fixed effects and relative amplitude at baseline (D0) as covariate: 1) in terms of evolution of mean relative amplitude (expressed as change from baseline) over time (D7, D14, D21, D28, D35 and D42) and 2) at the three first post-baseline times (D7, D14 and D21). The Hochberg procedure was used for the comparison between treatment groups at D7, D14 and D21 in order to take into account the multiplicity of tests.

Sensitivity analysis:

The same model was used, in the AAS, with the W0 HAM-D total score as covariate and the country as adjustment factor (fixed effect) in addition to the factors Treatment, Time and Treatment*Time interaction and the relative amplitude at baseline.

Secondary analysis:

The main analysis model was also implemented in the SUB-AAS with W0 HAM-D total score ≥ 25.

Secondary criteria:

- Over W0-W6:
  - The main analysis model was also used in the AAS for mean sleep efficiency, mean sleep latency and mean actual wake time (all expressed in terms of change from baseline) in order to study the overall treatment effect and the treatment effect (to be compared to 5%) at each post-baseline time (D7, D14, D21, D28, D35 and D42) (complementary analyses).
  - The difference between agomelatine and sertraline groups was estimated in the FAS using:
    - For HAM-D total score:
      - A two-way analysis of covariance with factors treatment, centre (as random effect) and W0 HAM-D total score as covariate, for the change from baseline to the last post-baseline value.
      - A 95% confidence interval for the response to treatment (decrease of total score from baseline of at least 50%) taking into account the last post-baseline value.
      - A Chi-square test at W2 for the response to treatment (complementary analysis).
    - For CGI items 1 and 2 and LSEQ Getting off to sleep and Quality of sleep scores: a two-sided Student's t test for independent samples, on last post-baseline value for CGI criteria and at W2 for LSEQ items (complementary analyses).
    - For HAM-A total score and sub-scores: a general linear model with baseline as covariate, for the change from baseline to the last post-baseline value (complementary analyses).
  - Other criteria: descriptive analysis.
- Over W0-W24:
  - The difference between agomelatine and sertraline groups was studied in the FAS using a Chi-square test for the response to treatment taking into account the last post-baseline value of HAM-D total score (complementary analysis).
- Other criteria: descriptive analysis.

Safety analysis: Descriptive analysis in the Safety Set.

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: Agomelatine (S 20098)	**Page:**	

SUMMARY OF RESULTS

STUDY POPULATION AND OUTCOME

In all, 313 patients were included and randomised (according to IVRS), 154 patients in the agomelatine group and 159 in the sertraline group. In the Randomised Set, patients were aged from 18 to 60 years with a mean ± SD of 43.9 ± 10.3 years old and were mainly female (70.6%). According to the DSM-IV-TR criteria, all patients had Major Depressive Disorder mainly of moderate intensity (74.4% of patients), and mainly presenting recurrent episodes (70.3% of patients).

Disposition of patients

Randomised Set		**Agomelatine**	**Sertraline**	**All**
Double-blind treatment period (W0-W6)				
Randomised	**n (%)**	**154 (100)**	**159 (100)**	**313 (100)**
In compliance with the protocol	n (%)	95 (61.7)	88 (55.3)	183 (58.5)
With a protocol deviation before or at inclusion	n (%)	59 (38.3)	71 (44.7)	130 (41.5)
Withdrawn due to	**n (%)**	**21 (13.6)**	**30 (18.9)**	**51 (16.3)**
Adverse event	n (%)	5 (3.2)	14 (8.8)	19 (6.1)
Lack of efficacy	n (%)	4 (2.6)	8 (5.0)	12 (3.8)
Recovery	n (%)	1 (0.6)	-	1 (0.3)
Non-medical reason	n (%)	7 (4.5)	6 (3.8)	13 (4.2)
Protocol deviation	n (%)	4 (2.6)	2 (1.3)	6 (1.9)
Lost to Follow-up	**n (%)**	**-**	**-**	**-**
Completed the W0-W6 period	**n (%)**	**133 (86.4)**	**129 (81.1)**	**262 (83.7)**
Not ongoing in the extension period	**n (%)**	**17 (11.0)**	**15 (9.4)**	**32 (10.2)**
Double-blind treatment extension period (W6-W24)				
Ongoing in the extension period	**n (%)**	**116 (100)**	**114 (100)**	**230 (100)**
Withdrawn due to	**n (%)**	**19 (16.4)**	**23 (20.2)**	**42 (18.3)**
Adverse event	n (%)	3 (2.6)	3 (2.6)	6 (2.6)
Lack of efficacy	n (%)	6 (5.2)	10 (8.8)	16 (7.0)
Recovery	n (%)	2 (1.7)	1 (0.9)	3 (1.3)
Non-medical reason	n (%)	4 (3.4)	6 (5.3)	10 (4.3)
Protocol deviation	n (%)	3 (2.6)	2 (1.8)	5 (2.2)
Lost to Follow-up	**n (%)**	**1 (0.9)**	**1 (0.9)**	**2 (0.9)**
Completed the W6-W24 period	**n (%)**	**97 (83.6)**	**91 (79.8)**	**188 (81.7)**
Analysis Sets				
Included Set	n	155*	159	314*
Randomised Set (RS)	n (%)[a]	154 (99.4)	159 (100)	313 (99.7)
Full Analysis Set (FAS)	n (%)[b]	150 (97.4)	157 (98.7)	307 (98.1)
Actigraphy Analysis Set (AAS)	n (%)[b]	117 (76.0)	116 (73.0)	233 (74.4)
SUB-AAS with W0 HAM-D total score ≥ 25	n (%)[c]	76 (65.0)	77 (66.4)	153 (65.7)
Safety Set	n (%)[a]	152 (98.1)	159 (100)	311 (99.0)

**: One patient received treatment kit dispensed without calling IVRS at inclusion visit.*
%[a]: % of the Included Set; %[b]: % of the Randomised Set; %[c]: % of the AAS.

During the W0-W6 period, 51 patients (16.3%) withdrew from the study, the reasons for withdrawal being mainly adverse events (6.1%), non-medical reason (4.2%), and lack of efficacy (3.8%). The rate of withdrawal was lower in the agomelatine group (13.6%) than in the sertraline group (18.9%) explained particularly by the withdrawals due to adverse event (3.2% of patients in the agomelatine group and 8.8% in the sertraline group) and lack of efficacy (2.6% and 5.0%, respectively). In the subgroup of patients with daily dose increase at W2 (25.3% of randomised patients in the agomelatine group and 24.5% in the sertraline group), no patient was withdrawn from the study between W2 and W6 in the agomelatine group, while 6 patients withdrew in the sertraline group, of which 4 for lack of efficacy. In all, 262 patients completed the W0-W6 period, *i.e.* 133 (86.4%) in the agomelatine group and 129 (81.1%) in the sertraline group.

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: Agomelatine (S 20098)	**Page:**	

SUMMARY OF RESULTS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Overall, 230 patients, among patients who completed the W0-W6 period, entered the extension W6-W24 period, 116 in the agomelatine group and 114 in the sertraline group. Out of them, 42 patients (18.3%) withdrew from the study, mainly due to lack of efficacy (7.0%) and non-medical reason (4.3%). During this period, the rate of withdrawal also was lower in the agomelatine group (16.4%) than in the sertraline group (20.2%), particularly because of the lower withdrawal rate due to lack of efficacy in the agomelatine group: 5.2% *versus* 8.8%, respectively.

Overall, 188 patients of 313 (60.1% of RS) completed the 24-week period (97 [63.0%] in the agomelatine group and 91 [57.2%] in the sertraline group). Over the W0-W24 period, 93 patients (29.7% of RS) withdrew from the study: 40 patients (26.0%) under agomelatine and 53 patients (33.3%) under sertraline.

In the RS, the mean number of previous depressive episodes was 2.9 ± 2.8 episodes and the current MDD episode lasted for 4.7 ± 4.2 months on average. Melancholic features were present in approximately a quarter of patients. The mean BIS-11 total score was 67.6 ± 10.5.

No clinically relevant differences were noted between agomelatine and sertraline groups for main demographic data and characteristics of MDD at baseline. The main efficacy parameters were similar on average in both groups at inclusion: HAM-D 17-item total score = 26.1 ± 2.7 in the agomelatine group and 26.5 ± 3.0 in the sertraline group and CGI severity of illness score = 4.7 ± 0.7 in both groups.

In the Actigraphy Analysis Set, used for the analysis of the primary efficacy criterion, baseline characteristics and main efficacy parameters were similar to those observed in the Randomised Set. Especially, the mean values of relative amplitude were respectively 0.87 ± 0.08 in the agomelatine group and 0.85 ± 0.11 in the sertraline group.

In the Safety Set, during the W0-W6 period, the treatment duration was 39.0 ± 9.9 days on average (median 42 days). The duration was similar in both groups: 40.2 ± 7.8 days and 37.9 ± 11.5 days in the agomelatine and sertraline groups, respectively.

During the W0-W24 period, the mean treatment duration was 124.6 ± 63.0 days (median 167 days). The duration tended to be higher in the agomelatine group than in the sertraline group (131.8 ± 58.9 days *versus* 117.8 ± 66.1 days).

The overall compliance (from W0 to W24) was satisfactory (95.0 ± 11.0% in the agomelatine group and 91.3 ± 17.6% in the sertraline group).

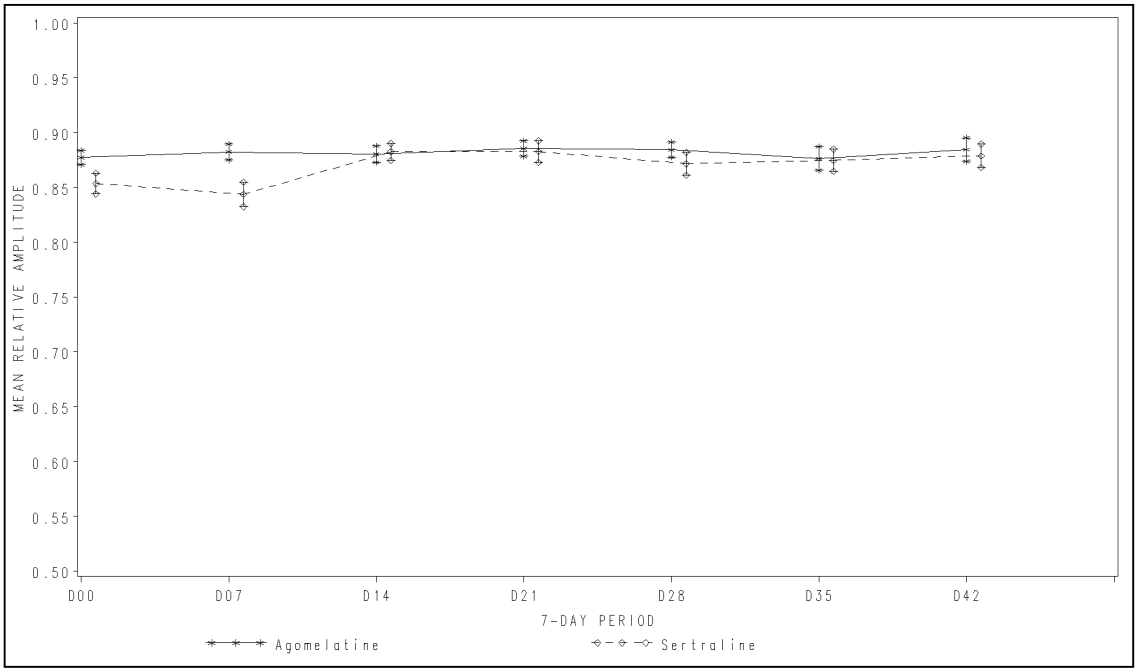
Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: Agomelatine (S 20098)	**Page:**	

EFFICACY RESULTS

- **Primary assessment criterion**

The evolution of the mean relative amplitude over the time in the AAS is presented in the graph below and the main results are detailed in the table.

Mean Relative Amplitude: Value (mean ± SEM) over each 7-day period - AAS



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: Agomelatine (S 20098)	**Page:**	

SUMMARY OF RESULTS (Cont'd)

EFFICACY RESULTS (Cont'd)

Difference between treatment groups in terms of evolution over time (D7, D14, D21, D28, D35 and D42) and at the three first post-baseline times (D7, D14 and D21) has been analysed in the Actigraphy Analysis Set.

Mean Relative Amplitude - Change from baseline - Difference between treatment groups in terms of evolution over time and over the 3 first post-baseline 7-day periods - AAS

		Agomelatine (N = 117)	***Sertraline (N = 116)***
Treatment	p-value (1)	0.847	
Time	p-value (1)	0.024	
Treatment*Time	p-value (1)	**0.023**	
D07 – D00	n	113	111
	Mean ± SD	0.0060 ± 0.0645	-0.0104 ± 0.0931
	E(SE) (2)	-0.0272 (0.0104)	
	95% CI (3)	[-0.0478 ; -0.0067]	
	p-value (4) (a)	**0.010**	
D14 – D00	n	107	97
	Mean ± SD	0.0030 ± 0.0707	0.0262 ± 0.0834
	E(SE) (2)	0.0119 (0.0089)	
	95% CI (3)	[-0.0057 ; 0.0295]	
	p-value (4) (b)	0.184	
D21 – D00	n	108	85
	Mean ± SD	0.0087 ± 0.0642	0.0255 ± 0.0975
	E(SE) (2)	0.0063 (0.0098)	
	95% CI (3)	[-0.0130 ; 0.0256]	
	p-value (4) (c)	0.521	

*Mixed-effects Model with Repeated Measures: model with treatment, time and treatment*time interaction as factors and relative amplitude at baseline as covariate*

(1) Effect of model factors

(2)Estimate (Standard Error) of the difference between adjusted treatment group means obtained from this model: Sertraline minus Agomelatine

(3) 95% confidence interval of the estimate

(4) Adjusted treatment effect

Adjustment for multiplicity using Hochberg procedure:

(a) p-value to be compared to 0.017

(b) p-value to be compared to 0.025

(c) p-value to be compared to 0.050

In the AAS, the evolution of the mean RA over the time was statistically different between the agomelatine group and the sertraline group (Treatment * Time interaction, p = 0.023).

In the agomelatine group, the mean RA remained stable over the time, while, in the sertraline group, the mean RA decreased between D0 and D7 (see figure and table). From D14, the mean RA in the sertraline group joined up with that of the agomelatine group.

The difference between the 2 groups in the mean change from baseline at D7 was statistically significantly in favour of agomelatine (E = -0.0272, 95% CI [-0.0478; -0.0067], p = 0.010 to be compared to 0.017, Hochberg procedure).

Similar results were observed with the sensitivity analysis (additional adjustment for country and W0 HAM-D total score).

Findings were similar in the subset of more severely depressed patients but statistical significance was not reached due to the lack of statistical power.

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: Agomelatine (S 20098)	**Page:**	

SUMMARY OF RESULTS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **Secondary assessment criteria**
  - **Efficacy on rest/activity circadian rhythms:**
    - Circadian organisation

In the AAS, the mean average activity during the sequence of the 10 most active hours increased between baseline and last post-baseline value in the agomelatine group (386.6 ± 6914.9) whereas it decreased in the sertraline group (-430.5 ± 5934.2).

The mean average activity during the sequence of the 5 least active hours decreased in both groups between baseline and last post-baseline value: -120.8 ± 1302.8 in the agomelatine group and -366.8 ± 1367.1 in the sertraline group.

The time to onset of the M10 and L5 sequences, as well as the interdaily stability, the intradaily variability and the cosine acrophase time, remained stable between baseline and the last post-baseline value.

- Sleep organisation

The evolution of the objective sleep parameters over the D0-D42 period (Sleep efficiency, Sleep latency and Actual wake time), evaluated by actigraphy data in the AAS, showed a significant overall treatment effect in favour of agomelatine, *i.e.* significantly greater sleep efficiency ($p < 0.0001$), significantly shorter sleep latency ($p < 0.0001$) and significantly shorter actual wake time ($p = 0.018$).

In addition to this global assessment, data of each period of recording were analyzed and the changes from baseline for mean sleep efficiency and mean sleep latency are presented in the next table.

The mean sleep efficiency (%), expressed in terms of change from baseline to each post-baseline 7-day period, increased under agomelatine and decreased under sertraline. There was a statistically significant difference between groups at each period in favour of agomelatine. The difference was highly significant at D7 ($p < 0.0001$) showing the fast improvement of sleep disorders in the agomelatine group.

The mean sleep latency (min), expressed in terms of change from baseline to each post-baseline 7-day period, decreased on agomelatine treatment whereas it increased on sertraline treatment during the D0-D42 period, with a statistically significant difference between groups at each period in favour of agomelatine.

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: Agomelatine (S 20098)	**Page:**	

SUMMARY OF RESULTS (Cont'd)

EFFICACY RESULTS (Cont'd)

Actigraphy: Sleep organisation - Change from baseline - Difference between treatment groups over each post-baseline 7-day period - AAS

		Mean sleep efficiency (%)		***Mean sleep latency (min)***	
		Agomelatine (N = 117)	***Sertraline (N = 116)***	***Agomelatine (N = 117)***	***Sertraline (N = 116)***
D00	n	117	114	117	114
	Mean ± SD	77.236 ± 8.208	76.528 ± 9.262	22.50 ± 14.62	23.48 ± 19.82
	Min - Max	50.18 - 94.26	34.73 - 92.07	2.3 - 80.6	3.1 - 121.7
D07 – D00	n	117	111	117	111
	Mean ± SD	1.029 ± 4.216	-1.710 ± 5.728	-2.97 ± 13.57	4.85 ± 24.56
	E(SE) (1)	-2.896 (0.651)		8.399 (2.467)	
	95% CI (2)	[-4.180 ; -1.613]		[3.538 ; 13.260]	
	p-value (3)	**< 0.0001**		**< 0.001**	
D14 – D00	n	112	99	112	99
	Mean ± SD	0.782 ± 4.179	-0.497 ± 5.389	-3.22 ± 14.94	4.09 ± 17.68
	E(SE) (1)	-1.500 (0.629)		7.784 (2.082)	
	95% CI (2)	[-2.739 ; -0.260]		[3.681 ; 11.888]	
	p-value (3)	**0.018**		**< 0.001**	
D21 – D00	n	112	91	112	91
	Mean ± SD	1.422 ± 4.866	-1.013 ± 6.047	-2.84 ± 15.22	5.82 ± 21.68
	E(SE) (1)	-2.345 (0.719)		8.873 (2.332)	
	95% CI (2)	[-3.763 ; -0.927]		[4.275 ; 13.471]	
	p-value (3)	**0.001**		**< 0.001**	
D28 – D00	n	105	85	105	85
	Mean ± SD	1.221 ± 5.008	-1.720 ± 7.057	-1.40 ± 16.30	7.64 ± 23.38
	E(SE) (1)	-3.083 (0.796)		8.988 (2.681)	
	95% CI (2)	[-4.652 ; -1.513]		[3.703 ; 14.273]	
	p-value (3)	**< 0.001**		**< 0.001**	
D35 – D00	n	99	77	99	77
	Mean ± SD	1.140 ± 5.221	-1.286 ± 6.931	-1.24 ± 16.24	7.30 ± 24.94
	E(SE) (1)	-2.225 (0.823)		8.600 (2.889)	
	95% CI (2)	[-3.849 ; -0.601]		[2.902 ; 14.297]	
	p-value (3)	**0.007**		**0.003**	
D42 – D00	n	88	70	88	70
	Mean ± SD	1.593 ± 5.102	-1.177 ± 7.094	-2.35 ± 15.75	6.52 ± 22.57
	E(SE) (1)	-2.748 (0.839)		7.935 (2.757)	
	95% CI (2)	[-4.404 ; -1.093]		[2.491 ; 13.380]	
	p-value (3)	**0.001**		**0.005**	

*Mixed-effects Model with Repeated Measures: model with treatment, time and treatment*time interaction as factors and baseline as covariate:*

(1) Estimate (Standard Error) of the difference between adjusted treatment group means: Sertraline minus Agomelatine

(2) 95% Confidence Interval of the estimate

(3) Adjusted treatment effect (p-value 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: Agomelatine (S 20098)	**Page:**	

SUMMARY OF RESULTS (Cont'd)

EFFICACY RESULTS (Cont'd)

Short-term efficacy:

- **Efficacy on depression**
  - **HAM-D-17 item scale**

Results of the evolution of the HAM-D total score over the W0-W6 period (last post-baseline assessment) in the FAS are presented in the table below.

HAM-D total score - Change from baseline to last post-baseline assessment over the W0-W6 period - FAS

HAM-D total score		***Agomelatine* *(N = 150)***	***Sertraline* *(N = 157)***
W0	n	150	156
	Mean ± SD	26.1 ± 2.8	26.5 ± 3.0
Last post baseline value	n	150	156
(over W0-W6)	Mean ± SD	10.3 ± 7.0	12.1 ± 8.3
Last post baseline - W0	n	150	156
(over W0-W6)	Mean ± SD	-15.8 ± 7.3	-14.4 ± 8.7
	E(SE) (1)	1.68 (0.77)	
	95% CI (2)	[0.15 ; 3.20]	
	p-value (3)	**0.031**	

(1) Estimate (Standard Error) of the difference between adjusted treatment group means: Sertraline minus Agomelatine
(2) 95% confidence interval of the estimate
(3) Centre and baseline adjusted treatment effect: General linear model with baseline as covariate and centre as random effect.

The mean decrease of the HAM-D total score from baseline to the last post-baseline value over the W0-W6 period was statistically significantly greater in the agomelatine group than in the sertraline group (-15.8 ± 7.3 and -14.4 ± 8.7, respectively) with an estimated between-group adjusted difference of 1.68 (95% CI [0.15 ; 3.20], p = 0.031).

At W2, in the FAS, the difference between treatment groups in the responder (score decrease of at least 50% from baseline) rates, 20.0% of patients in the agomelatine group *versus* 10.9% in the sertraline group, was statistically significant (complementary analysis, E = -9.10 [-17.16 ; -1.05], p = 0.027).

Consistently, the percentage of patients responders to the treatment at the last post-baseline assessment was higher in the agomelatine group (70.0%) than in the sertraline group (61.5%) with an estimated difference of -8.46 (95% CI [-19.05 ; 2.12]). The percentage of patients in remission (HAM-D total score < 7), at the last post-baseline assessment, was 32.7% in the agomelatine group *versus* 28.8% in the sertraline group.

- **CGI scale**

In the FAS, the last post-baseline mean value of the CGI severity of illness score (item 1) over the W0-W6 period was lower in the agomelatine group (2.5 ± 1.1) than in the sertraline group (2.8 ± 1.3) with a statistically significant difference in favour of agomelatine of 0.28 (95% CI [0.01 ; 0.56], p = 0.043). Similarly, the mean CGI global improvement score (item 2) at last post-baseline assessment was 1.8 ± 1.0 in the agomelatine group *versus* 2.1 ± 1.2 in the sertraline group, with a statistically significant difference in favour of agomelatine (estimated difference = 0.29, 95% CI [0.04 ; 0.54], p = 0.023). Concerning the response to treatment (CGI global improvement score equal to 1 or 2) and the remission (CGI global improvement score equal to 1), the percentages of responders and remitters were 83.3% and 46.7%, respectively, in the agomelatine group and 76.9% and 37.8%, respectively, in the sertraline group.

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: Agomelatine (S 20098)	**Page:**	

SUMMARY OF RESULTS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **HAM-A scale**

In the FAS, the mean decreases in HAM-A total, psychic anxiety, and somatic anxiety scores from baseline to the last post-baseline value (W0-W6 period) were statistically significantly greater in the agomelatine group than in the sertraline group (baseline-adjusted analysis):

- Total score: -14.5 ± 9.8 in the agomelatine group *versus* -13.1 ± 11.0 in the sertraline group, E = 2.34 [0.43 ; 4.26], p = 0.017.
- Psychic anxiety score: -8.6 ± 5.1 in the agomelatine group *versus* -7.8 ± 6.1 in the sertraline group, E = 1.26 [0.11 ; 2.40], p = 0.031.
- Somatic anxiety score: -5.8 ± 5.5 in the agomelatine group *versus* -5.3 ± 5.6 in the sertraline group, E = 1.00 [0.11 ; 1.90], p = 0.028.

- **Efficacy on sleep from self-rating questionnaires**

The LSEQ provided results on the subjective sleep evaluation (4 scores): Getting off to sleep score, Quality of sleep score, Sleep awakening score and Integrity of behaviour score.
Overall, in the FAS, the 4 mean scores decreased, *i.e.* improved, during the W0-W6 period in both treatment groups. For each score, the mean last post-baseline value was lower in the agomelatine group than in the sertraline group: 34.861 ± 18.362 and 38.780 ± 17.244, respectively, for the Getting off to sleep score; 32.372 ± 19.511 and 35.392 ± 20.922, respectively, for the Quality of sleep score; 38.873 ± 20.226 and 40.434 ± 20.074, respectively, for the Sleep awakening score; and 39.780 ± 18.838 and 41.823 ± 21.554, respectively, for the Integrity of behaviour score.
At W2, the Getting off to sleep and Quality of sleep mean scores were statistically significantly lower in the agomelatine group than in the sertraline group (E = 7.40 [3.38 ; 11.41], p < 0.001 and E = 5.21 [0.67 ; 9.75], p = 0.025, respectively).

In the FAS, the mean ESS total score decreased in both groups, indicating a reduction in daytime sleepiness, with a better overall improvement in the agomelatine group: -2.8 ± 4.7 in the agomelatine group *versus* -2.1 ± 3.9 in the sertraline group.

- **Efficacy on rest/activity circadian rhythms (subjective evaluation)**

In both groups, the sleep and circadian rhythm disorder questionnaire score improved and the CSM score remained stable.

Long-term efficacy:

During the W0-W24 period, in the FAS, the mean decrease of the HAM-D total score from baseline to last post-baseline value tended to be greater in the agomelatine group (-17.7 ± 8.4) than in the sertraline group (-16.4 ± 10.3). The rate of responders to treatment, according to the HAM-D total score at the last post-baseline evaluation over the W0-W24 period, was statistically significantly higher in the agomelatine group than in the sertraline group: 76.0% *versus* 63.5% (p = 0.017). The rate of patients in remission tended to be higher in the agomelatine group (55.3%) than in the sertraline group (51.3%).
Considering the CGI scale over the W0-W24 period in the FAS, the mean last post-baseline values of items 1 and 2 tended to be lower in the agomelatine group than in the sertraline group. The percentage of responders to treatment and remitters were 78.0% and 56.7%, respectively, in the agomelatine group, *versus* 71.2% and 56.4%, respectively, in the sertraline group.

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: Agomelatine (S 20098)	**Page:**	

SAFETY RESULTS

Emergent adverse events

Emergent adverse events (EAE) were defined as all adverse events which occurred between the first treatment administration date and the last treatment administration date + 1 day or adverse events occurring before the first treatment administration date but worsening between the first administration treatment date and the last treatment administration date + 1 day, over the W0-W6/WEND period and the W0-W24/WEND period.

- **Short-term safety** (W0-W6/WEND period):

W0-W6/WEND period: *Short-term safety* **Number of patients with:**		**Agomelatine** (N = 152)	**Sertraline** (N = 159)
At least one emergent adverse event	n (%)	73 (48.0%)	78 (49.1%)
At least one treatment-related emergent adverse event	n (%)	42 (27.6%)	42 (26.4%)
At least one emergent adverse event leading to treatment discontinuation	n (%)	4 (2.6%)	18 (11.3%)
At least one emergent serious adverse event	n (%)	1 (0.7%)	2 (1.3%)

n: number of patients affected
%: n/N x 100

During this period, in the Safety Set, the percentage of patients with at least one emergent adverse event was similar in the 2 treatment groups: 48.0% in the agomelatine group and 49.1% in the sertraline group.

In both groups, the most frequently affected system organ classes (SOCs) were Nervous System disorders (19.7% in the agomelatine group, and 18.2% in the sertraline group), Gastrointestinal disorders (17.8% and 19.5%, respectively) and Infections and infestations (10.5% and 11.9%, respectively). Psychiatric disorders were more frequently reported in the sertraline group (11.9%) than in the agomelatine group (4.6%), as well as Skin and Subcutaneous tissue disorders (9.4% *versus* 3.3%, respectively). On the contrary, General disorders and administration site conditions (e.g fatigue) were more frequently reported in the agomelatine group (7.2%) than in the sertraline group (3.1%).
In both groups, the most common emergent adverse events (≥ 5% of the patients in any group) were headache (8.6% in the agomelatine group and 10.1% in the sertraline group), dry mouth (5.3% and 5.0%, respectively), diarrhoea (3.9% and 5.7%, respectively), fatigue (5.9% and 1.3%, respectively) and hyperhidrosis (none and 5.0%, respectively).

Overall, 12 patients (7.9%) in the agomelatine group and 8 patients (5.0%) in the sertraline group experienced 13 and 12 severe emergent adverse events, respectively, of which 7 and 9 severe EAE were considered treatment-related (mainly common AEs under antidepressants), respectively. Among the severe emergent adverse events, 11 were recovered in the agomelatine group and 9 in the sertraline group.

The incidence of patients with treatment-related emergent adverse event was similar in the 2 treatment groups (27.6% of patients in the agomelatine group and 26.4% in the sertraline group).

Emergent adverse events leading to treatment discontinuation were more frequent in the sertraline group (11.3%) than in the agomelatine group (2.6%), mainly due to Psychiatric disorders (5.7% *versus* none, respectively).

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: Agomelatine (S 20098)	**Page:**	

SAFETY RESULTS (Cont'd)

Emergent adverse events (Cont'd)

- **Long-term safety** (W0-W24/WEND period):

W0-W24/WEND period: ***Long-term safety*** **Number of patients with:**		**Agomelatine** (N = 152)	**Sertraline** (N = 159)
At least one emergent adverse event	n (%)	89 (58.6%)	90 (56.6%)
At least one treatment-related emergent adverse event	n (%)	45 (29.6%)	46 (28.9%)
At least one emergent adverse event leading to treatment discontinuation	n (%)	10 (6.6%)	20 (12.6%)
At least one emergent serious adverse event	n (%)	3 (2.0%)	4 (2.5%)

n: number of patients affected
%: n/N x 100

During this period, in the Safety Set, the percentage of patients with at least one emergent adverse event was similar in the 2 treatment groups: 58.6% in the agomelatine group and 56.6% in the sertraline group.

In both groups, the most frequently affected SOCs were Nervous System disorders (23.0% in the agomelatine group, and 22.6% in the sertraline group), Gastrointestinal disorders (21.1% and 22.6%, respectively), Infections and infestations (19.7% and 18.2%, respectively) and Musculoskeletal and connective tissue disorders (11.2% and 11.9%, respectively). Psychiatric disorders were more frequently reported in the sertraline group (13.8%) than in the agomelatine group (5.9%), and similarly for Skin and Subcutaneous tissue disorders (10.1% *versus* 5.9%, respectively).
In both groups, the most common emergent adverse events (≥ 5% of the patients in any group) were headache (9.2% in the agomelatine group and 11.9% in the sertraline group), nasopharyngitis (8.6% and 7.5%, respectively), diarrhoea (6.6% and 6.9%, respectively), dry mouth (5.3% and 6.3%, respectively), fatigue (6.6% and 2.5%, respectively) and hyperhidrosis (1.3% and 5.0%, respectively).
Overall, 16 patients (10.5%) in the agomelatine group and 12 patients (7.5%) in the sertraline group experienced 19 and 16 severe emergent adverse events, respectively. Out of these severe emergent adverse events, 9 were considered treatment-related (mainly common AEs under antidepressants) in both groups, 16 were recovered in the agomelatine group and 12 were recovered in the sertraline group.

The incidence of patients with treatment-related emergent adverse event was similar in the 2 treatment groups (29.6% in the agomelatine group and 28.9% in the sertraline group).

Emergent adverse events leading to treatment discontinuation were more frequent in the sertraline group (12.6%) than in the agomelatine group (6.6%), mainly due to Psychiatric disorders (5.7% *versus* 2.0%, respectively).

Serious adverse events
No death was reported during the study.
In the Safety Set, 9 patients (2.9%) experienced at least one serious adverse event (SAE). Among them, 7 patients (2.3%) had at least one emergent SAE during the 24-week treatment period: 3 patients (2.0%) in the agomelatine group (bunion operation, scar excision and cholecystitis) and 4 patients (2.5%) in the sertraline group (cellulitis, prostate cancer, sciatica and depression). All SAEs were recovered or recovering. No SAE was related to the study treatment according to the investigator; 2 cases of depression in the sertraline group were reported as SAEs and considered by the investigator as related to lack of efficacy.

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: Agomelatine (S 20098)	**Page:**	

SAFETY RESULTS (Cont'd)

Clinical laboratory evaluation

During the W0-W6 period, no clinically relevant changes in mean biochemical and hematological values were observed between the baseline and the last assessment on treatment, in both groups, except for GGT (8.0 ± 110.0 and -1.3 ± 15.0 IU/L in the agomelatine and sertraline groups, respectively; similar median: -1 and 0 in each group, respectively).

During the W0-W24 period, differences between agomelatine and sertraline groups were observed for ASAT (respective mean changes 5.0 ± 31.1 IU/L and 0.0 ± 6.6 IU/L, similar median: 0 in both groups), ALAT (respective mean changes 5.4 ± 39.9 IU/L and -0.4 ± 10.3, similar median: -1 and 0, respectively) and GGT (respective mean changes 9.9 ± 109.3 IU/L and 0.8 ± 18.7 IU/L, similar median: 0 in both groups).

During the study, emergent PCSA values of transaminases (both ASAT and ALAT, between 3 and 8 times upper the normal limit) were detected in 3 patients under agomelatine 25 mg, associated in 1 of them with emergent PCSA value of GGT. These liver parameters abnormalities were reported as non-serious EAEs (moderate intensity) of which 2 were recovered and 1 was recovering by the end of the study, and considered by the investigator as probably related to the treatment in only 1 patient.

No case of emergent PCSA values for ALAT and ASAT enzymes was reported either under sertraline or under agomelatine 50 mg.

Besides, 1 patient in the agomelatine 25 mg group presented with an out-of-reference-range value of ALAT at WEND with emergent clinically significance according to the investigator, reported as a no-treatment-related AE which recovered.

Two patients on agomelatine and 1 patient on sertraline presented with emergent PCSA values of GGT, while the transaminase levels were within the normal range. In all these patients, the GGT value was already out-of-reference-range (considered as clinically relevant by the investigator in 1 patient in each treatment group) at baseline.

Two patients under agomelatine had emergent PCSA values of total bilirubin, not considered as clinically relevant by the investigator.

No PCSA value of alkaline phosphatase was reported during the study.

CONCLUSION

A significant difference on rest/activity rhythm parameter (Relative Amplitude) was observed in this study between agomelatine (25-50 mg/day) and sertraline (50-100 mg/day) at the end of the first week of treatment in favour of agomelatine. This difference was associated with a fast sleep improvement in the agomelatine group observed on sleep efficiency, sleep latency and actual wake time as measured by actimetry and a deterioration in the sertraline group. This early improvement was also reported on the subjective sleep evaluation, Leeds questionnaire, on the getting off to sleep and quality of sleep items with a significant difference in favour of agomelatine after 2 weeks of treatment.

In addition, this study showed the superior antidepressant efficacy of agomelatine compared to sertraline, as well as a better effect on anxiety symptoms after 6 weeks.

This study confirmed the good tolerability profile of agomelatine in short-term (6 weeks) as well as in long-term (24 weeks) treatment.

Date of the report: 16 July 2008