Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Effects of agomelatine (25 to 50 mg/day) on circadian rhythms in patients with Major Depressive Disorder.** **An exploratory 6-week open, flexible dose, international multicentre, non-comparative study.**
Test drug code	**S 20098 (Agomelatine: Valdoxan®)**
Indication	**Major Depressive Disorder**
Development phase	**III**
Protocol code	**CL3-20098-080**
Study initiation date	**26 July 2012**
Study completion date	**25 July 2014**
National coordinators	[redacted]
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	**30 June 2015**
Version of the report	**Final version**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** **Valdoxan®** **Name of Active Ingredient:** **Agomelatine (S20098)**		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study:
Effects of agomelatine (25 to 50 mg/day) on circadian rhythms in patients with Major Depressive Disorder.
An exploratory 6-week open, flexible dose, international multicentre, non-comparative study.
Protocol No.: CL3-20098-080.
EudraCT No.: 2010-024191-25.
The description of the study protocol given hereafter includes the modifications of the 3 substantial amendments to the protocol.

National coordinators: [redacted]

Study centres:
For patients with Major Depressive Disorder (MDD patients): In all, 16/18 centres in 3 countries included at least one patient: 3 centres in Austria (6 patients included), 6 in Germany (89 patients included) and 7 in Poland (28 included patients).
For Healthy volunteers (HV): 1 centre in Germany included 43 HVs.

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
- For MDD patients: • Initiation date: 26 July 2012 (date of first visit first patient) • Completion date: 16 April 2014 (date of last visit last patient) - For Healthy Volunteers (HV): • Initiation date: 15 April 2014 (date of first visit first participant) • Completion date: 25 July 2014 (date of last visit last participant)	phase III

Objectives:
To assess the treatment effects of agomelatine on the circadian rhythms in MDD patients by evaluating circadian parameters like the Dim Light Melatonin Onset (DLMO), the Core Body temperature (CBT), Heart Rate (HR), the timing of sleep and their internal alignment. The circadian profile of patients with MDD at baseline and during the study (with agomelatine treatment) was defined.

To assess the effects of agomelatine on depression and its acceptability in MDD patients.

To compare the baseline circadian profile of MDD patients with the circadian profile of HVs. For this purpose, a group of HVs (matched in classes of age and gender) was included in a specific cohort to define the circadian parameters in a normal control group without treatment.

To assess, in MDD patients, the relationship between candidate genes (including clock genes) polymorphisms and treatment response / actimetric parameters in a pharmacogenetic sub-study. Pharmacogenetic results are described in a separate report.

Methodology:
This was a phase III multicentric study:

- For MDD patients: international, multicentric, exploratory open, using a flexible dosage in patients suffering from Major Depressive Disorder.
  Patients received agomelatine 25 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. The criteria for increasing the dose at W2 were defined by the Sponsor, based on clinical considerations, before the study beginning.
- For HV: exploratory monocentric study without treatment. HV had to match in classes of age and sex to the population of MDD patients.

This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of participants:
Total planned: 150 participants included (120 MDD patients and 30 HV).
Included: 123 MDD patients and 43 HV.

Diagnosis and main criteria for selection:

- MDD patients: male or female outpatients, aged between 18 (or legal majority of age) and 60 inclusive, fulfilling DSM-IV-TR criteria for MDD, single episode or recurrent ($\leq$ 3 including the current episode), with a current episode ($\geq$ 4 weeks, $\leq$ 12 months) of moderate to severe intensity with HAM-D-17 total score $\geq$ 22, sum of HAM-D items 5+6 $\geq$ 3 and HAD depression score $\geq$ 11.
- Healthy volunteers: male or female, age 18 to 60 inclusive, matched in classes of age and sex to population of MDD patients, without circadian rhythms/sleep perturbations, HAD-D $\leq$ 7, PSQI total score $<$ 5, MMSE $\geq$ 28, ESS $\leq$ 7.

Test drug:

- MDD patients: agomelatine tablets of 25 mg, 1 or 2 tablets daily taken orally once a day at 8 p.m.
- HV: not applicable.

Batch No. L0038972; L0044584.

Comparator:
Not applicable.

Duration of treatment:
For MDD patients:

- Screening period (without treatment): maximum 10 days (from pre-selection visit, ASS1, and selection visit, ASS2, to inclusion visit, W0).
- Open active treatment period: 6 weeks (from W0 to W6).
- Follow-up period (without treatment): 1 week follow-up after W6, or in case of premature withdrawal.

For HV (no treatment [maximum 18 days without treatment]):

- Selection period: maximum 10 days (from selection visit, ASSE to inclusion visit, D1).
- Evaluation period: 8 days (from D1 to D8); from D1 to D6 morning, HV were at home for the assessment period outside the clinical unit; then at D6 afternoon, HV came to the clinical unit for hospitalisation until D8 morning.
- Study end visit (D8, RUNO): HVs were discharged from the clinical unit.

Criteria for evaluation:

Efficacy measurements:

No primary criterion had been defined for this exploratory study.

- **Circadian parameters for both participants cohorts:**
  - Circadian parameters time points:
    - Dim Light Melatonin Onset (DLMO) assessed by salivary melatonin. DLMO was assessed at W0, W2 and W6 (from samples taken the previous evening) for MDD patients and on D7 for HVs.
    - Sleep parameters (sleep start time, sleep end time, sleep midpoint, actual sleep, sleep efficiency, sleep latency, go to bed time and get up time), determined by actimetry and by the sleep log. The actimetry data were recorded over 5-7 days from ASS2 to W0, from W0 to W2 and from W4 to W6 for MDD patients and over 7 days from D1 to D8 morning for HVs.
    - Minimal Core Body Temperature (CBT_{min}), Maximal Core Body Temperature (CBT_{max}) and Mid-Range Crossing body temperature time (CBT mid-range crossing), measured during sleep time, determined by eatable telemetric pills.
    - Minimal Heart Rate (HR_{min}), Maximal Heart Rate (HR_{max}) and Mid-Range Crossing heart rate (HR mid-range crossing) measured during sleep time by sensor belt.
      CBT and HR were recorded over a 1-day period, 2 days before W0, W2 and W6 for MDD patients and on D6 for HVs.
  - Phase angle differences (PADs), defined as time intervals between several circadian parameters mentioned above, and calculated as measures of circadian alignment between sleep, melatonin and temperature rhythm:
    - PAD1: sleep midpoint - DLMO.
    - PAD2: CBT_{min} time - sleep midpoint.
    - PAD3: sleep end time - CBT_{min}.
    - PAD4: sleep end time - DLMO.
    - PAD5: CBT_{min} time - DLMO.

    PADs were determined at baseline, W2 and W6 for MDD patients and at D7 for HVs.
- **Depressive symptoms for MDD patients:**
  - Hamilton Depression Rating Scale 17 items (HAM-D-17): total score, response to treatment (defined as a decrease from baseline ≥ 50%), sum of HAM-D items 5 and 6. HAM-D-17 was rated by the investigator at ASS1, W0, W2, W4 and W6.
  - Clinical Global Impression Scale (CGI): item 1 (severity of depression) and item 2 (global improvement) scores, response to treatment (CGI item 2 = 1or 2). CGI was assessed by the investigator at ASS1 and W0 (only item 1), W2, W4 and W6.
- **Clinical benefit on morning condition, social functioning and daytime functioning for MDD patients:**
  - Sheehan Disability Scale (SDS) scores, completed by the patients at ASS1, W2 and W6.
  - Numeric scales scores, rated by the patients at W0, W2, W4 and W6.

Safety measurements:

- For MDD patients:
  - Adverse events assessed at each visit.
  - Laboratory parameters (biochemistry and haematology): results available at ASS2, W4 (only liver parameters) and Wend.
  - Clinical examination: vital signs (sitting systolic blood pressure, sitting diastolic blood pressure, heart rate), body weight and BMI at ASS1, W0 and W6.
  - ECG abnormalities, to be available at ASS2 and Wend.
- For HV:
  - Adverse events, assessed at each visit.
  - Laboratory parameters, results available at D1 and D8.
  - Vital signs (supine and standing systolic blood pressure, diastolic blood pressure, heart rate) and aural body temperature at ASSE, inclusion and RUNO. Body weight and BMI were measured at ASSE and RUNO.

Criteria for evaluation (Cont'd):

Other assessments not specifically related to efficacy or safety:

- For MDD patients:
  - Measurement of agomelatine saliva concentration.
    Agomelatine saliva concentrations were measured on the same saliva samples collected for DLMO measurement and were used for agomelatine pharmacokinetic analysis. It was assessed at W2 and W6 from samples taken the previous evening. Only samples taken after drug intake (expected at 8 p.m.) were assessed for agomelatine saliva concentrations analysis. The samples analysed were the first 4 samples collected after study drug intake (8 p.m.) and then hourly until bed time.
    Melatonin and agomelatine concentrations in saliva were measured at a bioanalytical centre with previously validated methods.
  - Serum Brain Derived Neurotrophic Factor (BDNF), at ASS1, W2 and W6.
- For HV: serum and plasma Brain Derived Neurotrophic Factor (BDNF), on D7 at 8 a.m., 1 p.m., 6 p.m. and bedtime.

Statistical methods:

Analysis Set

The main analysis sets were:

- Included Set of MDD patients (IS-MDD): all included patients.
- Included Set of Healthy Volunteers (IS-HV): all included healthy volunteers.
- Full Analysis Set (FAS): all included patients, having taken at least one dose of study medication and having a value at baseline and at least one post-baseline value for any efficacy criterion other than relative to circadian rhythms.
- Circadian analysis Set of MDD patients (CAS-MDD): all included patients having taken at least one dose of study medication and having at least one interpretable value at baseline and after baseline for any efficacy criterion related to circadian rhythms.
- Circadian analysis Set of Healthy Volunteers (CAS-HV): all included healthy volunteers having at least one interpretable value for any criterion related to circadian rhythms.
- Safety Set: all included patients having taken at least one dose of study medication.

Considering the study was exploratory, no primary criterion was defined.

Efficacy analyses

Descriptive statistics were provided for all analytical approaches of criteria relative to circadian parameters over the W0-W6 period for patients of the CAS-MDD. DLMO, CBT, sleep organisation, HR and PADs were presented using values at each visit and changes from baseline to each post-baseline visit.

Descriptive statistics were provided for all analytical approaches of criteria relative to depression and general functioning over the W0-W6 period for patients of the FAS and the CAS-MDD. HAM-D-17 scale, SDS, CGI scale and numeric scales were presented using values at each visit and changes from baseline to each post-baseline visit if applicable.

Safety analyses

Safety analyses were performed in the Safety Set for MDD patients and the Included Set for Healthy Volunteers.

For MDD patients, descriptive statistics, presented by primary system organ class and/or preferred term (depending on the analysis), were provided for serious adverse events over the 6-week treatment period, for emergent adverse events over the 6-week treatment period, and for emergent adverse events occurring after treatment period.

A listing of healthy volunteers with adverse events during the study period was provided.

Other assessments not specifically related to efficacy or safety

For MDD patients, serum BDNF was described using value at baseline and at each post-baseline visit and change from baseline to each post-baseline visit in the CAS-MDD and in the FAS. The relationship between serum BDNF level and HAM-D total score was explored using descriptive statistics, correlation, ROC curve and AUC. Description of serum BDNF level was also performed according to the treatment response.

Statistical methods (Cont'd):
Pharmacokinetics analysis for MDD patients
The individual saliva concentrations were fit to an existing population pharmacokinetic model which had been developed for agomelatine (Chenel, 2008; Peigné, 2012). As agomelatine was measured in saliva and not in plasma, a known correlation between agomelatine plasma and saliva concentrations was used to back-calculate plasma concentrations from saliva concentrations, in order to derive individual plasma pharmacokinetic parameters.
The following pharmacokinetic parameters were computed from the empirical Bayesian estimates: t_{max}, C_{max}, $t_{1/2z}$, and AUC.

SUMMARY - CONCLUSIONS

DISPOSITION OF PARTICIPANTS AND ANALYSIS SETS

Disposition of MDD patients

Status	MDD patients Agomelatine
W0-W6	
Included	**123**
Withdrawn due to	**15 (12.2)**
Adverse event	2 (1.6)
Protocol deviation	4 (3.3)
Lack of efficacy	1 (0.8)
Non-medical reason	8 (6.5)
Completed the W0-W6 period	**108 (87.8)**
Full Analysis Set (FAS)	**119 (96.7)**
Circadian Analysis Set (CAS-MDD)	**117 (95.1)**
Safety Set (SS)	**122 (99.2)**
Pharmacokinetic Set (PK)	**107 (87.0)**

Disposition of Healthy Volunteers

Status	HV No treatment
D1-D7	
Included	**43**
Withdrawn due to	**4 (9.3)**
Non-medical reason	4 (9.3)
Completed the D1-D7 period	**39 (90.7)**
Circadian Analysis Set (CAS-HV)	**30 (69.8)**

A total of 150 *MDD patients* were selected and 123 were included for the study. At W2, 30.1% (37 patients) had a dose increase. Over the W0-W6 period, 12.2% of MDD had a treatment withdrawal: 1.6% for adverse event, 6.5% for non-medical reason, 3.3% for protocol deviation and 0.8% for lack of efficacy. Overall, 87.8% of MDD patients completed the W0-W6 period.

A total of 43 *Healthy Volunteers (HV)* were selected and included for the study. Among the 43 included HV, 13 were replaced, owing to non-interpretable values on circadian parameters. Over the D1-D7 period, 9.3% of HV had a treatment withdrawal, all due to an actimetry measurement failure. Overall, 90.7% of HV completed the D1-D7 period.

No included participant was lost to follow-up during the study.

SUMMARY - CONCLUSIONS (Cont'd)

BASELINE CHARACTERISTICS

At baseline in the IS, MDD patients were 44.6 ± 10.6 years old on average *versus* 41.3 ± 12.0 years old for HV. The proportion of males was slightly greater in MDD patients (48.8%) than in HV (41.9%).

For MDD patients, according to DSM-IV criteria, 56.9% of patients were diagnosed as recurrent MDD, and 43.1% had a single episode. In all, 82.1% of patients had a moderate MDD and 17.9% a severe MDD without psychotic feature. According to DSM-IV diagnosis of melancholic features, all patients had melancholic features.

Mean duration of the current MDE was 5.2 ± 2.6 months (median 4.4 months). Previous psychotropic drug treatment taken within one year prior to pre-selection was reported in 60.2% of patients, mainly SSRIs (28.5%) and other antidepressants (23.6%).

At baseline, the mean HAD depression sub-score was 15.4 ± 2.7. All patients had a depression score ≥ 11 as required in the pre-selection criteria. The mean HAD anxiety sub-score was 13.7 ± 3.8. Most of the patients (98, 79.7%) had an anxiety sub-score ≥ 11 indicating that patients felt at least moderately anxious. Then, 15.5% of patients (19) had an anxiety sub-score between 8 and 10, and 4.9% (6 patients) had a sub-score between 0 and 7.

The PSQI total score at inclusion ranged from 5 to 19, with a mean of 12.1 ± 3.0.

For HV, the mean MMSE total score was 30, ranging from 29 to 30, indicating a normal cognitive function at selection. This was confirmed by the M.I.N.I. The mean HAD depression and anxiety scores were 0.8 ± 1.2 and 1.5 ± 1.5, respectively, with all participants having an anxiety and a depression scores ≤ 7, as required by the protocol.

Regarding the quality of sleep and daytime sleepiness in HV, the PSQI total score at ASSE ranged from 0 to 4 with a mean of 2.3 ± 1.1. Participants did not show excessive daytime sleepiness according to the Epworth Sleepiness total score, with a mean of 3.3 ± 2.2 at ASSE, ranging from 0 to 7, as required by the protocol.

As regards to the efficacy parameters for depression and daytime and social functioning at baseline in the IS-MDD, HAM-D-17-item total score was 25.1 ± 2.7 and CGI severity of illness score was 4.6 ± 0.6. According to SDS, on average, patients felt markedly disrupted by symptoms for the 3 domains: work and activity (8.4 ± 1.5), social life (8.1 ± 1.5), and family life and home responsibilities (7.8 ± 1.9).

In the CAS, MDD patients were 44.5 ± 10.8 years old on average *versus* 41.5 ± 12.7 years old for HV. The proportion of males was similar in MDD patients (49.6%) and in HV (50.0%). MDD patients and HV were matched for age and gender.

The screening of sleep organisation in the CAS showed no relevant differences between MDD patients (at baseline) and HV (during study) for mean sleep start time (23h51 ± 1h13 *versus* 23h42 ± 0h28), mean sleep end time (7h21 ± 1h20 *versus* 7h21 ± 0h45), mean sleep midpoint time (3h37 ± 1h09 *versus* 3h31 ± 0h32), mean sleep efficiency (79.07 ± 8.57% *versus* 83.83 ± 4.37%), mean go to bed time (23h31 ± 1h16 *versus* 23h32 ± 0h27) and mean get up time (7h26 ± 1h20 *versus* 7h25 ± 0h46).

The mean sleep latency was longer in MDD patients than in HV (19.95 ± 22.93min *versus* 10.10 ± 6.31min). The mean actual sleep was slightly shorter in MDD patients than in HV (373.40 ± 62.35min *versus* 396.09 ± 34.29min).

Regarding the main circadian parameters in the CAS, the mean DLMO time was reported earlier in MDD patients than in HV (20h58 ± 1h03 at baseline *versus* 21h29 ± 0h37 at D7). CBTmin time was observed slightly later in MDD patients than in HV (4h49 ± 1h50 at baseline *versus* 4h31 ± 1h29 at D6). A longer phase angle difference for mean sleep midpoint-DLMO (PAD1) was observed in MDD patients than in HV (6h26 ± 1h06 at baseline *versus* 5h58 ± 0h38 at RUNO). Concerning CBTmin and PADs, no clear distinction of baseline profiles between MDD patients and HV could be defined.

EXTENT OF EXPOSURE

In the IS-MDD, mean treatment duration was 39.5 ± 8.1 days (median 42.0 days) over the W0-W6 period. Global compliance over the W0-W6 period was satisfactory (96.8 ± 12.6%). During the study, MDD patients took their treatment around 20h17min ± 0h51, which was in accordance with the protocol recommendations of taking agomelatine at 20h.

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

- Circadian parameters and sleep organisation

In the CAS-MDD, the mean DLMO time was reported earlier after 6 weeks of agomelatine treatment than at baseline (mean advance: 0h16min ± 0h58min, median: 0h25min).

An advance of mean CBTmin time was also observed at W6 (mean change from baseline to W6: -0h38 ± 1h27, median: -0h34). The same trends were observed for CBTmax time (mean change: -0h37 ± 1h24, median: -0h42) and CBT mid-range crossing (mean change: -0h34 ± 1h21, median: -0h41). Similarly, the mean time of HRmin was reported earlier at W6 than at baseline (mean change from baseline to W6: -0h28 ± 2h01, median: -0h20). Similar trends were observed for HRmax (mean change: -0h12 ± 2h46, median: -0h13) and HR mid-range crossing (mean change: -0h24 ± 2h24, median: -0h10).

The evolution of sleep parameters over the W0-W6 period, evaluated by actimetry in the CAS-MDD, showed a trend toward an improvement after agomelatine treatment, *i.e.* greater actual sleep duration (mean increase: 7.7 ± 53.6 min, median: 6.3 min), shorter sleep latency (mean decrease: -2.4 ± 24.9 min, median: 0.3 min) and advanced sleep start time (mean advance: -0h10 ± 1h00, median: -0h13).

As regards to the phase angle differences (PADs), heterogeneous changes were observed depending on the parameters used. The PAD between DLMO and mid-sleep (PAD1) did not significantly vary over the W0-W6 period in patients of the CAS-MDD (mean change between baseline and W6: 0h00 ± 1h10, median: 0h14). However the interval between the CBTmin time and the sleep end time (PAD3) was extended by on average 0h37 min (± 1h25min, median: 0h30min). Also the PAD between DLMO and sleep end time (PAD4) was extended by on average 0h13min ± 1h09min (median: 0h22min) between baseline and W6. The interval between sleep midpoint and CBTmin time (PAD2) as well as between DLMO and CBTmin time (PAD5) were shorter after 6 weeks of agomelatine treatment (mean change: -0h26 ± 1h29, median -0h27, for PAD2 and -0h25 ± 1h43, median: -0h19 for PAD5).

- Efficacy on depression

A decrease of the mean HAM-D-17 total score from baseline to the last post-baseline value over the W0-W6 period was observed in the FAS (-11.1 ± 6.9). Consistently, the percentage of responders to the treatment at the last post-baseline assessment progressively increased over the W0-W6 period, to reach 47.9% of responders at the last post-baseline assessment.

In the FAS, the mean CGI severity of illness and global improvement scores decreased through the visits over the W0-W6 period. At the last post-baseline assessment, the mean scores were 3.3 ± 1.2 (median: 3.0) and 2.3 ± 1.1 (median: 2.0), respectively. The response to treatment according to the CGI (global improvement score equal to 1 or 2) showed that the percentage of responders was 57.1% at the last post-baseline assessment.

- Efficacy on global functioning and morning condition

In the FAS, the 3 mean SDS scores decreased over the W0-W6 period. Mean changes between baseline and the last post-baseline assessment were:

- Work and activity: -3.0 ± 2.5.
- Social life: -3.2 ± 2.4.
- Family life and home responsibilities: -2.7 ± 2.6.

Morning condition and day time functioning, assessed by subjective evaluation on a scale from 0 to 10, improved over the W0-W6 period in the FAS. Mean changes between baseline and the last post-baseline assessment were as follows:

- Awakening from sleep last week: 1.7 ± 2.9.
- Morning concentration last week: 2.2 ± 2.9.
- Morning working performance last week: 2.6 ± 2.7.
- Daytime overall functioning last week: 2.2 ± 2.4.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

In the Safety Set (only MDD patients)

- **Emergent adverse events**

Overall summary of adverse events in the Safety Set

		Agomelatine (N = 122)
Patients having reported		
at least one emergent adverse event	n (%)	40 (32.8)
at least one treatment-related emergent adverse event	n (%)	15 (12.3)
Patients having experienced		
at least one serious adverse event	n (%)	1 (0.8)
at least one serious emergent event	n (%)	1 (0.8)
at least one treatment-related serious adverse event	n (%)	-
Patients with treatment withdrawal		
due to an emergent adverse event	n (%)	2 (1.6)
due to an emergent serious adverse event	n (%)	-
due a treatment-related emergent adverse event	n (%)	2 (1.6)
due a treatment-related emergent serious adverse event	n (%)	-
Patients who died	n (%)	-

During the W0-W6 period, in the Safety Set, the incidence of patients presenting with at least one EAE was low in the agomelatine group (32.8%). The most frequently affected system organ classes (SOC) were nervous system disorders (15.6%), infections and infestations (8.2%) and gastrointestinal disorders (7.4%). The most frequently reported EAEs (> 2%) in the agomelatine group were headache (10.7%), nasopharyngitis (5.7%), diarrhoea and paraesthesia (2.5% for both events).

Emergent adverse events were mainly mild or moderate. The incidence of patients with at least one severe emergent adverse event was low (4.1%).

Overall, 12.3% of patients reported at least one treatment-related emergent adverse event. None of the treatment-related emergent adverse events were reported by more than 2 patients.

No death was reported during the study.

During the ASS1-W6/Wend period, one MDD patient had 3 serious adverse events, all emergent over the 6-month treatment period: abdominal pain lower, pyrexia and nausea. None of these events were considered as treatment-related, and none led to study drug withdrawal.

Emergent adverse events led to premature treatment withdrawal in 2 MDD patients (1.6% of the safety Set). One patient had alanine aminotransferase increased and one patient had diarrhoea and abdominal pain upper. All events were considered as treatment-related. Both patients recovered.

- **Laboratory tests**

In the SS, no clinically relevant changes over time were detected for biochemical, haematological and liver parameters.
During the ASS1-Wend period, 3 patients in the agomelatine group had an emergent PCSA biochemical value: high PCSA value of urea, high PCSA value of triglycerides and low PCSA value of glucose.
No emergent PCSA values were reported for haematological parameters.

Regarding liver acceptability, PCSA values of liver parameters were observed in one patient. This patient had emergent PCSA high value for ALT (3.5 ULN) associated with out-of-reference-range high value of AST (1.5 ULN). Alanine aminotransferase increased was reported as an adverse event. It was considered as treatment-related and led to study drug withdrawal. According to the investigator, the patient recovered 49 days after the last intake date. According to the Liver Safety Committee the case was unlikely related to the study drug.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Other safety evaluations**

No clinically relevant changes over time were detected during the W0-W6 period, in the SS, for weight, sitting blood pressure, and heart rate.
Regarding BMI during the W0-W6 period in the Safety Set, most patients (91.8%) remained in the same BMI class, two patients had a BMI increase (from underweight to normal and from overweight to obese) and 4 patients had a BMI decrease (1 patient from obese to overweight, 2 from overweight to normal and 1 from normal to underweight).

In the IS-HV

In the IS-HV, 3 participants experienced 4 adverse events of mild or moderate intensity during the study: 2 had headache and 1 had ALT increased and GGT increased. None of these events was serious and all participants recovered.

As regards to the haematological and biochemical parameters, 3 participants had 4 PCSA values during the study (1 for ALT and GGT and 2 for triglycerides).

There were no relevant differences between ASSE and RUNO for mean supine HR and body temperature, whereas mean supine blood pressure was slightly lower at RUNO than ASSE.
As regards to the BMI class, the proportion of participants within each category of BMI was similar at ASSE and RUNO visits.

OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

BDNF results in Healthy Volunteers
In the IS-HV, a slight decrease in median (Q1 ; Q3) serum BDNF was observed on D7 in both men and women from 1 p.m. until 6 p.m.: from 28.2 (20.9 ; 30.9) ng/ml to 26.2 (17.8 ; 30.5) ng/ml in men and from 31.5 (27.9 ; 36.8) ng/ml to 28.9 (19.2 ; 34.4) ng/ml in women. As regards to plasma levels, the high percentage of values < LLOQ did not allow to conclude from these results.

BDNF results in MDD patients
In the IS-MDD, a high heterogeneity of serum BDNF level was noted whatever the visit and the response to treatment. No clear increase of BDNF under treatment was found neither in the responder group (median change from baseline to W6: 0.13 ng/ml) nor in the non-responder group (median change from baseline to W6: -0.06 ng/ml). No correlations between the serum BDNF level and the HAM-D total score were observed in MDD patients. No information was provided by serum BDNF level for prediction of the treatment response.

Pharmacokinetic results

Descriptive statistics of agomelatine pharmacokinetic parameters in plasma by dose

Agomelatine dose (mg)	N	AUC_{24} [1] (ng.h/mL)	C_{max} [1] (ng/mL)	t_{max} [2] (h)	$t_{1/2\ z}$ [1] (h)
25	160	34.9 ± [redacted]	32.1 ± [redacted]	0.40 [0.10-6.00]	2.14 ± 0.43 (2.03) [1.94-5.71]
50	25	33.3 ± [redacted]	23.9 ± [redacted]	0.30 [0.10-7.00]	2.29 ± 0.88 (2.04) [1.81-6.21]

N: number of pharmacokinetic profiles(at W2 and W6)
[1]: mean ± SD
(median)
[min-max]
[2]: median
[min-max]

SUMMARY - CONCLUSIONS (Cont'd)
OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY (Cont'd)

The mean and median plasma PK parameters, based on the simulated plasma concentrations, showed that similar t_{max} and $t_{1/2,z}$ values were obtained for 25 and 50 mg doses, and the median AUC_{24} increased approximately proportionally with the dose between 25 and 50 mg.

At 25 mg, the median AUC_{24} in this study (ng.h/mL) was % higher than the AUC value in the combined population PK analysis (ng.h/mL) and the median C_{max} value in this study (ng/mL) was % higher than the C_{max} value in the combined population PK analysis (ng/mL). At 50 mg, the median AUC_{24} in this study (ng.h/mL) was % lower than the AUC value in the combined population PK analysis (ng.h/mL) and the median C_{max} value in this study (ng/mL) was % lower than the C_{max} value in the combined population PK analysis (ng/mL). The pharmacokinetic parameters obtained in this study are therefore within the known variability of agomelatine.

CONCLUSION
In conclusion, baseline characteristics of the included participants were in accordance with the inclusion criteria of the study. In the CAS, no clinically relevant differences between MDD patients and healthy volunteers at baseline were observed for demographic data: MDD patients and HV were matched for age and gender. Characteristics of sleep and other circadian parameters showed that sleep organisation was similar between the 2 groups, except for mean sleep latency that was longer in MDD patients and actual sleep that was shorter in MDD patients than in HV. MDD patients on average had an earlier DLMO and a later CBT min time than HV. No other clear distinction of baseline profiles of patients and HV could be defined.

As regards to the circadian parameters in MDD patients over the W0-W6 period, an advance in DLMO, CBTmin and HRmin time as well as a lengthening in the corresponding phase angle differences, especially between CBTmin time and the sleep end time, were observed. This was associated with a sleep improvement observed on sleep latency, sleep start time, and actual sleep duration and an improvement of patient's global and daytime functioning and morning condition.
In addition, an antidepressant effect was observed after 6 weeks of agomelatine treatment.
Agomelatine was well tolerated. No unexpected adverse event was reported.

Date of the report: 30 June 2015

Version of the report: Final version