Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Pharmacokinetics and safety of agomelatine in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) with Depressive or Anxiety Disorder.** **An open-labelled, multicentre, three-dose level, non-comparative study.**
Test drug code	**Agomelatine (S 20098)**
Indication	**Depressive or Anxiety Disorder**
Development phase	**Phase II**
Protocol code	**CL2-20098-075**
Study initiation date	**23 August 2013**
Study completion date	**14 March 2015**
Investigator	[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	**07 September 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:** Not applicable. **Name of Active Ingredient:** Agomelatine (S 20098)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Pharmacokinetics and safety of agomelatine in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) with Depressive or Anxiety Disorder.
An open-labelled, multicentre, three-dose level, non-comparative study.
Protocol No.: CL2-20098-075
EudraCT No.: 2012-003404-12
The description of the study protocol given hereafter includes the modifications of the two substantial amendments and the two non-substantial amendments to the protocol.

National investigators: [redacted]

Study centres:
10 centres located in 4 countries included 51 patients: 3 centres in Finland (6 patients), 1 centre in Estonia (1 patient), 3 centres in Hungary (26 patients), and 3 centres in Romania (18 patients).

Publication (reference):
Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 23 August 2013 Completion date: 14 March 2015	Phase II

Objectives:
The purpose of this study was to evaluate pharmacokinetics (PK) and safety of 3 doses of agomelatine (5, 10 and 25 mg) in male and female patients from 7 to less than 18 years suffering from a Depressive or Anxiety Disorder.
The primary objective was to evaluate the PK of 3 doses of agomelatine (5, 10 and 25 mg) in patients from 7 to less than 18 years suffering from a Depressive or Anxiety Disorder.
The secondary objectives were to:

- Provide safety data of 3 doses of agomelatine (5, 10 and 25 mg).
- Evaluate vigilance/sedation of 3 doses of agomelatine (5, 10 and 25 mg).
- Evaluate the tablet acceptability of 3 doses of agomelatine (5, 10 and 25 mg).

Methodology:
This was a phase II, non-comparative, open-labelled, multicentre, three-dose level study (with intra-patient dose escalation) conducted in 51 patients evaluable for the primary objective with a primary diagnosis of Depressive or Anxiety Disorder, as per DSM-IV-TR criteria.
All included patients received agomelatine 5 mg on Day 1 (D1), then agomelatine 10 mg on D2, then agomelatine 25 mg on D3 taken between 6.00 p m. and 7.00 p.m. each evening. PK sampling was performed during this treatment period.
The study duration for participants was 7 to 11 days including a screening period of 3-7 days, an open-labelled treatment period of 3 days and a run-out (RUNO) visit the day after the last investigational medicinal product (IMP) intake.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned: at least 48 patients evaluable for the primary objective):

- At least 24 children participants from 7 to less than 12 years of age (at least 6 males and at least 6 females).
- At least 24 adolescent participants from 12 to less than 18 years of age (at least 12 males and at least 12 females).
- At least 6 post-pubertal females (post-pubertal was defined as being after menarche) and at least 6 pre-pubertal females in the above 2 subsets, irrespective of age group.

Note: the above text reflects the number of study participants by paediatric subset as amended following modification of the paediatric investigation plan.
Included: 51 patients:

- 24 children (14 males and 10 females [all pre-pubertal]).
- 27 adolescents (12 males and 15 females: 11 post-pubertal, 4 pre-pubertal)

Diagnosis and main criteria for inclusion:
The study population included children (aged from 7 to less than 12 years of age) and adolescents (from 12 to less than 18 years of age) with a primary diagnosis of Depressive or Anxiety Disorder, as per DSM-IV-TR criteria, including Major Depressive Episodes (MDE), Dysthymic Disorder, Separation Anxiety Disorder, Social Phobia, Specific Phobia and Generalised Anxiety Disorder (GAD). Patients had to be living with their legal representative during the study.
Any kind of psychotherapy and/or psychological intervention (structured or supportive) was authorised during the study.

Test drug:
Agomelatine was taken orally, once daily, between 6.00 p.m. and 7.00 p m. on D1, D2 and D3 as follows:

- One oral film-coated tablet of agomelatine 5 mg on D1.
- One oral film-coated tablet of agomelatine 10 mg on D2.
- One oral film-coated tablet of agomelatine 25 mg on D3.

Batch Nos.: L0046939, L0044520 and L0047440 for the 5, 10 and 25 mg doses, respectively.

Comparator (Reference product and/or placebo): Not applicable.

Duration of treatment: 3 days
Run-in period: NA (Selection; ASSE: 3-7 days)
Treatment period: 3 days (D1, D2, D3)
Wash-out / follow-up period: 1 day

Criteria for evaluation:
Pharmacokinetic measurements (primary):

- PK saliva samples taken on D1, D2, D3, 30 min before IMP intake, then 30 min, 1h, 2h, 3h and 4h after IMP intake, then every hour until bedtime, then at the patient's awakening the following morning and finally at RUNO.
- A single blood sample taken on D3, 1h after oral administration of agomelatine 25 mg.

Concentrations of agomelatine determined centrally using a previously developed method based on liquid-solid extraction and liquid chromatography coupled with tandem mass spectrometry detection (HPLC-MS/MS).
Key agomelatine PK parameters analysed were: maximum plasma concentration (C_{max}), area under the curve (AUC), terminal half-life ($t_{1/2}$), minimum plasma concentration (C_{trough}), and the time corresponding to C_{max} (t_{max}).
Safety measurements:

- Assessment of suicidal ideation and suicidal behaviour was performed using the Columbia Suicide Severity Rating Scale Children's version (C-SSRS-C) Baseline/Screening version at the selection visit and C-SSRS-C Since Last Visit version at RUNO.
- Physical examination including systolic blood pressure (SBP) and diastolic blood pressure (SBP) and heart rate (HR) assessed at each visit and body weight and body mass index assessed at selection and RUNO.
- 12-lead Electrocardiogram (ECG) assessed at selection and RUNO performed under the supervision of and assessed by a child cardiologist or by a cardiologist qualified in child ECG recording.

Blood clinical laboratory parameters: haematology, biochemistry and hormonal parameters (prolactin, estradiol, cortisol, thyroid stimulating hormone [TSH], follicle stimulating hormone [FSH], luteinising hormone [LH], testosterone) for samples collected at selection (all parameters and serological markers), D1, D2, D3 (1h after IMP intake; hormonal parameters only) and RUNO (all parameters). Analysed centrally.

Safety measurements (Cont'd):

- Urinalysis (drug screening, pregnancy test) and breath alcohol test at screening, inclusion (no pregnancy test at inclusion) and RUNO (no breath alcohol test at RUNO). Assessed locally.
- Adverse events (AEs) assessed at each visit; also collected using the Pediatric Adverse Event Rating Scale (PAERS). The PAERS Youth form was self-rated by patient, the PAERS Parent form was self-rated by the parent/legally authorised representative on the patient's AEs, and the PAERS Clinician form was rated by the investigator based on a review of the PAERS youth and PAERS parent forms.

Other measurements:

- Vigilance/sedation visual analogue scale (VAS) at D1, D2 and D3 (at $T_{0\text{-}30min}$ and T_{0+1h}). Scored on a scale of 0 to 3: wide awake (0), rather awake (1), rather sleepy (2) or very sleepy (3).
- Choice reaction time (CRT) test at D1, D2 and D3 (at $T_{0\text{-}30min}$ and T_{0+1h}) to objectively and quantitatively measure sedative effects of drug.
- Tablet acceptability after the IMP intake on D1, D2 and D3. Scored on a scale of 0 to 3: very easy (0), easy (1), difficult (2) or very difficult (3).

Statistical methods: statistical analysis was performed according to the statistical analysis plan written by I.R.I.S based on the protocol and was finalised before database lock. IMP doses considered were agomelatine 5, 10 and 25 mg, corresponding to the doses taken on D1, D2 and D3 respectively.

Analysis Set: analysis sets were defined as follows:
Included Set: all included patients.
Safety Set: all included patients having taken at least one dose of agomelatine.
Two subgroups were defined for both sets: 1) Children: patients aged from 7 years to less than 12 years at selection; 2) adolescents: patients aged from 12 years to less than 18 years at selection.

Pharmacokinetic analysis: a population modelling approach was used to characterise the PK of agomelatine in a paediatric population using pooled PK data from two clinical studies (CL2-20098-075 and CL2-20098-044). The starting model was based on previous knowledge of agomelatine PK in adults, with PK model building performed in three stages. Materials and methods for PK analyses are described in a separate report.

Study outcome and safety analysis: disposition of patients, baseline characteristics and patient follow-up were described overall and for some criteria by age subgroup. All safety analyses were performed in the Safety Set, overall and by age subgroup and by sex for hormonal parameters only. Qualitative or quantitative descriptive statistics were provided depending on the nature of the variables.

Other analyses: all analyses relative to other criteria not specifically related to PK or safety – vigilance and sedation and tablet acceptability – were performed in the Safety Set, overall and by age subgroup

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 51 patients were included of whom 49 patients completed the study (96.1%), including all 27/27 adolescents and 22/24 children (91.7%). The 2 children who discontinued the study prematurely discontinued on D2, after IMP administration, one due to the IMP-related EAEs of fatigue (not serious) and one due to withdrawal of consent.

A small proportion of patients presented protocol deviations at or before inclusion (3 adolescents [11.1%] and 1 child [4.2%]). A higher proportion presented protocol deviations during the study (14 adolescents [51.9%] and 10 children [41.7%]), largely consisting of IMP intake and PK sampling time deviations.

All patients were included in the Safety Set.

Table 1 Disposition of patients and analysis sets

	Adolescents (N = 27)	Children (N = 24)	All (N = 51)
Included	**27**	**24**	**51**
Withdrawn due to	**-**	**2 (8.33)**	**2 (3.92)**
- adverse event	-	1 (4.17)	1 (1.96)
- non-medical reason	-	1 (4.17)	1 (1.96)
Completed	**27 (100)**	**22 (91.67)**	**49 (96.08)**
Safety set	**27 (100)**	**24 (100)**	**51 (100)**

SUMMARY – CONCLUSIONS (Cont'd)

BASELINE CHARACTERISTICS

Demographics and other baseline characteristics were in line with selection/inclusion criteria defined in the study protocol for each age category. The mean age was 12.4 years, 14.8 years for adolescents and 9.8 years for children. Twelve (12) males and 15 females were included in the adolescent age category and 14 males and 10 females were included in the child age category. Of the 25 female patients, 11 (44.0%) were post-pubertal and 14 (56.0%) were pre-pubertal. The majority of patients (> 70% overall) were hospitalised for the study procedures: 70.4% of adolescents and 70.8% of children.

The majority of patients (39 [76.5%]) had a primary diagnosis of MDD. Five (5) patients (9.9%) had a primary diagnosis of GAD and 4 patients (7.8%) had a primary diagnosis of Dysthymic Disorder. Separation Anxiety Disorder and Specific Phobia were the primary diagnoses in 2 patients (3.9%) and 1 patient (2.0%), respectively.

The majority of patients had not made any suicide attempt during their lifetime (96.1%); 1 adolescent and 1 child had previously attempted suicide. Within the previous 6 months prior to screening, 4 adolescents (14.8%) and 4 children (16.7%) had experienced suicidal ideations.

Overall, 29 patients (56.9%) had taken at least one previous psychotropic treatment (18 adolescents [66.7%] and 11 children [45.8%]).

EXTENT OF EXPOSURE

All except 2 patients received the 3 planned doses of agomelatine (5, 10 and 25 mg); the 2 children prematurely withdrawn from the study received the first 2 doses only (5 and 10 mg).

PHARMACOKINETIC RESULTS

No covariates showed a significant effect on agomelatine PK and thus none was retained in the PK model. Individual PK parameters were used for the computation of individual plasma concentration-time profiles and derived secondary PK parameters (AUC, C_{max} and t_{max}). Median AUC was 4.18, 7.09 and 19 ng.h/mL after 5, 10 and 25 mg agomelatine administration, respectively. Median C_{max} was 1.63, 2.69 and 9.68 ng/mL after 5, 10 and 25 mg agomelatine administration, respectively. As in adults, agomelatine is rapidly eliminated in the paediatric population, and consequently the parameters $t_{1/2}$ and C_{trough} were not computed due to the high number of values below the limit of quantification. Results of this analysis will be used to support dose selection for the efficacy studies in the paediatric population, based on the assumption that the exposure/efficacy relationship is the same between adults and the paediatric population.

Table 2 Plasma pharmacokinetic parameters

	Dose (mg)	N	5th Pctl	Median	95th Pctl	Mean	CV (%)
AUC (ng h/mL)	5	51	1.97	4.18	19.1	20.8	518
	10	51	3.90	7.09	41.7	29.6	413
	25	49	7.76	19.0	147	42.9	205
C_{max} (ng/mL)	5	51	0.766	1.63	10.8	11.4	550
	10	51	1.10	2.69	19.4	17.1	457
	25	49	1.97	9.68	87.6	23.6	243

AUC: area under the curve; C_{max}: maximum plasma concentration; CV: coefficient of variation; Pctl.: percentile

SAFETY RESULTS

- Emergent adverse events

For **all patients**, a total of 17 of the 51 patients included (33.3%) reported at least one EAE.

The most frequently affected SOC overall was nervous system disorders (10 patients [19.6%]) followed by general disorders and administration site conditions (6 patients [11.8%]) and gastrointestinal disorders (5 patients [9.8%]). For each dose received, there were slight differences in the frequency of SOCs affected. The SOC nervous system disorders was the only SOC affected that tended to increase in frequency with agomelatine dose: 4 patients (7.8%) at 5 mg, 5 patients (9.8%) at 10 mg and 6 patients (12.2%) at 25 mg.

The most frequently reported EAEs overall were hypersomnia (5 patients [9.8%]), fatigue (4 patients [7.8%]) and dizziness, dry mouth and somnolence (3 patients [5.9%] each). Hypersomnia was reported at a higher frequency for the 25 mg dose than for 5 or 10 mg (1 patient [2.0%] on 5 mg, 1 patient [2.0%] on 10 mg and 4 patients [8.2%] on 25 mg).

There were no severe EAEs during the study. Overall, the majority of EAEs were of mild intensity (78.9%). Overall, 12 patients (23.5%) had 23 EAEs considered to be related to the treatment: 5.9% at 5 mg, 7.8% at 10 mg and 20.4% at 25 mg (including events assessed at RUNO only and automatically assigned to the 25 mg dose: ECG QT prolonged in 2 patients [4.1%] (not confirmed by the expert), and leukopenia and neutropenia in 1 patient each [2.0%]).

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

One patient (child) had 2 mild EAEs of fatigue considered related to treatment that led to withdrawal from the study on D2. There were no deaths or serious EAEs during the study. One patient (adolescent) experienced 2 severe non-emergent SAEs after the end of the study, not considered related to treatment (13 days post-RUNO; bipolar II disorder and suicidal behaviour).

The majority of the EAEs reported in this population correspond either to those commonly reported in paediatric patients (nasopharyngitis, conjunctivitis bacterial, influenza, acne) or to known EAEs reported with agomelatine in adults (anxiety, headache, dizziness, somnolence, diarrhoea and fatigue). Those not previously reported in adults include ECG QT prolonged (not confirmed by the expert), leukopenia and neutropenia.

A very similar pattern was observed in **adolescents**. A total of 10 adolescents (37.0%) reported at least one EAE. A total of 7 **children** (29.2%) reported at least one EAE. However, given the low numbers of adolescents and especially children reporting EAEs, no notable difference was observed between the adolescent and the child age categories.

Table 3 Overall summary for adverse events in all patients, adolescents and children in the Safety Set

All patients		**ALL (N = 51)**	**Agomelatine 5 mg (N = 51)**	**Agomelatine 10 mg (N = 51)**	**Agomelatine 25 mg (N = 49)**
Patients having reported					
at least one emergent adverse event	n (%)	17 (33.3)	10 (19.6)	8 (15.7)	11(22.4)
at least one treatment-related emergent adverse event	n (%)	12 (23.5)	3 (5.9)	4 (7.8)	10 (20.4)
Patients having experienced					
at least one serious adverse event (including death)	n (%)	1 (2.0)	-	-	-
at least one serious emergent event (including death)	n (%)	-	-	-	-
at least one treatment-related serious adverse event	n (%)	-	-	-	-
Patients with treatment withdrawal					
due to an emergent adverse event	n (%)	1 (2.0)	-	1 (2.0)	
due to an emergent serious adverse event	n (%)	-	-	-	-
due a treatment-related emergent adverse event	n (%)	1 (2.0)	-	1 (2.0)	-
due a treatment-related emergent serious adverse event	n (%)	-	-	-	-
Patients who died	n (%)	-	-	-	-
Adolescents		**ALL (N = 27)**	**Agomelatine 5 mg (N = 27)**	**Agomelatine 10 mg (N = 27)**	**Agomelatine 25 mg (N = 27)**
Patients having reported					
at least one emergent adverse event	n (%)	10 (37.0)	6 (22.2)	5 (18.5)	8 (29.6)
at least one treatment-related emergent adverse event	n (%)	8 (29.6)	2 (7.4)	3 (11.1)	7 (25.9)
Patients having experienced					
at least one serious adverse event (including death)	n (%)	1 (3.7)	-	-	-
Patients with treatment withdrawal					
due to an emergent adverse event	n (%)	-	-	-	-
Children		**ALL (N = 24)**	**Agomelatine 5 mg (N = 24)**	**Agomelatine 10 mg (N = 24)**	**Agomelatine 25 mg (N = 22)**
Patients having reported					
at least one emergent adverse event	n (%)	7 (29.2)	4 (16.7)	3 (12.5)	3 (13.6)
at least one treatment-related emergent adverse event	n (%)	4 (16.7)	1 (4.2)	1 (4.2)	3 (13.6)
Patients having experienced					
at least one serious adverse event (including death)	n (%)	-	-	-	-
Patients with treatment withdrawal					
due to an emergent adverse event	n (%)	1 (4.2)	-	1 (4.2)	-
due a treatment-related emergent adverse event	n (%)	1 (4.2)	-	1 (4.2)	-

SUMMARY – CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

- Laboratory tests

Overall, there were no clinically relevant changes in mean or median biochemistry, haematology or liver function values over time for all patients, adolescents or children, except for a slight increase in the mean bilirubin in children. No PCSA values for biochemical and liver parameters were reported and no emergent out-of-reference-range biochemistry or liver function values were reported as EAEs. Two patients (1 adolescent and 1 child) had emergent out-of-reference-range haematology values (at RUNO) reported as EAEs: moderate neutropenia (PCSA) with mild leukopenia and lymphocytosis (not related to IMP according to the investigator) and mild neutropenia and leukopenia (both related to IMP according to the investigator).
For all patients, mean or median values for all hormonal parameters for which reference ranges were available remained within the reference range throughout the study, except for testosterone in the male adolescents subgroup, in whom the mean testosterone values were below the reference range after baseline. Low testosterone values were reported throughout the study including at baseline in pre-pubertal females (3/14 at baseline; 2, 3 and 4 patients after the 5, 10 and 25 mg doses, respectively), post-pubertal females (2/11 at baseline; 4, 2 and 6 patients after the 5, 10 and 25 mg doses, respectively; 4 at RUNO), male children (14/14 at baseline; 14, 13 and 12 patients after the 5, 10 and 25 mg doses, respectively; 13 at RUNO) and male adolescents (6/12 at baseline; 9, 8 and 9 patients after the 5, 10 and 25 mg doses, respectively; 6 at RUNO). In pre-pubertal and post-pubertal females or male children and adolescents, the decrease observed in mean cortisol after agomelatine administration is explained by the fact that blood sampling on D1, D2 and D3 were taken in the evening. In post-pubertal females mean estradiol increased after agomelatine administration and did not return to baseline values at RUNO. In post-pubertal females, male children and male adolescents, prolactin levels increased after agomelatine administration and returned to near baseline values at RUNO for all groups except male adolescents. In all cases, the mean prolactin levels remained in the reference range. High prolactin in 1 patient (adolescent male) was reported as a mild EAE after the 25 mg dose (not considered related to the IMP).

- Vital signs, clinical examination and other observations related to safety

Overall, there were no clinically relevant changes in blood pressure, heart rate, weight or BMI during the study for all patients, adolescents or children. One (1) patient (adolescent) experienced the EAE of moderate blood pressure increased, which was not considered related to IMP. Two (2) patients (1 adolescent, 1 child) had an emergent abnormal ECG parameter finding, both reported as mild ECG QT prolonged (both recovering) and considered related to the IMP. The 2 cases were reviewed by an independent cardiologist who stated that neither patient presents a QT prolongation based on Fridericia correction for QT interval.
No patient completed suicide during the study. Of the patients who had a positive response to one or more C-SSRS-C items at baseline (*i.e.* 1, 2, 7 and 9 patients according to item representing suicidal ideation/behaviour over the patient's lifetime before the study), all but 2 (2/9) patients had a negative response during the study (2 adolescents experienced suicidal ideation [and therefore suicidality]). No child had a positive response to any of the C\SSRS-C items during the study.

- Criteria related to vigilance and sedation

Overall, there was a tendency for a proportion of patients to become less vigilant after IMP intake, which increased with dose: after the 5, 10 and 25 mg dose, 20 (39.2%), 23 (45.1%) and 29 (59.2%) patients, respectively shifted down at least 1 VAS category. Consequently, the percentage of patients 'rather sleepy' increased after IMP intake: 7.8%, 9.8% and 14.3% of patients pre-dose versus 29.4%, 33.3% and 36.7% of patients post dose for the 5, 10 and 25 mg doses, respectively. The differences were smaller for the percentage of patients 'very sleepy': 2.0% (1 patient) and 0 patients pre-dose and 3.9% (2 patients) and 6.1% (3 patients) post dose for the 10 and 25 mg doses, respectively (no difference for the 5 mg dose [1 patient]). There was also a small number of patients who became more vigilant after IMP intake (6 [11.8%], 3 [5.9%] and 4 [8.2%] patients, after the 5, 10 and 25 mg doses respectively).
Regarding the CRT test, for all patients, adolescents and children, the median motor and reaction time changes from pre-dose to post dose values were increases from baseline, in the region of 0-20.5 ms, but one decrease in reaction time for children (-13.5 ms). These changes were not clinically relevant.

- Compliance and tablet acceptability

All patients were 100% compliant with treatment. The large majority (> 90%) found the round 5 and 10 mg tablets very easy to swallow. This percentage was smaller with the larger, oblong 25 mg tablet (69%). The remaining patients found the tablets easy to swallow.

CONCLUSION

The PK of agomelatine was characterized in a paediatric population. Results of this analysis will be used to support dose selection for the efficacy studies in the paediatric population, based on the assumption that the exposure/efficacy relationship is the same between adults and the paediatric population.
The administration of 3 increasing single oral doses of agomelatine (5, 10 and 25 mg) over 3 consecutive days in adolescents and children with Depressive or Anxiety Disorder was well tolerated. Two events of ECG QT prolonged were reported and considered IMP-related by the investigator. According to expert's statement, these two cases are not QT prolongations based on Fridericia correction for QT interval. One event of neutropenia (PCSA value) was reported and not considered IMP-related by the investigator. Vigilance assessed by VAS decreased slightly after agomelatine dosing. There was no evidence of agomelatine sedative effect measured by CRT. Treatment compliance was high and tablet acceptability was good.

Date of the report: 07 September 2015

Version of the report: Final Version