3.0 STUDY SYNOPSIS

Name of the sponsor: **I.R.I.S.**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Thymanax®	**Volume:**	
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Title of study: Efficacy and safety of agomelatine with flexible dose (25 mg/day with blinded potential adjustment at 50 mg) given orally for 8 weeks in Indian outpatients with Major Depressive Disorder.

A randomised double-blind national multicentric study with parallel groups, *versus* sertraline (50 mg/day with blinded potential adjustment at 100 mg).

Protocol No.: CL3-20098-074

Coordinator

[redacted]

Study centres: Multicentric national study (10 active centres)

Study period	**Study development phase**
Study duration per participant: 10 weeks Completion date: April 2012	Phase III (registration)

Objectives

The primary objective of this study was to assess the agomelatine efficacy *versus* sertraline, using the Hamilton Depression Rating Scale 17 items, after an 8-week treatment period in Indian outpatients suffering from moderate to severe Major Depressive Disorder (MDD).

The secondary objective was to provide safety data on agomelatine in the Indian population.

The purpose of the study was to obtain registration and marketing authorisation for Valdoxan® (Thymanax®) in India.

Methodology

Double-blind, parallel group, national, multicentric, randomised study *versus* sertraline.

Flexible dosage for agomelatine: blinded adjustment to agomelatine 50 mg if insufficient improvement at Week 2 (W2).

Flexible dosage for sertraline: blinded adjustment to sertraline 100 mg if insufficient improvement at W2.

Number of participants

Planned: 200 (100 by treatment group)
Included: 200 (100 by treatment group)

Diagnosis and main criteria for inclusion

Indian outpatients of both genders aged between 18 and 65 years (inclusive), fulfilling DSM-IV-TR criteria for MDD of moderate to severe intensity, single or recurrent episode (≥ 4 weeks, ≤ 12 months) with HAM-D-17 total score ≥ 22, CGI-S ≥ 4, HAD-D ≥ 11.

Study drug: Agomelatine 25 mg – oral route – 1 or 2 capsules per day at bedtime

Comparator: Sertraline 50 mg – oral route – 1 or 2 capsules per day at bedtime

Duration of treatment: 8 weeks. No treatment given during selection and follow up periods.

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Criteria for evaluation

Efficacy measurements

Primary efficacy criterion

- HAM-D-17 total score

Secondary efficacy criteria

- Clinical global impression (CGI) (severity of illness and global improvement scores),
- HAM-A (psychic anxiety and somatic anxiety scores and total score),
- HAD (depression and anxiety scores),
- Sheehan disability scale (SDS) (work, social life and family life/home responsibilities scores, number of days lost and number of underproductive days),
- Leeds Sleep evaluation Questionnaire (LSEQ) (getting off to sleep, quality of sleep, sleep awakening and integrity of behaviour scores).

Safety measurements

- Adverse events
- Vital signs: Heart rate, blood pressure
- Body weight
- Laboratory parameters

Statistical methods

Efficacy analysis

Primary criterion

-Main analysis

The difference between agomelatine and sertraline was assessed in the Full Analysis Set (FAS) on the change from baseline to last post-baseline value of the HAM-D-17 total score on the W0-W8 period, using a two-way analysis of covariance model on factor treatment, with pooled centre (fixed effect) and baseline HAM-D-17 total score as covariates and without interaction.

- Sensitivity analysis

An unadjusted analysis on the last post-baseline value was performed to assess the robustness of the main analysis results.

- Secondary analyses

The within-group evolution of HAM-D-17 total score over time on the W0-W8 period was studied in the FAS using for each treatment group a one-way analysis of variance model on factor visit with repeated measures. Two-sided 95% confidence intervals (CI) with Dunnett adjustment were presented for the comparison of each post-baseline visit to baseline.

Descriptive statistics were also provided by treatment group for HAM-D total score expressed as value at each visit, last post-baseline value and change from baseline at each visit and to last post-baseline value on the W0-W8 period. Descriptive statistics on the W0-W8 period were also provided by centre.

Secondary criteria:

For each secondary criterion, descriptive statistics were provided by treatment group in the FAS on the W0-W8 period and also by centre for the CGI scores.

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Safety analysis:
For every safety measurement, descriptive statistics were provided by treatment group in the Safety Set.

Result summary:
Study population and outcome:

Disposition of patients

	Agomelatine	**Sertraline**
Included (randomised)	**100**	**100**
Lost to follow-up	**2 (2.0)**	**-**
Withdrawn		
Due to adverse event	2 (2.0)	3 (3.0)
Due to non-medical reason	13 (13.0)	8 (8.0)
Due to recovery	-	1 (1.0)
Due to protocol deviation	-	-
Due to lack of efficacy	6 (6.0)	5 (5.0)
Completed the study	**77 (77.0)**	**83 (83.0)**
Analysis Set		
Randomised Set	**100**	**100**
Full analysis set	**97**	**94**
Safety Set	**100**	**99**

200 patients (37.1±10.5 years, 50% of males and females) with moderate to severe MDD were included and randomised: 100 patients in the agomelatine group and 100 patients in the sertraline group.
Except a less severe disease in the agomelatine group (21% of patients had a severe diagnosis without psychotic features *versus* 32% in the sertraline group), there were no relevant differences in baseline characteristics between groups including efficacy parameters at baseline.

Efficacy results:

Primary criterion: HAM-D-17 total score

The mean reduction in the HAM-D-17 total score between baseline and last post-baseline value was similar in both treatment groups. The estimated (adjusted) between-group difference (sertraline minus agomelatine) from the main analysis was -1.74 (95% CI: [-3.85 ; 0.37]), with no statistically significant difference between both study treatments. Similar results were obtained in the sensitivity unadjusted analysis.

HAM-D-17 total score : Main analysis and sensitivity analysis in the FAS

		Agomelatine (N=97)	**Sertraline (N = 94)**
Descriptive statistics			
Value at baseline (W0)	n	97	94
	Mean ± SD	26.6±2.5	27.1±3.3
	Min – Max	22 – 34	22 -37
Last post baseline value	n	97	94
	Mean ± SD	12.8±8.0	11.2±8.1
	Min – Max	0 – 33	0 – 35
Change from baseline to last post-baseline value	n	97	94
	Mean ± SD	-13.8±7.9	-15.8±7.6
	Min – Max	-28 – 6	-31 – 3
Statistical analysis: Estimate of difference between groups			
Main analysis (*)	E (SE) (1)	-1.74 (1.07)	
	95% CI (3)	[-3.85; 0.37]	
Sensitivity analysis (**)	E (SE) (2)	-1.53 (1.16)	
	95% CI (3)	[-3.82; 0.77]	

(*) on the change from baseline to last post-baseline value: Analysis of covariance model on factor treatment with pooled centre (fixed effect) and baseline as covariates
(**) on the last post-baseline value: unadjusted analysis

(1) Estimate (Standard Error) of the difference between adjusted treatment group means: sertraline minus agomelatine
(2) Estimate (Standard Error) of the difference between treatment group means: sertraline minus agomelatine
(3) Two-sided 95% Confidence Interval of the estimate

The within-group evolution in HAM-D-17 total score over time on the W0-W8 period were statistically significant ($p<0.0001$) in both treatment groups. For both treatment groups, a statistically significant improvement from baseline was observed at each post-baseline visit. This confirmed that both treatments are effective antidepressants.

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Secondary efficacy parameters

Evolution of other efficacy parameters (obtained from CGI, HAM-A, HAD, SDS) were similar in both treatment groups.

Secondary efficacy criteria: last (post-baseline) value or change from baseline to last post-baseline value (FAS)

		Agomelatine (N=97)	Sertraline (N = 94)
CGI *(CGI-S: last post-baseline value/ CGI-I: last value)*			
Severity of illness score (CGI-S)	Mean ± SD	2.7±1.1	2.5±1.1
Global improvement score (CGI-I)	Mean ± SD	2.1±1.1	1.9±1.0
HAM-A *(change from baseline to last post-baseline value)*			
Total score	Mean ± SD	-14.4±11.1	-16.8±10.4
Psychic anxiety score	Mean ± SD	-8.1±6.1	-9.5±5.7
Somatic anxiety score	Mean ± SD	-6.3±5.7	-7.3±5.2
HAD *(change from baseline to last post-baseline value)*			
Depression score	Mean ± SD	-10.9±5.4	-11.6±5.2
Anxiety score	Mean ± SD	-6.9±5.9	-7.9±5.1
SDS *(change from baseline to last post-baseline value)*			
Work	Mean ± SD	-5.3±2.8	-6.2±2.5
Social life	Mean ± SD	-5.1±2.7	-5.7±2.9
Family life/home responsibility	Mean ± SD	-5.0±2.9	-5.5±2.8
Number of days lost	Mean ± SD	-2.6±2.5	-2.8±2.2
Number of unproductive days	Mean ± SD	-3.5±2.5	-3.5±2.0
LSEQ *(last value)*			
Getting off to sleep	Mean ± SD	29.0±22.9	23.1±18.4
Quality of sleep	Mean ± SD	27.6±23.0	22.0±17.7
Sleep awakening	Mean ± SD	28.0±21.4	24.2±19.1
Integrity of behaviour	Mean ± SD	31.5±21.9	26.3±18.3

Safety results:

Both drugs were well tolerated. During the treatment period, there were relatively fewer emergent adverse events (EAEs) reported in the agomelatine group compared to the sertraline group: 17.0% of patients in the agomelatine group *versus* 24.2% in the sertraline group reported at least one EAE. In particular, there were relatively fewer patients who experienced Gastrointestinal disorders in the agomelatine group (7.0% *versus* 11.1%, respectively) and Nervous system disorders (4.0% *versus* 8.1%).

There were 8.0% of patients in the agomelatine group *versus* 20.2% of patients in the sertraline group who experienced at least one EAE considered by the investigator as related to treatment.

The majority of the EAEs (60.0%) were considered of mild intensity in the agomelatine group while the majority of the EAEs (51.9%) in the sertraline group were considered of moderate intensity.

The most frequent EAEs in the agomelatine group were constipation (3.0% of patients *versus* 2.0% in the sertraline group) and headache (3.0% *versus* 2.0%). The most frequent EAE in the sertraline group was nausea (6.1% *versus* 1.0% in the agomelatine group).

One patient in each group experienced at least one serious emergent adverse event during the treatment period:

- Completed suicide and depression in the agomelatine group which occurred 7 days after the treatment initiation (D8).
- Homicide in the sertraline group which occurred 47 days after treatment initiation (D48). This patient completed suicide while the study drug had been stopped for 3 days (D51) (Serious AE emergent after treatment).

Excepted the two completed suicides, there was no other death during the study.

Summary of EAEs during the 8-week treatment period (Safety Set)

		Agomelatine (N=100)	**Sertraline (N = 99)**
At least one EAE	n (%)	17 (17.0)	24 (24.2)
At least one EAE related to treatment	n (%)	8 (8.0)	20 (20.2)
At least one severe EAE	n (%)	2 (2.0)	1 (1.0)
At least one serious EAE	n (%)	1 (1.0)	1 (1.0)
At least one EAE leading to study drug withdrawal	n (%)	1 (1.0)	2 (2.0)
Fatal EAE	n (%)	1 (1.0)	-

Regarding laboratory tests, there were no relevant changes in biochemical or haematological parameters on treatment (from baseline (Selection visit) to W8/WEND visit). No relevant between-group differences were evidenced. No PCSA values were reported for transaminases in the agomelatine group *versus* one PCSA value for ASAT (x5.1) and ALAT (x3.8) in the sertraline group.

Regarding sitting blood pressure, heart rate and weight, neither clinically relevant changes nor differences between groups over time were detected during the study for these assessments.

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CONCLUSION:

This multicentric, double-blind, randomised study conducted in 200 Indian outpatients confirmed the antidepressant efficacy of agomelatine 25-50 mg/day on HAM-D-17 total score (primary criterion) as compared to sertraline 50-100 mg/day on moderate to severe MDD after an 8-week treatment period. Regarding safety, the study showed that agomelatine 25-50 mg/day was well tolerated in Indian patients over 8-week treatment period.