



Clinical trial results:

Efficacy and safety of agomelatine (25mg/day with blinded potential adjustment to 50mg/day) versus escitalopram (10mg/day with blinded potential adjustment to 20mg/day) given orally for 12 weeks in non-depressed out-patients with severe Generalized Anxiety Disorder. A 12-week randomised, double-blind, versus escitalopram, 2-arm parallel groups, international multicenter study with a 9-month extension period

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-003699-37
Trial protocol	CZ DE HU PL FI SK
Global end of trial date	11 February 2015

Results information

Result version number	v1 (current)
This version publication date	31 March 2016
First version publication date	31 March 2016

Trial information

Trial identification

Sponsor protocol code	CL3-20098-089
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 Rue carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2015
Global end of trial reached?	Yes
Global end of trial date	11 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the efficacy of agomelatine (25-50 mg/d) versus escitalopram (10-20 mg/d) using HAM-A scale after a 12-week treatment period.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Criteria leading to a mandatory withdrawal from the study were:

- Absence of written consent or consent withdrawal by the patient.
- Suicidal risk, according to investigator's judgment and/or with a suicidal ideation of 4 or 5 on C-SSRS.
- Any suicide attempt during the study whatever its severity.
- Pregnancy.
- ALT or AST > 8 x ULN, or ALT or AST > 5 x ULN and sustained after two weeks of close monitoring; for all patients except patients in Czech Republic.
- ALT or AST > 5 x ULN for patients in Czech Republic only.
- ALT or AST > 3 x ULN and total bilirubin > 2x ULN.
- ALT or AST > 3 x ULN with clinical signs of hepatitis.
- Any signs and symptoms of liver problems.
- Occurrence of a serotonin syndrome.
- Occurrence of seizures.
- Signs of cardiac arrhythmia (except isolated supraventricular extrasystolia).

Other criteria for premature withdrawal from the study were:

- Any event or circumstance related or unrelated to treatment justifying the discontinuation of the treatment in the investigator's opinion.
- Treatment failure, i.e. lack of efficacy which in the opinion of the investigator required the patients to be withdrawn.
- Adverse event.
- Any protocol deviation which jeopardized the patient's safety.
- Any medical event requiring administration of an unauthorised concomitant treatment.
- Lost to follow-up.

In order to avoid emergence of discontinuation syndrome following abrupt treatment discontinuation, a 1-week tapering period was used for patients under escitalopram, as recommended in the SmPC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Slovakia: 28
Country: Number of subjects enrolled	Czech Republic: 125
Country: Number of subjects enrolled	Finland: 40
Country: Number of subjects enrolled	Germany: 70
Country: Number of subjects enrolled	Hungary: 72
Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	Canada: 49
Country: Number of subjects enrolled	Russian Federation: 65
Worldwide total number of subjects	523
EEA total number of subjects	384

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	519
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Non-depressed patients suffering from severe Generalized Anxiety Disorder according to DSM-IV-TR, Hamilton Anxiety rating scale (HAM-A) and Montgomery-Åsberg Depression Rating Scale (MADRS). Legal age for majority to 65 years old (inclusive) out-patients of both genders, fulfilling DSM-IV-TR criteria for GAD confirmed by M.I.N.I questionnaire.

Period 1

Period 1 title	Double-blind treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	agomelatine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	agomelatine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

one capsule daily: 25 or 50 mg agomelatine (dose adaptation at W4 according to blinded pre-defined criteria)

Arm title	escitalopram
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	escitalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

one capsule daily: 10 or 20 mg escitalopram (dose adaptation at W4 according to blinded pre-defined criteria)

Number of subjects in period 1	agomelatine	escitalopram
Started	261	262
Completed	212	220
Not completed	49	42
non-medical reason	21	15
Adverse event, non-fatal	15	19
Cure, remission, improvement	-	1
Lack of efficacy	13	3
Protocol deviation	-	4

Period 2

Period 2 title	Optional extension period of 12 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	agomelatine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	agomelatine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One capsule daily of agomelatine 25 or 50 mg.

Arm title	escitalopram
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	escitalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One capsule daily of escitalopram 10 or 20 mg.

Number of subjects in period 2^[1]	agomelatine	escitalopram
Started	200	206
Completed	181	197
Not completed	19	9
non-medical reason	8	5
Adverse event, non-fatal	3	2
Lost to follow-up	1	-
Lack of efficacy	5	2
Protocol deviation	2	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Overall, 432 patients completed the W0-W12 period whereas 406 patients starting the extension period at W12: the difference was due to 26 patients who did not enter in this optional extension period at W12.

Period 3

Period 3 title	Optional extension period of 40 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	agomelatine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	agomelatine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One capsule daily of agomelatine 25 or 50 mg.

Arm title	escitalopram
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	escitalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

one capsule daily: 10 or 20 mg escitalopram

Number of subjects in period 3^[2]	agomelatine	escitalopram
Started	77	82
Completed	67	71
Not completed	10	11
non-medical reason	5	8
Adverse event, non-fatal	1	1
Cure, remission, improvement	1	1
Lack of efficacy	3	-
Protocol deviation	-	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Overall, 378 patients completed the extension period at W24 whereas 159 patients continued in the extension period at W24. The difference was due to 219 patients who stopped the extension period at W24 (all patients having not yet performed W24 visit before the approval of the amendment No. 4 had to stop the extension period at W24).

Baseline characteristics

Reporting groups

Reporting group title	agomelatine
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Reporting group description: -

Reporting group title	escitalopram
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Reporting group description: -

Reporting group values	agomelatine	escitalopram	Total
Number of subjects	261	262	523
Age categorical			
Units: Subjects			
Adults (18-64 years)	260	259	519
From 65-84 years	1	3	4
Age continuous			
Units: years			
arithmetic mean	41.1	40.9	
standard deviation	± 12.3	± 12	-
Gender categorical			
Units: Subjects			
Female	176	185	361
Male	85	77	162

End points

End points reporting groups

Reporting group title	agomelatine
Reporting group description: -	
Reporting group title	escitalopram
Reporting group description: -	
Reporting group title	agomelatine
Reporting group description: -	
Reporting group title	escitalopram
Reporting group description: -	
Reporting group title	agomelatine
Reporting group description: -	
Reporting group title	escitalopram
Reporting group description: -	
Subject analysis set title	Full analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients of the randomised set having taken at least one dose of IMP and having a value at baseline (W0) and at least one post-baseline value for the primary efficacy criterion on the W0-W12 period.	

Primary: HAM-A total score

End point title	HAM-A total score
End point description:	
End point type	Primary
End point timeframe:	
At each visit from selection to W52 visit i.e.: selection, W0, W2, W4, W8, W12, W16, W24, W32, W40, W48 and W52. The main analysis was on the change from baseline to W12 using the Last Observation Carried Forward (LOCF) approach for missing data at W12.	

End point values	agomelatine	escitalopram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	261		
Units: score				
arithmetic mean (standard deviation)	-16 (± 9.1)	-16.9 (± 8.4)		

Statistical analyses

Statistical analysis title	Main analysis
Comparison groups	agomelatine v escitalopram

Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.195
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	0.44
Variability estimate	Standard error of the mean
Dispersion value	0.69

Notes:

[1] - Non-inferiority test centred on a non-inferiority margin of 1.5: one-sided p-value to be compared to 0.025

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported at each visit over the whole duration of the study. Adverse events presented here at those reported during the W0-W53 treatment period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	escitalopram
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Reporting group description: -

Reporting group title	agomelatine
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Reporting group description: -

Serious adverse events	escitalopram	agomelatine	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 262 (6.11%)	8 / 260 (3.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal squamous cell carcinoma			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			

subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Activities of daily living impaired			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired driving ability			
subjects affected / exposed	0 / 262 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Nightmare			
subjects affected / exposed	0 / 262 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			

subjects affected / exposed	0 / 262 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep disorder			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 262 (0.38%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Traumatic haematoma			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial ischaemia			

subjects affected / exposed	1 / 262 (0.38%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 262 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	0 / 262 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amblyopia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			

subjects affected / exposed	0 / 262 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Alcoholic pancreatitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 262 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Swelling face			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Escherichia sepsis			

subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 262 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	escitalopram	agomelatine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 262 (65.65%)	146 / 260 (56.15%)	
Investigations			
Weight increased			
subjects affected / exposed	9 / 262 (3.44%)	5 / 260 (1.92%)	
occurrences (all)	9	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 262 (4.20%)	8 / 260 (3.08%)	
occurrences (all)	12	8	
Headache			
subjects affected / exposed	37 / 262 (14.12%)	33 / 260 (12.69%)	
occurrences (all)	50	41	
Tension headache			
subjects affected / exposed	3 / 262 (1.15%)	8 / 260 (3.08%)	
occurrences (all)	6	11	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 262 (4.20%)	13 / 260 (5.00%)	
occurrences (all)	12	13	

Gastrointestinal disorders	Constipation			
	subjects affected / exposed	0 / 262 (0.00%)	8 / 260 (3.08%)	
	occurrences (all)	0	8	
Diarrhoea	subjects affected / exposed	14 / 262 (5.34%)	6 / 260 (2.31%)	
	occurrences (all)	17	6	
Dry mouth	subjects affected / exposed	6 / 262 (2.29%)	10 / 260 (3.85%)	
	occurrences (all)	6	11	
Nausea	subjects affected / exposed	49 / 262 (18.70%)	21 / 260 (8.08%)	
	occurrences (all)	58	23	
Skin and subcutaneous tissue disorders				
Hyperhidrosis	subjects affected / exposed	13 / 262 (4.96%)	2 / 260 (0.77%)	
	occurrences (all)	13	2	
Psychiatric disorders				
Anxiety	subjects affected / exposed	10 / 262 (3.82%)	8 / 260 (3.08%)	
	occurrences (all)	10	9	
Insomnia	subjects affected / exposed	17 / 262 (6.49%)	11 / 260 (4.23%)	
	occurrences (all)	18	11	
Infections and infestations				
Nasopharyngitis	subjects affected / exposed	14 / 262 (5.34%)	17 / 260 (6.54%)	
	occurrences (all)	15	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2013	Applicable to all countries, for all new patients and patients already included, and was set up (mainly) to: - Specify that assessments to be carried out by a psychiatrist in the frame of this study were GAD diagnosis - Add the participation of Finland and Slovakia - Comply with German requirement regarding contraceptive methods - Clarify the non-selection criteria : Patients previously not responder to agomelatine, escitalopram or citalopram during the past 12 months whatever the indication were not selected - Add non-selection criteria due to the Escitalopram SmPC update: Known angle-closure glaucoma or history of glaucoma - Specify that concomitant use of medicinal products inducing hypokalaemia/hypomagnesaemia was to be used with caution as it could induce a risk of malignant arrhythmias with Escitalopram (Escitalopram SmPC update) - Allow the use of rescue medication for occasional sleep disorder during the extension period. Occasional intake of hypnotics limited to zolpidem, zopiclone, eszopiclone were allowed after W12 if needed and according to the investigator's judgment - Specify technical performance of ePRO - Clarify scoring methods of SHAPS - Ensure a more accurate follow-up and analysis of suicidal ideation and behaviour - Harmonize the management of cases of overdose throughout agomelatine studies - Explain that hospitalisation planned before the study and hospitalisation due to social reason were to be reported in the PROCEDURE form of the eCRF - Insert the last versions of THAT, C-SSRS, DSMIV-TR, HAD and SDS scales which have been used by the patients in the study - Correct some mistake/inaccuracy: *Urinary drug screening was done only at selection, not at the end of the study *Harmonization of the selection condition regarding treatment with thyroid hormones and menopause HRT : they could not be started, stopped or modified within the 3 months prior to inclusion visit and not selection visit.
31 March 2014	Applicable to all countries for all new patients and patients already included in the 3 month-period. Patients who had reached W24 before approval of this amendment were not concerned. The aim of this amendment was to shorten the optional extension period from a 9-month-period to a 3-month period for all the patients not reaching W24 when the approval for this amendment was obtained (decision taken for strategic reasons from the Sponsor). It allowed to ensure a 6-month treatment period for the patients who were entered in the extension period after approval of the amendment. Patients having already performed W24 visit before this amendment approval were to continue the extension period up to W52. In addition, the interim analysis initially planned was suppressed and all the data were analysed after the end of the study for all patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

