Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

Agomelatine

Therapeutic Area of Trial

Major Depressive Disorder (MDD)

Approved Indication

Treatment of major depressive episodes in adults

Study Number

CAGO178A2304

Title

A 52-week, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of the long-term efficacy, tolerability and safety of agomelatine 25 and 50 mg in the prevention of relapse of Major Depressive Disorder (MDD) following open-label treatment of 16-24 weeks

Phase of Development

Phase III

Study Start/End Dates

26-Apr-2007 to 24-Sep-2009

Study Design/Methodology

This study used a randomized, double-blind, placebo-controlled, multicenter, parallel-group design to assess the long-term efficacy, tolerability and safety of agomelatine 25 and 50 mg in the prevention of relapse of Major Depressive Disorder (MDD) over a period of 52 weeks following an open-label treatment of 16-24 weeks.

The study consisted of the following 4 phases: (1) Screening phase, (2) Open-label treatment phase including an acute treatment period followed by a stabilization period, (3) a double-blind continuation phase and (4) a follow-up phase.

Patients received open-label treatment with agomelatine 25 mg during the acute treatment period (duration of 4 to 12 weeks). Patients with no partial response to treatment by Week 4 had their dosage increased to 50 mg of agomelatine. Patients who demonstrated full response

entered the 12-week stabilization period while the others were withdrawn. During the stabilization period, patients were maintained at the dosage level from the time they achieved full response during the acute-treatment period. Patients who successfully completed the 12-week stabilization period were equally randomized to the double-blind continuation phase to receive either agomelatine at the same dosage as during the stabilization period or matching placebo for 52 weeks.

Centers

60 centers in United States.

Publication

None

Objectives

Primary objective

To compare the efficacy of agomelatine 25 and 50 mg given once daily (o.d.) to placebo in the prevention of relapse of MDD over a period of 52 weeks, as measured by time to relapse, where relapse was defined by the occurrence of any one of the following during the double-blind treatment phase:

Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) total score = 16 at two consecutive visits

- Hospitalization due to depression
- Suicide attempt or suicide
- Discontinuation due to lack of efficacy according to investigator judgment

Secondary objective(s)

- Evaluate the safety and tolerability of agomelatine 25 and 50 mg o.d. compared to placebo.

Evaluate the efficacy of agomelatine 25 and 50 mg o.d. compared to placebo with respect to:

- Proportion of patients who demonstrate clinical improvement at the end of the double-blind continuation phase, where improvement is defined by a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression – Improvement (CGI-I).
- Proportion of patients experiencing relapse during the double-blind continuation phase
- Proportion of patients who achieve remission at the end of the double-blind continuation phase, whereby remission is defined by a total score of = 7 on the $HAM\text{-}D_{17}$.
- Change from randomization to the end of double-blind continuation phase on the Hospital Anxiety and Depression Scale (HAD) total score.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral agomelatine 25 mg or 50 mg film-coated tablets, given once daily

Reference Product(s), Dose(s), and Mode(s) of Administration

Matching oral placebo tablets given once daily

Criteria for Evaluation

Primary variable

Time from randomization to relapse, defined by the occurrence of any one of the following:

- HAM-D_{17} total score = 16 at two consecutive visits
- Hospitalization due to depression
- Suicide attempt or suicide
- Discontinuation due to lack of efficacy according to investigator judgment

Secondary variables

- Proportion of patients demonstrating clinical improvement at the end of Double-blind Continuation Phase defined as a CGI-I score of 1 or 2
- Proportion of patients experiencing relapse during the Double-blind continuation phase since randomization
- Proportion of patients achieving remission at the end of Double-blind Continuation Phase by a total score of =7 on the HAM-D_{17}
- Change from baseline on the Hospital Anxiety and Depression (HAD) total score at the end of Double-blind Continuation Phase

Safety and tolerability

Safety assessments consisted of monitoring and recording all AEs and SAEs which were reported during the Open-label Treatment and Double-blind continuation phase (with their severity, duration, and relationship to study drug). In addition safety assessments included physical examination, laboratory tests (blood, urine, and liver function tests), vital signs and ECGs to detect any clinically notable change from baseline.

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

As the primary efficacy analysis, survival curves of time to relapse were estimated by the product-limit (Kaplan-Meier) method and compared between the agomelatine and placebo groups using a log-rank test at the two-sided alpha level of 5%. The primary efficacy analysis was conducted on the ITT population.

Proportion of patients experiencing relapse since randomization, proportion of patients

demonstrating clinical improvement at the end of Double-blind Continuation Phase, and proportion of patients achieving remission at the end of Double-blind Continuation Phase were compared between agomelatine and placebo groups using Chi-square test. Change from baseline in the HAD total score at the end of Double-blind Continuation Phase was analyzed by analysis of covariance with the treatment as a fixed effect and the baseline HAD total score as a covariate.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Male and female adults (18 to 70 years of age inclusive) who signed the informed consent form
- Diagnosis of MDD with recurrent episode according to DSM-IV criteria
- A history of at least two previous episodes of major depression plus the current episode,
- A clinician-rated HAM-D_{17} total score = 22 at screening and baseline

Exclusion criteria:

- History of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, eating disorder, obsessive-compulsive disorder;
- Any other current Axis I disorder other than MDD, which is the main focus of treatment;
- History of alcohol or substance abuse in the 3 months prior to screening; history of alcohol or substance dependence in the 6 months prior to screening;
- Use of any psychoactive medication after the screening visit.
- Patients previously treated with agomelatine;
- Female patients who were not using effective contraception, were breast feeding, or who had a positive serum pregnancy test at screening or a positive urine pregnancy test at baseline.

Other protocol-defined exclusion criteria were applied.

Number of Subjects

Patient disposition at the end of open-label treatment phase by maximum daily dose - All treated patients

Disposition Reason	Agomelatine 25 mg N = 294 n (%)	Agomelatine 50 mg N = 339 n (%)	All Agomelatine N = 633 n (%)
Entered Acute Treatment Period	294 (100.0)	339 (100.0)	633 (100.0)
Completed Acute Treatment Period	181 (61.6)	225 (66.4)	406 (64.1)
Discontinued during Acute Treatment Period	113 (38.4)	114 (33.6)	227 (35.9)
Entered Stabilization Period	181 (61.6)	225 (66.4)	406 (64.1)
Discontinued during Stabilization Period	54 (18.4)	71 (20.9)	125 (19.7)
Completed the Open-label Treatment Phase	127 (43.2)	154 (45.4)	281 (44.4)
Discontinued during Open-Label Treatment Phase	167 (56.8)	185 (54.6)	352 (55.6)
Entered the Double-blind Continuation Phase	127 (43.2)	154 (45.4)	281 (44.4)
Discontinued during Open-label Treatment Phase			
Abnormal laboratory value(s)	1 (0.3)	0	1 (0.2)
Abnormal test procedure result(s)	0	0	0
Administrative problems	4 (1.4)	4 (1.2)	8 (1.3)
Adverse Event(s)	33 (11.2)	28 (8.3)	61 (9.6)
Death	0	0	0
Lost to follow-up	36 (12.2)	15 (4.4)	51 (8.1)
Protocol deviation	19 (6.5)	13 (3.8)	32 (5.1)
Subject withdrew consent	35 (11.9)	33 (9.7)	68 (10.7)
Subject's condition no longer requires study drug	0	0	0
Unsatisfactory therapeutic effect	39 (13.3)	92 (27.1)	131 (20.7)

Patient disposition at the end of the double-blind continuation phase, by double-blind treatment - All randomized patients

Disposition Reason	Agomelatine 25 mg N = 64 n (%)	Agomelatine 50 mg N = 76 n (%)	All Agomelatine N = 140 n (%)	Placebo N = 141 n (%)	All N = 281 n (%)
Completed 12 months of study	28 (43.8)	34 (44.7)	62 (44.3)	73 (51.8)	135 (48.0)
Discontinued	36 (56.3)	42 (55.3)	78 (55.7)	68 (48.2)	146 (52.0)
Abnormal laboratory value(s)	0	1 (1.3)	1 (0.7)	0	1 (0.4)
Administrative problems	2 (3.1)	3 (3.9)	5 (3.6)	5 (3.5)	10 (3.6)
Adverse Event(s)	3 (4.7)	3 (3.9)	6 (4.3)	3 (2.1)	9 (3.2)
Lost to follow-up	7 (10.9)	3 (3.9)	10 (7.1)	11 (7.8)	21 (7.5)
Protocol deviation	3 (4.7)	2 (2.6)	5 (3.6)	5 (3.5)	10 (3.6)
Subject withdrew consent	8 (12.5)	14 (18.4)	22 (15.7)	11 (7.8)	33 (11.7)
Unsatisfactory therapeutic effect	13 (20.3)	16 (21.1)	29 (20.7)	33 (23.4)	62 (22.1)

Demographic and Background Characteristics

Demographics, by double-blind treatment - All randomized patients

Demographic Variable	25 mg N = 64 n (%)	Agomelatine 50 mg N = 76 n (%)	All Agomelatine N = 140 n (%)	Placebo N = 141 n (%)	All N = 281 n (%)
Age (Years) at Visit 16					
n	64	76	140	141	281
Mean	46.4	44.6	45.4	45.3	45.4
SD	11.31	12.98	12.23	12.25	12.22
Median	48.5	45.0	47.0	47.0	47.0
Min	20	22	20	20	20
Max	65	67	67	68	68
Sex					
Female	42 (65.6%)	46 (60.5%)	88 (62.9%)	88 (62.4%)	176 (62.6%)
Male	22 (34.4%)	30 (39.5%)	52 (37.1%)	53 (37.6%)	105 (37.4%)
Race					
Caucasian	46 (71.9%)	55 (72.4%)	101 (72.1%)	102 (72.3%)	203 (72.2%)
Black	11 (17.2%)	10 (13.2%)	21 (15.0%)	18 (12.8%)	39 (13.9%)
Asian	1 (1.6%)	0	1 (0.7%)	3 (2.1%)	4 (1.4%)
Native American	0	1 (1.3%)	1 (0.7%)	1 (0.7%)	2 (0.7%)
Pacific islander	0	0	0	0	0
Other	6 (9.4%)	10 (13.2%)	16 (11.4%)	17 (12.1%)	33 (11.7%)

Clinician rated assessments at baseline, by double-blind treatment - All randomized patients

Characteristic Variable	Agomelatine 25 mg N = 64 n (%)	Agomelatine 50 mg N = 76 n (%)	All Agomelatine N = 140 n (%)	Placebo N = 141 n (%)	All N = 281 n (%)
Baseline HAM-D_{17} total score					
n	64	76	140	141	281
Mean	4.6	6.1	5.4	6.0	5.7
SD	3.55	3.35	3.52	3.33	3.43

Baseline is the last assessment on or before the first dose of study drug in double-blind continuation phase.

Primary Objective Result(s)

Time from randomization to relapse by double-blind treatment - ITT population

			Percentile of time to relapse				Agomelatine vs. Placebo		
Treatment	Patients with/ relapse	Patients censored	25th	95% CI	50th	95% CI	p-value	Hazard ratio	95% CI
Agomelatine (N = 139)	32	107	242.0	(116.0, NA)	NA	(NA, NA)	0.6668	0.90	(0.56, 1.45)
Placebo (N = 141)	37	104	154.0	(94.0, NA)	NA	(NA, NA)			

N is the number of ITT patients; 25th and 50th percentile of time to relapse were estimated using Kaplan-Meier method. P-value and hazard ratio are based on log-rank test.

A hazard ratio < 1 indicates better prevention of relapse in the Agomelatine group as compared to placebo

Secondary Objective Result(s)

Proportion of patients with CGI-I clinical improvement at Week 52 (LOCF) - ITT population

Treatment	Clinical improvement Total	n (%)	p-value
Agomelatine (N = 139)	138	97 (70.3)	0.5715
Placebo (N = 141)	140	94 (67.1)	

N is the number of ITT patients.
Total is the number of patients with a value at Week 52 using LOCF.
Clinical improvement is defined by a score of 1 'very much improved' or 2 "much improved" on the CGI-I scale.
P-value is based on Chi-square test.

Proportion of patients experiencing relapse by treatment - ITT population

Treatment	Relapse n (%)	p-value
Agomelatine (N = 139)	32 (23.0)	0.5319
Placebo (N = 141)	37 (26.2)	

Proportion of patients with clinical remission at Week 52 (LOCF) - ITT population

Treatment	Clinical improvement Total	n (%)	p-value
Agomelatine (N = 139)	138	71 (51.4)	0.4050
Placebo (N = 141)	140	79 (56.4)	

N = number of ITT patients; Total = number of patients with a value at Week 52 using LOCF.
Clinical remission was defined as a HAM-D_{17} total score = 7.
P-value is based on Chi-square test.

Change from baseline to Week 52 (LOCF) in the HAD total score - ITT population

Treatment	n	Baseline Mean (SE)	Mean (SE) at endpoint	LS Mean Change (SE)	Agomelatine vs. Placebo Difference in LS Mean Change Mean (SE)	95% CI	p-value
Agomelatine (N = 139)	138	10.4 (0.63)	12.7 (0.74)	-2.3 (0.65)	-1.3 (0.92)	(-3.1,0.5)	0.1546
Placebo (N = 141)	140	10.9 (0.62)	11.8 (0.76)	-0.9 (0.65)			

HAD is the Hospital Anxiety and Depression Scale.
N = number of ITT patients; n = number of patients with a value at both baseline and Week 52 using LOCF.
Baseline is the last value before the first dose of study drug in double-blind continuation phase.
Least square means, confidence intervals and p-values were derived from an ANCOVA model with treatment group and the corresponding baseline score as explanatory variables.
Change from baseline=baseline score-post-baseline score. A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.

Safety Results

Adverse events by primary system organ class and double-blind treatment (Double-blind continuation phase) - Safety population

Primary system organ class	Agomelatine 25 mg N = 64 n (%)	Agomelatine 50 mg N = 75 n (%)	All Agomelatine N = 139 n (%)	Placebo N = 140 n (%)
Patients with AE(s)	48 (75.0)	51 (68.0)	99 (71.2)	101 (72.1)
Cardiac disorders	1 (1.6)	1 (1.3)	2 (1.4)	6 (4.3)
Ear & labyrinth disorders	1 (1.6)	1 (1.3)	2 (1.4)	4 (2.9)
Endocrine disorders	0	0	0	1 (0.7)
Eye disorders	2 (3.1)	0	2 (1.4)	2 (1.4)
Gastrointestinal disorders	11 (17.2)	18 (24.0)	29 (20.9)	24 (17.1)
General disorders & administration site conditions	9 (14.1)	5 (6.7)	14 (10.1)	13 (9.3)
Immune system disorders	0	2 (2.7)	2 (1.4)	4 (2.9)
Infections & infestations	26 (40.6)	23 (30.7)	49 (35.3)	51 (36.4)
Injury, poisoning & procedural complications	9 (14.1)	10 (13.3)	19 (13.7)	27 (19.3)
Investigations	7 (10.9)	6 (8.0)	13 (9.4)	16 (11.4)
Metabolism & nutrition disorders	5 (7.8)	0	5 (3.6)	6 (4.3)
Musculoskeletal & connective tissue disorders	10 (15.6)	7 (9.3)	17 (12.2)	32 (22.9)
Neoplasms benign, malignant & unspecified (incl cysts and polyps)	0	1 (1.3)	1 (0.7)	2 (1.4)
Nervous system disorders	14 (21.9)	12 (16.0)	26 (18.7)	38 (27.1)
Psychiatric disorders	12 (18.8)	10 (13.3)	22 (15.8)	20 (14.3)
Renal & urinary disorders	3 (4.7)	2 (2.7)	5 (3.6)	2 (1.4)
Reproductive system & breast disorders	2 (3.1)	1 (1.3)	3 (2.2)	6 (4.3)
Respiratory, thoracic & mediastinal disorders	5 (7.8)	5 (6.7)	10 (7.2)	12 (8.6)
Skin & subcutaneous tissue disorders	2 (3.1)	6 (8.0)	8 (5.8)	17 (12.1)
Social circumstances	0	1 (1.3)	1 (0.7)	0
Vascular disorders	1 (1.6)	5 (6.7)	6 (4.3)	5 (3.6)

Primary system organ classes are presented alphabetically.
A subject with multiple adverse events within a primary system organ class was counted only once.

10 Most Frequently Reported AEs in the all Agomelatine group by Preferred Term n (%)

Frequent adverse events by preferred term and treatment (Double-blind continuation phase) - Safety population

Preferred Term	Agomelatine 25 mg N = 64 n (%)	Agomelatine 50 mg N = 75 n (%)	All Agomelatine N = 139 n (%)	Placebo N = 140 n (%)
Patients with AE(s)	48 (75.0)	51 (68.0)	99 (71.2)	101 (72.1)
Headache	8 (12.5)	8 (10.7)	16 (11.5)	24 (17.1)
Nasopharyngitis	8 (12.5)	7 (9.3)	15 (10.8)	13 (9.3)
Upper respiratory tract infection	7 (10.9)	8 (10.7)	15 (10.8)	10 (7.1)
Diarrhea	4 (6.3)	7 (9.3)	11 (7.9)	7 (5.0)
Insomnia	4 (6.3)	4 (5.3)	8 (5.8)	8 (5.7)
Anxiety	3 (4.7)	4 (5.3)	7 (5.0)	7 (5.0)
Sinusitis	2 (3.1)	5 (6.7)	7 (5.0)	4 (2.9)
Nausea	4 (6.3)	2 (2.7)	6 (4.3)	2 (1.4)
Vomiting	2 (3.1)	4 (5.3)	6 (4.3)	1 (0.7)
Back pain	3 (4.7)	2 (2.7)	5 (3.6)	11 (7.9)

Preferred terms were sorted in descending order of frequency in the all Agomelatine group.
A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or adverse events leading to discontinuation, by open-label/double-blind treatment - All treated patients

	Agomelatine 25mg/ N = 167 n (%)	Agomelatine 50mg/ N = 186 n (%)	Agomelatine 25mg/25mg N = 63 n (%)	Agomelatine 50mg/50mg N = 75 n (%)
Deaths	0	0	0	0
SAEs	7 (4.2)	10 (5.4)	1 (1.6)	3 (4.0)
Discontinuations due to AEs	32 (19.2)	29 (15.6)	3 (4.8)	2 (2.7)
Psychiatric AEs	45 (26.9)	49 (26.3)	10 (15.9)	13 (17.3)
	Agomelatine 25mg/Placebo N = 64 n (%)	**Agomelatine 50mg/Placebo N = 77 n (%)**	**Agomelatine 25mg/50mg N =0 n (%)**	**Agomelatine 50mg/25mg N = 1 n (%)**
Deaths	0	0	0	0
SAEs	1 (1.6)	8 (10.4)	0	0
Discontinuations due to AEs	1 (1.6)	2 (2.6)	0	0
Psychiatric AEs	9 (14.1)	23 (29.9)	0	0

Patients who did not receive double blind (DB) treatment were summarized under "Agomelatine 25 mg/" and

"Agomelatine 50 mg/" groups. Patients with DB treatment were summarized under the remaining 6 groups (even if the SAE occurred under open-label treatment).
Deaths and SAE that occurred during the entire study were reported in this table. This included 1 SAE that occurred in Screening (group 50 mg/) and three SAEs that occurred after study drug was completed (groups 25mg/, 50mg/Placebo and 50mg/Placebo). Discontinuation due to AEs and Psychiatric AEs that occurred during the open-label and double-blind Phases were reported.

Other Relevant Findings

There were some instances of newly occurring LFT elevations. Overall, 32 patients experienced LFT elevations, including 29 patients in the open-label treatment phase and 3 patients in the double-blind continuation phase (placebo group).

Date of Clinical Trial Report

Date Inclusion on Novartis Clinical Trial Results Database

22-Sep-2010

Date of Latest Update

17-Sep-2010