Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

Agomelatine

Therapeutic Area of Trial

Major Depressive Disorder

Approved Indication

Investigational

Study Number

CAGO178A2302

Title

An 8-week, randomized, double-blind, fixed dosage, placebo-controlled, parallel-group, multi-center study of the efficacy, safety and tolerability of agomelatine 25 mg and 50 mg in the treatment of Major Depressive Disorder (MDD)

Phase of Development

Phase III

Study Start/End Dates

04-Dec-2006 to 10-Jan-2008

Study Design/Methodology

The study was an eight-week, randomized, fixed-dose, double-blind, placebo-controlled, parallel-group, multi-center design in patients with MDD. Patients were randomized in a 1:1:1 ratio to receive treatment with once daily agomelatine 25 mg/d, agomelatine 50 mg/d or placebo in the evening at approximately one hour before bedtime.

The study comprised a Pre-randomization Phase (Screening Period) of up to 14 days duration, a Randomization Phase including a Baseline Visit, an eight-week Treatment Phase, and a one-week off-drug Follow-up Phase. Patients who completed the Double-blind Treatment Phase at Week 8/Visit 8 were eligible for participation in the Open-label Extension Phase. Patients who did not enter the Open-label Extension Phase were scheduled for the off-drug Follow-up Phase.

Centers

49 centers in the USA.

Publication

Ongoing.

Objectives

Primary objective(s)

To demonstrate the efficacy of agomelatine 25 mg and 50 mg given once a day (o.d.) versus placebo, at Week 8, in the treatment of MDD.

Main Secondary objective(s)

- Evaluate, at Week 8, the efficacy of 25 and 50 mg agomelatine given once daily compared to placebo with respect to:
  - Proportion of patients who demonstrated clinical improvement
  - Proportion of patients who demonstrated clinical response
  - Proportion of patients who achieved clinical remission
  - Clinician-rated Hamilton Depression rating scale ($HAM\text{-}D_{17}$) subscale scores (Maier, anxiety, retardation and sleep)
  - Subjective sleep (onset and quality)
- Evaluate the safety and tolerability of 25 and 50 mg agomelatine given once daily compared to placebo for the treatment of MDD.

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

Oral agomelatine film-coated tablets of 25 mg or 50 mg daily.

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

Matching placebo film-coated oral tablets.

Criteria for Evaluation

Primary variable

- Change from baseline to Week 8 on the total score of the clinician-rated $HAM\text{-}D_{17}$ scale.

Secondary variables

- Clinical improvement, defined as a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression - Improvement (CGI-I) scale at Week 8.
- Clinical response, defined by a reduction of at least 50% in the baseline clinician-rated $HAM\text{-}D_{17}$ total score at Week 8.

- Remission, defined as a total score of $\leq$7 on the HAM-D_{17} at Week 8.
- Change from baseline to Week 8 on the clinician-rated HAM-D_{17} subscale scores (Maier, anxiety, retardation and sleep).
- Subjective sleep (onset and quality), as measured by the scores at Week 8 of the Leeds Sleep Evaluation Questionnaire (LSEQ) domains, "Getting to sleep" and "Quality of sleep".
- Safety variables are described below.

Safety and tolerability

The assessment of safety was based mainly on the frequency of AEs, serious adverse events (SAEs), changes in laboratory values, electrocardiograms (ECGs) and vital signs during the 8-week treatment period.

Statistical Methods

Primary endpoint

Each agomelatine dose was compared to placebo in the change from baseline to Week 8 (LOCF) on the HAM-D_{17} total score, using least square means derived by an analysis of covariance (ANCOVA) model with treatment, pooled center (fixed effect), and baseline HAM-D_{17} total score as explanatory variables, and with no interaction. Since two null hypotheses were tested simultaneously, the Hochberg procedure was used to adjust for multiplicity. Differences versus placebo were calculated such that positive treatment differences indicate a better outcome for the agomelatine group compared to the placebo group.

The primary efficacy analysis was performed on the Intent-to-treat (ITT) population.

Secondary endpoints

A logistic regression model with treatment and baseline HAM-D_{17} total score as explanatory variables was used for clinical improvement, clinical response, and clinical remission at Week 8 (LOCF).

An ANCOVA model, similar to the primary efficacy analysis (with the corresponding baseline scores or baseline HAM-D_{17} total score for LSEQ scores), was performed at Week 8 (LOCF) for change from baseline in the HAM-D_{17} subscale scores (Maier, anxiety, retardation and sleep), and for LSEQ domain scores "getting off to sleep" and "quality of sleep".

All efficacy analyses were performed on the ITT population.

The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fell outside of pre-determined ranges. All safety analyses were performed on the safety population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Main inclusion criteria

- Male and female adults, 18 through 70 years of age, inclusive
- Diagnosis of MDD, single or recurrent episode, according to Diagnostic Statistical Manual-IVth edition criteria
- Clinician-rated HAM-D_{17} total score $\geq$22 at screening and baseline
- CGI-Severity score $\geq$4 at screening and baseline

Main 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 focus of treatment
- Substance or alcohol abuse within the last 3 months, or dependence within the last 6 months
- Concomitant psychotropic medication, including herbal preparations and melatonin
- Female patients of child-bearing potential not using effective contraception
- Psychotherapy of any type
- History of hepatic impairment (e.g. Child-Pugh Classification)

Other protocol-defined Inclusion/Exclusion criteria were used

Number of Patients

Patient disposition at the end of Double-blind Treatment Phase, by treatment - randomized patients

Disposition Reason	Agomelatine 25 mg N = 168 n (%)	Agomelatine 50 mg N = 169 n (%)	All Agomelatine N = 337 n (%)	Placebo N = 166 n (%)	All N = 503 n (%)
Completed	129 (76.8)	130 (76.9)	259 (76.9)	133 (80.1)	392 (77.9)
Discontinued	39 (23.2)	39 (23.1)	78 (23.1)	33 (19.9)	111 (22.1)
Abnormal test procedure results	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Administrative problems	0 (0.0)	2 (1.2)	2 (0.6)	0 (0.0)	2 (0.4)
Adverse event(s)	7 (4.2)	9 (5.3)	16 (4.7)	8 (4.8)	24 (4.8)
Lost to follow-up	11 (6.5)	15 (8.9)	26 (7.7)	9 (5.4)	35 (7.0)
Protocol deviation	6 (3.6)	2 (1.2)	8 (2.4)	0 (0.0)	8 (1.6)
Subject withdrew consent	11 (6.5)	7 (4.1)	18 (5.3)	9 (5.4)	27 (5.4)
Unsatisfactory therapeutic effect	3 (1.8)	4 (2.4)	7 (2.1)	7 (4.2)	14 (2.8)
Continued into open-label extension phase	120 (71.4)	123 (72.8)	243 (72.1)	115 (69.3)	358 (71.2)

Demographic Characteristics

Demographics by treatment - randomized patients

Demographic Variable	Agomelatine 25 mg N = 168	Agomelatine 50 mg N = 169	All Agomelatine N = 337	Placebo N = 166	All N = 503
Baseline Age (years)					
<45 n (%)	84 (50.0)	83 (49.1)	167 (49.6)	86 (51.8)	253 (50.3)
45 - <65 n (%)	80 (47.6)	83 (49.1)	163 (48.4)	72 (43.4)	235 (46.7)
≥65 n (%)	4 (2.4)	3 (1.8)	7 (2.1)	8 (4.8)	15 (3.0)
Age (Years)					
N	168	169	337	166	503
Mean	43.2	43.8	43.5	43.0	43.3
SD	11.82	11.96	11.88	13.11	12.28
Median	44.5	45.0	45.0	44.0	44.0
Range	19.0 – 70.0	19.0 – 65.0	19.0 – 70.0	19.0 – 70.0	19.0 – 70.0
Sex					
Female n (%)	114 (67.9)	108 (63.9)	222 (65.9)	107 (64.5)	329 (65.4)
Male n (%)	54 (32.1)	61 (36.1)	115 (34.1)	59 (35.5)	174 (34.6)
Race					
Caucasian n (%)	124 (73.8)	131 (77.5)	255 (75.7)	123 (74.1)	378 (75.1)
Black n (%)	31 (18.5)	25 (14.8)	56 (16.6)	30 (18.1)	86 (17.1)
Asian n (%)	5 (3.0)	4 (2.4)	9 (2.7)	3 (1.8)	12 (2.4)
Native American n (%)	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.6)	3 (0.6)

Pacific islander n (%)	1 (0.6)	1 (0.6)	2 (0.6)	0 (0.0)	2 (0.4)
Other n (%)	6 (3.6)	7 (4.1)	13 (3.9)	9 (5.4)	22 (4.4)

Primary Objective Result(s)

Change from baseline to Week 8 (LOCF) in the HAM-D_{17} total score - ITT population

Treatment	n	Baseline Mean (SE)	Mean (SE) at endpoint	LS mean change (SE)	Treatment group vs. placebo Difference in LS mean change Mean (SE)	95% CI	p-value
Agomelatine 25 mg (N = 158)	158	26.8 (0.26)	15.0 (0.64)	11.8 (0.61)	2.2 (0.85)	(0.5, 3.9)	0.010*
Agomelatine 50 mg (N = 161)	161	26.8 (0.26)	15.9 (0.65)	10.8 (0.61)	1.2 (0.85)	(-0.4, 2.9)	0.144
Placebo (N = 163)	163	26.4 (0.23)	17.1 (0.62)	9.6 (0.60)			

SE = Standard Error, CI = Confidence Interval, LS = Least Square

* indicates statistical significance (compared at 0.025 level – Hochberg procedure)

Secondary Objective Result(s)

Proportion of patients with CGI-I clinical improvement at Week 8 (LOCF) - ITT population

	Clinical improvement		Statistical analysis		
Treatment	Total	n (%)	Odds ratio	95% CI for odds ratio	p-value
Agomelatine 25 mg (N = 158)	158	74 (46.8)	1.52	(0.97, 2.38)	0.065
Agomelatine 50 mg (N = 161)	161	64 (39.8)	1.14	(0.73, 1.79)	0.568
Placebo (N = 163)	163	60 (36.8)			

Clinical improvement was defined by a score of 1 “very much improved” or 2 “much improved” on the CGI-I scale.
CI = Confidence Interval

Proportion of patients with clinical response at Week 8 (LOCF) - ITT population

	Clinical response				
Treatment	Total	n (%)	Odds ratio	95% CI for Odds ratio	p-value
Agomelatine 25 mg (N = 158)	158	74 (46.8)	1.78	(1.13, 2.79)	0.013*
Agomelatine 50 mg (N = 161)	161	67 (41.6)	1.44	(0.91, 2.26)	0.116
Placebo (N = 163)	163	54 (33.1)			

Clinical response was defined as ≥50% reduction in the HAM-D_{17} total score from baseline.
* indicates statistical significance at 0.05 level. CI = Confidence Interval

Proportion of patients with clinical remission at Week 8 (LOCF) - ITT population

	Clinical remission		Statistical analysis		
Treatment	Total	n (%)	Odds ratio	95% CI for odds ratio	p-value
Agomelatine 25 mg (N = 158)	158	35 (22.2)	1.71	(0.96, 3.04)	0.070
Agomelatine 50 mg (N = 161)	161	28 (17.4)	1.25	(0.69, 2.28)	0.457
Placebo (N = 163)	163	24 (14.7)			

Clinical remission was defined as a HAM-D_{17} total score ≤7. CI = Confidence Interval

Change from baseline to Week 8 (LOCF) in the HAM-D_{17} Maier sub-scale score – ITT population

					Treatment group versus placebo Difference in LS mean change		
Treatment	n	Baseline Mean (SE)	Mean (SE) at endpoint	LS mean change (SE)	Mean (SE)	95% CI	p-value
Agomelatine 25 mg (N = 158)	158	12.8 (0.15)	7.4 (0.33)	5.5 (0.32)	1.1 (0.45)	(0.2, 2.0)	0.013*

Agomelatine 50 mg (N = 161)	161	12.8 (0.15)	7.9 (0.33)	5.0 (0.32)	0.6 (0.45)	(-0.2, 1.5)	0.158
Placebo (N = 163)	163	12.8 (0.14)	8.5 (0.33)	4.4 (0.32)			

HAM-D_{17} Maier sub-scale is defined as the sum of the following items of the HAM-D_{17} rating scale: 1 (depressed mood), 2 (feelings of guilt), 7 (work and activities), 8 (retardation), 9 (agitation), 10 (psychic anxiety)

SE = Standard Error, CI = Confidence Interval, LS = Least Square

* Indicating statistical significance at the 0.05 level.

Change from baseline to Week 8 (LOCF) in the HAM-D_{17} Anxiety sub-scale score - ITT population

					Treatment group versus placebo Difference in LS mean change		
Treatment	**n**	**Baseline Mean (SE)**	**Mean (SE) at endpoint**	**LS mean change (SE)**	**Mean (SE)**	**95% CI**	**p-value**
Agomelatine 25 mg (N = 158)	158	8.5 (0.15)	5.2 (0.23)	3.3 (0.21)	0.3 (0.30)	(-0.3, 0.9)	0.277
Agomelatine 50 mg (N = 161)	161	8.5 (0.15)	5.5 (0.23)	3.1 (0.21)	0.1 (0.29)	(-0.5, 0.7)	0.751
Placebo (N = 163)	163	8.6 (0.13)	5.6 (0.22)	3.0 (0.21)			

HAM-D_{17} Anxiety sub-scale is defined as the sum of the following items of the HAM-D_{17} rating scale: 10 (psychic anxiety), 11 (somatic anxiety), 12 (somatic-gastrointestinal), 13 (somatic general), 15 (hypochondriasis), 17 (insight).

SE = Standard Error, CI = Confidence Interval, LS = Least Square

Change from baseline to Week 8 (LOCF) in the HAM-D_{17} Retardation sub-scale score - ITT population

					Treatment group versus placebo Difference in LS mean change		
Treatment	**n**	**Baseline Mean (SE)**	**Mean (SE) at endpoint**	**LS mean change (SE)**	**Mean (SE)**	**95% CI**	**p-value**
Agomelatine 25 mg (N = 158)	158	8.7 (0.10)	5.1 (0.23)	3.6 (0.23)	0.7 (0.32)	(0.1, 1.4)	0.022*
Agomelatine 50 mg (N = 161)	161	8.8 (0.12)	5.4 (0.24)	3.3 (0.23)	0.5 (0.32)	(-0.2, 1.1)	0.157
Placebo (N = 163)	163	8.5 (0.11)	5.8 (0.24)	2.9 (0.23)			

HAM-D_{17} Retardation sub-scale is defined as the sum of the following items of the HAM-D_{17} rating scale: 1 (depressed mood), 7 (work and activities), 8 (retardation), 14 (genital symptoms).

SE = Standard Error, CI = Confidence Interval, LS = Least Square

*Indicating statistical significance at the 0.05 level

Change from baseline to Week 8 (LOCF) in the HAM-D_{17} sleep sub-scale score – ITT population

Treatment	n	Baseline Mean (SE)	Mean (SE) at endpoint	LS mean change (SE)	Treatment group versus placebo Difference in LS mean change Mean (SE)	95% CI	p-value
Agomelatine 25 mg (N = 158)	158	4.8 (0.11)	2.2 (0.16)	2.6 (0.16)	0.7 (0.22)	(0.2, 1.1)	0.004*
Agomelatine 50 mg (N = 161)	161	4.9 (0.10)	2.6 (0.17)	2.3 (0.16)	0.3 (0.22)	(-0.1, 0.8)	0.129
Placebo (N = 163)	163	4.8 (0.10)	2.9 (0.16)	1.9 (0.16)			

HAM-D_{17} Sleep sub-scale is defined as the sum of the following items of the HAM-D_{17} rating scale: 4, 5, 6 (early, middle, and late insomnia)

SE = Standard Error, CI = Confidence Interval, LS = Least Square

* Indicating statistical significance at the 0.05 level

LSEQ "Getting to sleep" and "Quality of sleep" domain scores at Week 8 (LOCF) – ITT population

LSEQ analysis	Treatment	n	LS mean (SE) at end-point	Treatment group versus Placebo Difference in LS means Mean (SE)	95% CI	p-value
Getting to sleep	**Agomelatine 25 mg (N = 158)**	158	61.5 (1.45)	9.7 (2.01)	(5.8, 13.7)	< 0.001*
	Agomelatine 50 mg (N = 161)	161	59.7 (1.43)	7.9 (2.00)	(4.0, 11.9)	< 0.001*
	Placebo (N = 163)	162	51.8 (1.42)			
Quality of sleep	**Agomelatine 25 mg (N = 158)**	158	62.1 (1.78)	10.7 (2.47)	(5.9, 15.6)	< 0.001*
	Agomelatine 50 mg (N = 161)	161	56.8 (1.75)	5.4 (2.45)	(0.6, 10.3)	0.027*
	Placebo (N = 163)	162	51.4 (1.74)			

LSEQ – Leeds Sleep Evaluation Questionnaire

SE = Standard Error, CI = Confidence Interval, LS = Least Square

* indicates statistical significance at the 0.05 level

Safety Results

Adverse Events by System Organ Class

Adverse events by primary system organ class and treatment (Double-blind Treatment Phase) (at least 2% incidence by group) - Safety population

Primary system organ class	Agomelatine 25 mg N = 163 n (%)	Agomelatine 50 mg N = 167 n (%)	All Agomelatine N = 330 n (%)	Placebo N = 165 n (%)
Patients with AE(s)	114 (69.9)	118 (70.7)	232 (70.3)	108 (65.5)
Nervous system disorders	61 (37.4)	47 (28.1)	108 (32.7)	45 (27.3)
Gastrointestinal disorders	41 (25.2)	35 (21.0)	76 (23.0)	49 (29.7)
Infections & infestations	26 (16.0)	36 (21.6)	62 (18.8)	26 (15.8)
General disorders & administration site conditions	27 (16.6)	11 (6.6)	38 (11.5)	11 (6.7)
Musculoskeletal & connective tissue disorders	14 (8.6)	20 (12.0)	34 (10.3)	9 (5.5)
Psychiatric disorders	16 (9.8)	18 (10.8)	34 (10.3)	22 (13.3)
Skin & subcutaneous tissue disorders	11 (6.7)	16 (9.6)	27 (8.2)	8 (4.8)
Respiratory, thoracic & mediastinal disorders	9 (5.5)	10 (6.0)	19 (5.8)	11 (6.7)
Injury, poisoning & procedural complications	8 (4.9)	5 (3.0)	13 (3.9)	5 (3.0)
Investigations	4 (2.5)	8 (4.8)	12 (3.6)	1 (0.6)
Reproductive system & breast disorders	4 (2.5)	7 (4.2)	11 (3.3)	1 (0.6)
Metabolism & nutrition disorders	3 (1.8)	7 (4.2)	10 (3.0)	3 (1.8)
Ear & labyrinth disorders	4 (2.5)	3 (1.8)	7 (2.1)	1 (0.6)
Renal & urinary disorders	5 (3.1)	2 (1.2)	7 (2.1)	0 (0.0)
Cardiac disorders	2 (1.2)	4 (2.4)	6 (1.8)	3 (1.8)

Primary system organ classes are sorted in descending order of frequency, as reported in the “All agomelatine” group. A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A subject with multiple adverse events within a primary system organ class is counted only once in the total row

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

10 most common adverse events by preferred term and treatment (Double-blind Treatment Phase) – Safety population

Preferred term	Agomelatine 25 mg N = 163 n (%)	Agomelatine 50 mg N = 167 n (%)	All Agomelatine N = 330 n (%)	Placebo N = 165 n (%)
Patients with AE (s)	114 (69.9)	118 (70.7)	232 (70.3)	108 (65.5)
Preferred term				
Headache	24 (14.7)	20 (12.0)	44 (13.3)	28 (17.0)
Somnolence	18 (11.0)	12 (7.2)	30 (9.1)	7 (4.2)
Diarrhea	14 (8.6)	10 (6.0)	24 (7.3)	11 (6.7)
Dizziness	16 (9.8)	8 (4.8)	24 (7.3)	5 (3.0)
Nausea	11 (6.7)	9 (5.4)	20 (6.1)	8 (4.8)
Fatigue	12 (7.4)	7 (4.2)	19 (5.8)	4 (2.4)
Nasopharyngitis	6 (3.7)	11 (6.6)	17 (5.2)	7 (4.2)
Sedation	12 (7.4)	5 (3.0)	17 (5.2)	7 (4.2)
Dry mouth	7 (4.3)	9 (5.4)	16 (4.8)	14 (8.5)
Upper respiratory tract infection	8 (4.9)	6 (3.6)	14 (4.2)	7 (4.2)

Preferred terms were sorted in descending order of frequency, as reported 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, Deaths and Other Significant Adverse Events

Deaths, other serious or clinically significant adverse events or adverse events leading to discontinuation, by treatment - Safety population

	Agomelatine 25 mg N = 163 n (%)	Agomelatine 50 mg N = 167 n (%)	All Agomelatine N = 330 n (%)	Placebo N = 165 n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs*	1 (0.6)	1 (0.6)	2 (0.6)	2 (1.2)
Discontinuation due to AEs	7 (4.3)	10 (6.0)	17 (5.2)	8 (4.8)

*SAEs – 1 spontaneous abortion (25 mg group), 1 myocardial infarction (agomelatine 50 mg group), 1 elective abortion (placebo group) and 1 breast cancer (placebo group)

Other Findings

No significant differences in ECG or vital sign findings were observed between patients taking agomelatine and those on placebo. There were no clinically relevant findings in urinalysis, hematology and biochemistry (besides animotransferases). Overall, six patients treated with agomelatine (1.9%) experienced newly occurring clinically notable elevations (>3x ULN) in

transaminases (ALT or AST); one patient (n = 1/157; 0.6%) in the agomelatine 25 mg/day group and five patients (n = 5/164; 3.0%) in the agomelatine 50 mg/day group compared to one patient (n = 1/157; 0.6%) in the placebo group. Two patients with transaminase (AST and/or ALT only) elevations (both in the agomelatine 50 mg/day group) discontinued the study treatment, and the enzyme levels decreased to within baseline levels after stopping the drug. In the four other agomelatine-treated patients, the transaminase levels returned to normal values with continuing agomelatine treatment in three of these patients (the 25 mg/day patient was lost to follow-up after completing the double-blind phase of the study so no return to baseline assessment could be made).

Date of Clinical Trial Report

23 Oct 2008

Date Inclusion on Novartis Clinical Trial Results Database

20 Feb 2009

Date of Latest Update

17 Feb 2009