Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

Agomelatine

Therapeutic Area of Trial

Major Depressive Disorder

Approved Indication

Investigational

Study Number

CAGO178A2301

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

11-Dec-2006 to 16-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

47 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, 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 as 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 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 ≤ 7 on the $HAM\text{-}D_{17}$ at Week 8.
- Change from baseline to Week 8 on the clinician-rated $HAM\text{-}D_{17}$ 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 the Double-blind Treatment Phase, by treatment – randomized patients

Disposition Reason	Agomelatine 25 mg N = 170 n (%)	Agomelatine 50 mg N = 168 n (%)	All Agomelatine N = 338 n (%)	Placebo N = 173 n (%)	All N = 511 n (%)
Completed	133 (78.2)	131 (78.0)	264 (78.1)	136 (78.6)	400 (78.3)
Discontinued	37 (21.8)	37 (22.0)	74 (21.9)	37 (21.4)	111 (21.7)
Administrative problems	2 (1.2)	1 (0.6)	3 (0.9)	1 (0.6)	4 (0.8)
Adverse event(s)	8 (4.7)	10 (6.0)	18 (5.3)	11 (6.4)	29 (5.7)
Lost to follow-up	11 (6.5)	13 (7.7)	24 (7.1)	13 (7.5)	37 (7.2)
Protocol deviation	7 (4.1)	2 (1.2)	9 (2.7)	0 (0.0)	9 (1.8)
Subject withdrew consent	5 (2.9)	6 (3.6)	11 (3.3)	8 (4.6)	19 (3.7)
Unsatisfactory therapeutic effect	4 (2.4)	5 (3.0)	9 (2.7)	4 (2.3)	13 (2.5)
Continued into open-label extension phase	110 (64.7)	111 (66.1)	221 (65.4)	108 (62.4)	329 (64.4)

Demographic Characteristics

Demographics by treatment - randomized patients

Demographic Variable	Agomelatine 25 mg N = 170	Agomelatine 50 mg N = 168	All Agomelatine N = 338	Placebo N = 173	All N = 511
Baseline Age (years)					
<45 n (%)	80 (47.1)	82 (48.8)	162 (47.9)	99 (57.2)	261 (51.1)
45 - < 65 n (%)	82 (48.2)	82 (48.8)	164 (48.5)	66 (38.2)	230 (45.0)
≥65 n (%)	8 (4.7)	4 (2.4)	12 (3.6)	8 (4.6)	20 (3.9)
Age (Years)					
n	170	168	338	173	511
Mean	44.6	43.8	44.2	43.1	43.8
SD	11.98	12.69	12.32	12.01	12.22
Median	45.5	45.0	45.0	43.0	44.0
Range	19.0 - 70.0	18.0 - 69.0	18.0 - 70.0	18.0 - 70.0	18.0 - 70.0
Sex					
Female n (%)	118 (69.4)	105 (62.5)	223 (66.0)	118 (68.2)	341 (66.7)
Male n (%)	52 (30.6)	63 (37.5)	115 (34.0)	55 (31.8)	170 (33.3)
Race					
Caucasian n (%)	119 (70.0)	126 (75.0)	245 (72.5)	128 (74.0)	373 (73.0)
Black n (%)	34 (20.0)	21 (12.5)	55 (16.3)	35 (20.2)	90 (17.6)
Asian n (%)	1 (0.6)	2 (1.2)	3 (0.9)	1 (0.6)	4 (0.8)
Native Americans n (%)	0 (0.0)	2 (1.2)	2 (0.6)	0 (0.0)	2 (0.4)
Other n (%)	16 (9.4)	17 (10.1)	33 (9.8)	9 (5.2)	42 (8.2)

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 = 156)	156	26.7 (0.25)	15.9 (0.62)	11.2 (0.65)	0.6 (0.88)	(-1.1, 2.3)	0.505
Agomelatine 50 mg (N = 161)	161	27.1 (0.29)	14.1 (0.61)	13.1 (0.63)	2.5 (0.87)	(0.8, 4.2)	0.004*
Placebo (N = 167)	167	27.1 (0.29)	16.6 (0.65)	10.6 (0.62)			

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

Treatment	Clinical improvement		Statistical analysis		
	Total	n (%)	Odds ratio	95% CI for odds ratio	p-value
Agomelatine 25 mg (N = 156)	156	70 (44.9)	1.23	(0.79, 1.92)	0.357
Agomelatine 50 mg (N = 161)	161	86 (53.4)	1.76	(1.13, 2.72)	0.012*
Placebo (N = 167)	167	66 (39.5)			

Clinical improvement was defined by a score of 1 “very much improved” or 2 “much improved” on the CGI-I scale
*Indicates statistical significance at the 0.05 level. CI = Confidence Interval

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

Treatment	Clinical response		Statistical analysis		
	Total	n (%)	Odds ratio	95% CI for odds ratio	p-value
Agomelatine 25 mg (N = 156)	156	66 (42.3)	1.20	(0.77, 1.88)	0.421
Agomelatine 50 mg (N = 161)	161	80 (49.7)	1.63	(1.05, 2.53)	0.029*
Placebo (N = 167)	167	63 (37.7)			

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

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

Treatment	Clinical remission		Statistical analysis		
	Total	n (%)	Odds ratio	95% CI for odds ratio	p-value
Agomelatine 25 mg (N = 156)	156	26 (16.7)	0.99	(0.55, 1.78)	0.983
Agomelatine 50 mg (N = 161)	161	36 (22.4)	1.43	(0.83, 2.48)	0.202
Placebo (N = 167)	167	28 (16.8)			

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

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

Treatment	n	Baseline Mean (SE)	Mean (SE) at endpoint	LS mean change	Treatment Group versus Placebo Difference in LS mean change

				(SE)	Mean (SE)	95% CI	p-value
Agomelatine 25 mg (N = 156)	156	12.9 (0.15)	8.0 (0.34)	5.0 (0.34)	0.3 (0.47)	(-0.7, 1.2)	0.582
Agomelatine 50 mg (N = 161)	161	13.1 (0.16)	6.9 (0.33)	6.2 (0.33)	1.4 (0.46)	(0.5, 2.3)	0.002*
Placebo (N = 167)	167	13.0 (0.15)	8.3 (0.34)	4.8 (0.33)			

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	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 = 156)	156	8.7 (0.14)	5.5 (0.21)	3.3 (0.22)	0.1 (0.30)	(-0.5, 0.7)	0.840
Agomelatine 50 mg (N = 161)	161	8.6 (0.17)	4.9 (0.22)	3.8 (0.21)	0.6 (0.30)	(0.0, 1.2)	0.035*
Placebo (N = 167)	167	8.7 (0.16)	5.5 (0.23)	3.2 (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

* Indicating statistical significance at the 0.05 level.

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

Treatment	n	Baseline Mean (SE)	Mean (SE) at end-point	LS mean change (SE)	Treatment Group versus Placebo Difference in LS mean change		
					Mean (SE)	95% CI	p-value
Agomelatine 25 mg (N = 156)	156	8.7 (0.11)	5.4 (0.23)	3.4 (0.24)	0.3 (0.32)	(-0.4, 0.9)	0.417
Agomelatine 50 mg (N = 161)	161	8.8 (0.12)	4.9 (0.23)	3.9 (0.23)	0.8 (0.32)	(0.2, 1.5)	0.010*
Placebo (N = 167)	167	8.7 (0.11)	5.7 (0.24)	3.1 (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 end-point	LS mean change (SE)	Treatment Group versus Placebo Difference in LS mean change		
					Mean (SE)	95% CI	p-value
Agomelatine 25 mg (N = 156)	156	4.8 (0.11)	2.4 (0.16)	2.5 (0.16)	0.2 (0.22)	(-0.2, 0.6)	0.344
Agomelatine 50 mg (N = 161)	161	5.0 (0.09)	2.3 (0.15)	2.7 (0.15)	0.4 (0.21)	(- 0.0, 0.8)	0.055
Placebo (N = 167)	167	5.0 (0.09)	2.7 (0.15)	2.3 (0.15)			

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

LSEQ 'Getting to Sleep' and 'Quality of Sleep' domain scores at Week 8 (LOCF) - ITT population

LSEQ analysis	Treatment	n	LS Mean (SE) at Endpoint	Treatment Group versus Placebo Difference in LS Means		
				Mean (SE)	95% CI	p-value
Getting to sleep	Agomelatine 25 mg (N = 156)	156	57.6 (1.55)	3.9 (2.11)	(-0.2),8.1)	0.064
	Agomelatine 50 mg (N = 161)	161	62.1 (1.51)	8.4 (2.09)	(4.2, 12.5)	<0.001*
	Placebo (N = 167)	166	53.7 (1.49)			
Quality of sleep	Agomelatine 25 mg (N = 156)	156	59.8 (1.86)	5.1 (2.54)	(0.1, 10.1)	0.046*
	Agomelatine 50 mg (N = 161)	161	62.4 (1.81)	7.7 (2.51)	(2.7, 12.6)	0.002*
	Placebo (N = 167)	166	54.7 (1.79)			

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 = 162 n (%)	Agomelatine 50 mg N = 163 n (%)	All Agomelatine N = 325 n (%)	Placebo N = 169 n (%)
Patients with AE(s)	123 (75.9)	121 (74.2)	244 (75.1)	126 (74.6)
Nervous system disorders	61 (37.7)	61 (37.4)	122 (37.5)	57 (33.7)
Gastrointestinal disorders	59 (36.4)	55 (33.7)	114 (35.1)	52 (30.8)
Infections & infestations	25 (15.4)	31 (19.0)	56 (17.2)	30 (17.8)
Psychiatric disorders	24 (14.8)	23 (14.1)	47 (14.5)	34 (20.1)
General disorders & administration site conditions	21 (13.0)	25 (15.3)	46 (14.2)	24 (14.2)
Musculoskeletal & connective tissue disorders	24 (14.8)	22 (13.5)	46 (14.2)	15 (8.9)
Investigations	12 (7.4)	15 (9.2)	27 (8.3)	12 (7.1)
Injury, poisoning & procedural complications	8 (4.9)	13 (8.0)	21 (6.5)	11 (6.5)
Respiratory, thoracic & mediastinal disorders	11 (6.8)	8 (4.9)	19 (5.8)	10 (5.9)
Skin & subcutaneous tissue disorders	10 (6.2)	9 (5.5)	19 (5.8)	9 (5.3)
Metabolism & nutrition disorders	12 (7.4)	4 (2.5)	16 (4.9)	3 (1.8)
Reproductive system & breast disorders	7 (4.3)	7 (4.3)	14 (4.3)	1 (0.6)
Eye disorders	2 (1.2)	7 (4.3)	9 (2.8)	6 (3.6)
Renal & urinary disorders	3 (1.9)	5 (3.1)	8 (2.5)	3 (1.8)
Ear & labyrinth disorders	6 (3.7)	1 (0.6)	7 (2.2)	3 (1.8)
Cardiac disorders	2 (1.2)	2 (1.2)	4 (1.2)	4 (2.4)
Vascular disorders	2 (1.2)	2 (1.2)	4 (1.2)	5 (3.0)

Primary System Organ Classes (SOCs) were sorted in descending order of frequency, as reported in the 'All agomelatine' group. A subject with multiple occurrences of an Adverse Event (AE) under one treatment was counted only once in the AE category for that treatment. A subject with multiple AEs within a primary SOC was 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

	Agomelatine 25 mg N = 162 n (%)	Agomelatine 50 mg N = 163 n (%)	All Agomelatine N = 325 n (%)	Placebo N = 169 n (%)
Patients with AE (s)	123 (75.9)	121 (74.2)	244 (75.1)	126 (74.6)
Preferred term				
Headache	29 (17.9)	24 (14.7)	53 (16.3)	24(14.2)
Nausea	20 (12.3)	19 (11.7)	39 (12.0)	10(5.9)
Diarrhea	18 (11.1)	16 (9.8)	34 (10.5)	12 (7.1)
Dizziness	13 (8.0)	15 (9.2)	28 (8.6)	8 (4.7)
Dry mouth	8 (4.9)	15 (9.2)	23 (7.1)	13 (7.7)
Somnolence	9 (5.6)	14 (8.6)	23 (7.1)	10 (5.9)
Sedation	14 (8.6)	8 (4.9)	22 (6.8)	9 (5.3)
Fatigue	8 (4.9)	9 (5.5)	17 (5.2)	7 (4.1)
Insomnia	8 (4.9)	9 (5.5)	17 (5.2)	18 (10.7)
Back pain	8 (4.9)	4 (2.5)	12 (3.7)	6 (3.6)

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 AEs or AEs leading to discontinuation, by treatment – Safety population

	Agomelatine 25 mg N = 162 n (%)	Agomelatine 50 mg N = 163 n (%)	All Agomelatine N = 325 n (%)	Placebo N = 169 n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs*	1 (0.6)	1 (0.6)	2 (0.6)	3 (1.8)
Discontinuation due to AEs	7 (4.3)	10 (6.1)	17 (5.2)	11 (6.5)

*SAEs = 1 Diabetes mellitus inadequate control (agomelatine 25 mg group), 1 Rhabdomyolysis (agomelatine 50 mg group, 1 Depression (placebo group), 1 Depression suicidal (placebo group), 1 Road traffic accident, coronary artery disease (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, seven patients treated with agomelatine (7/313; 2.2%) experienced newly occurring clinically notable elevations (>3x ULN) in aminotransaminases (ALT or AST); no patients in the agomelatine 25 mg/day group and seven patients (n = 7/156; 4.5%) in the agomelatine 50 mg/day group. Hepatobiliary comorbidities were present in the 50 mg group (e.g., cholecystitis, gallbladder disorder and hepatic steatosis). No placebo-treated patients had clinically notable increases. One patient with transaminase (AST and/or ALT only) elevations in the 50 mg group discontinued the study treatment and the enzyme levels decreased to within baseline levels after stopping the drug. In the other six patients, the transaminase levels returned to normal values while continuing agomelatine treatment.

Date of Clinical Trial Report

07-Aug-2008

Date Inclusion on Novartis Clinical Trial Results Database

20 Feb 2009

Date of Latest Update

17 Feb 2009