Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

Agomelatine

Therapeutic Area of Trial

Major depressive disorder

Approved Indication

Investigational drug

Study Number

CAGO178A2303

Title

An 8-week, multicenter, randomized, double-blind, placebo-and paroxetine-controlled study of the efficacy, safety and tolerability of agomelatine 25 or 50 mg given once daily in the treatment of Major Depressive Disorder (MDD)

Phase of Development

Phase III

Study Start/End Dates

28 Mar 2007 to 20 Jun 2008

Study Design/Methodology

The study used an 8-week, multi-center, randomized, placebo- and active-drug controlled, parallel group design in patients with MDD. A total of 503 patients were randomized to 25 mg agomelatine o.d., 20 mg paroxetine o.d. or placebo (1:1:1). Those patients who did not show the minimum required response at the end of Week 4 received an increase to dose level 2, (agomelatine 50 mg, paroxetine 40 mg or matching placebo).

The core study comprised a pre-randomization phase (screening and baseline) and an 8-week double-blind treatment phase followed by a one-week double-blind taper phase. Patients who completed the 8-week double-blind treatment phase remained on double-blind treatment for an additional week. During this time, patients on dose level 2 were tapered to dose level 1, while patients on dose level 1 were continued at the same dose level. Patients who did not enroll into the open-label extension phase and patients who prematurely discontinued were required to attend a follow-up visit.

Centers

51 centers in USA

Publication

Ongoing

Objectives

Primary objective(s)

To demonstrate the efficacy of agomelatine 25 mg or 50 mg given once daily compared to placebo, at Week 8, for treatment of MDD.

Main Secondary objectives

- Evaluate, at Week 8, sexual dysfunction in patients with MDD receiving agomelatine as compared to paroxetine
- Evaluate, at Week 8, the efficacy of 25 and 50 mg agomelatine given once daily compared to placebo for the treatment of MDD with respect to
    - Proportion of patients who demonstrated clinical improvement
    - Proportion of patients with MDD who achieved remission
    - Change from baseline to Week 8 on the total score and Anxiety subscale of the Hospital Anxiety and Depression Scale (HAD Symptoms of anxiety, Patient's function in daily life)
- To evaluate the safety and tolerability of 25 mg or 50 mg agomelatine given once daily compared to placebo and paroxetine 20 mg or 40 mg 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 and paroxetine 20 mg tablets

Criteria for Evaluation

Primary variables

- Change from baseline to Week 8 on the total score of clinician-rated Hamilton Depression Rating Scale (HAM-D_{17})

Main Secondary variables

- Change from baseline to Week 8 (LOCF) on the total score of the Arizona Sexual Experience Scale (ASEX)
- Evaluate the efficacy of 25 or 50 mg agomelatine given once daily compared to placebo with respect to
    - Proportion of patients with clinical improvement, as defined by a score of 1 (very much improved) or 2 (much improved) in Clinical Global Impression-Improvement (CGI-I) at Week 8 (LOCF)
    - Proportion of patients who achieved clinical remission as defined by a total score of = 7 on the HAM-D_{17} at Week 8 (LOCF).
    - Symptoms of anxiety and depression, as measured by the change from baseline to Week 8 (LOCF) on the total score of the Hospital Anxiety and Depression Scale (HAD).
- Safety variables as described below

Safety and tolerability

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

Statistical Methods

Primary end points

The treatment groups were compared 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 the following explanatory variables: treatment, pooled center (fixed effect), and the baseline HAM-D_{17} total score and with no interaction. All differences between treatment groups 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 ITT population.

Secondary end points

The following secondary efficacy variables were investigated based on an ANCOVA analysis similar to the primary efficacy analysis: change from baseline in ASEX total score to assess sexual

function (LOCF), change from baseline on the HAD total score (LOCF),

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

Analysis on ASEX was performed on the safety population comparing agomelatine to paroxetine. Analyses on other efficacy variables were performed on the ITT population comparing agomelatine or paroxetine to placebo.

The assessment of safety was mainly based 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 patients, 18 through 70 years of age, inclusive
- Diagnosis of MDD, single or recurrent episode, according to DSM-IV criteria;
- Clinician-rated HAM-D_{17} total score = 22 at screening and baseline

Main Exclusion Criteria

- History of non-response to paroxetine
- Patients who were previously treated with agomelatine
- History of: bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, eating disorder, obsessive-compulsive disorder
- Any other current Axis I disorder other than MDD which was the focus of treatment
- Substance or alcohol abuse within the last 3 months or dependence within the last 6 months
- Use of any psychoactive medication after the screening visit
- Female patients of child-bearing potential not using effective contraception,

Other protocol-defined inclusion/exclusion criteria were used

Number of Patients

Patients disposition at the end of the Double-blind treatment phase, by treatment – all randomized patients

Disposition Reason	Agomelatine N=169 n (%)	Placebo N=166 n (%)	Paroxetine N=168 n (%)	All N = 503 n (%)
Completed	133 (78.7)	125 (75.3)	130 (77.4)	388 (77.1)
Discontinued	36 (21.3)	41 (24.7)	38 (22.6)	115 (22.9)
Abnormal test procedure results	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Administrative problems	1 (0.6)	3 (1.8)	2 (1.2)	6 (1.2)
Adverse events	4 (2.4)	9 (5.4)	8 (4.8)	21 (4.2)
Lost to follow-up	17 (10.1)	11 (6.6)	15 (8.9)	43 (8.5)
Protocol deviation	6 (3.6)	6 (3.6)	5 (3.0)	17 (3.4)
Subject withdrew consent	6 (3.6)	8 (4.8)	6 (3.6)	20 (4.0)
Unsatisfactory therapeutic effect	1 (0.6)	4 (2.4)	2 (1.2)	7 (1.4)
Continued into open-label extension phase	116 (68.6)	106 (63.9)	112 (66.7)	334 (66.4)

Demographic Characteristics

Demographics by treatment – randomized patients

Demographic Variable		Agomelatine N=169	Placebo N=166	Paroxetine N=168	All N = 503
Baseline Age (years)	n	169	166	168	503
	Mean	42.1	42.9	43.7	42.9
	SD	13.07	11.78	12.70	12.53
Sex [n (%)]	Female	104(61.5)	111(66.9)	99(58.9)	314(62.4)
	Male	65(38.5)	55(33.1)	69(41.1)	189(37.6)
Race [n (%)]	Caucasian	107(63.3)	113(68.1)	105(62.5)	325(64.6)
	Black	39(23.1)	31(18.7)	33(19.6)	103(20.5)
	Asian	1(0.6)	2(1.2)	5(3.0)	8(1.6)
	Native American	1(0.6)	0(0.0)	2(1.2)	3(0.6)
	Pacific islander	1(0.6)	1(0.6)	2(1.2)	4(0.8)

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 (N = 162)	162	27.2(0.27)	17.1(0.58)	10.3(0.57)	0.5(0.80)	(-1.1,2.1)	0.539
Placebo (N = 158)	158	26.9(0.28)	17. 3(0.63)	9.8(0.58)			
Paroxetine (N = 163)	163	27.0(0.29)	14.0(0.59)	13.2(0.57)	3.4(0.79)	(1.9,5.0)	<0.001*

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

* indicating statistical significance versus placebo at the 0.05 level.

Secondary Objective Results

Change from baseline to Week 8 (LOCF) in the ASEX total score - Safety population

					Treatment group versus Paroxetine 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 (N = 167)	146	20.7(0.45)	19.0(0.51)	2.0(0.37)	-0.1(0.51)	(-1.1, 0.9)	0.783
Placebo (N = 163)	143	21.5(0.47)	19.9(0.50)	1.6(0.58)			
Paroxetine (N = 166)	143	21.2(0.46)	19.2(0.50)	2.1(0.37)			

SE = Standard Error, CI = Confidence Interval, LS = Least Square, ASEX is the Arizona Sexual Experience Scale

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

	Clinical improvement		**Treatment group vs. placebo**		
Treatment	**Total**	**n (%)**	**Odds ratio**	**95% CI for Odds ratio**	**p-value**
Agomelatine (N = 162)	162	70 (43.2)	1.22	(0.78, 1.90)	0.389
Placebo (N = 158)	158	61(38.6)			
Paroxetine (N = 163)	163	91 (56.2)	2.05	(1.31, 3.20)	0.002*

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

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

	Clinical remission		**Treatment group vs. placebo**		
Treatment	**Total**	**n (%)**	**Odds ratio**	**95% CI for Odds ratio**	**p-value**
Agomelatine (N = 162)	162	9 (5.6)	0.37	(0.17, 0.84)	0.018*
Placebo (N = 158)	158	22 (13.9)			
Paroxetine (N = 163)	163	37 (22.7)	1.85	(1.03, 3.34)	0.040*

Clinical remission was defined as a HAM-D_{17} total score = 7, CI = Confidence Interval, *Indicates statistical significance versus placebo at the 0.05 level. CI = Confidence Interval

Change from baseline to Week 8 (LOCF) in the HAD total 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 (N = 162)	161	27.3 (0.41)	19.8 (0.63)	7.4 (0.63)	1.3 (0.88)	(-0.4, 3.1)	0.130
Placebo (N = 158)	158	27.3 (0.45)	21.1 (0.70)	6.1 (0.64)			
Paroxetine (N = 163)	160	26.9 (0.43)	16.4 (0.65)	10.6 (0.63)	4.5 (0.88)	(2.8, 6.2)	< 0.001*

HAD is the Hospital Anxiety and Depression Scale, * Indicating statistical significance versus placebo 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

	Agomelatine	**Placebo**	**Paroxetine**
	N=167	**N=163**	**N=166**
Primary System Organ Class	**n (%)**	**n(%)**	**n (%)**
Patients with AEs	120(71.9)	130(79.8)	135(81.3)
Gastrointestinal disorders	54(32.3)	52(31.9)	72(43.4)
Nervous system disorders	50(29.9)	54(33.1)	64(38.6)
Infections and infestations	39(23.4)	29(17.8)	29(17.5)
Psychiatric disorders	25 (15.0)	32 (19.6)	35(21.1)
Musculoskeletal and connective tissue disorders	22 (13.2)	16 (9.8)	21(12.7)
General disorders and administrative site conditions	21 (12.6)	24 (14.7)	26(15.7)
Respiratory, thoracic and mediastinal disorders	13 (7.8)	15 (9.2)	11(6.6)
Investigations	11 (6.6)	11 (6.7)	9(5.4)
Metabolism and nutrition disorders	8 (4.8)	12 (7.4)	9(5.4)
Injury, poisoning and procedural complications	7 (4.2)	20(12.3)	13(7.8)
Reproductive system and breast disorders	7 (4.2)	7(4.3)	9(5.4)
Skin and subcutaneous tissue disorders	7 (4.2)	11(6.7)	13(7.8)
Renal and urinary disorder	5(3.0)	5(3.1)	4(2.4)
Vascular disorders	5(3.0)	5(3.1)	4(2.4)
Eye disorders	4 (2.4)	3 (1.8)	8(4.8)
Ear and labyrinth disorders	2(1.2)	4(2.5)	2(1.2)
Cardiac disorders	1(0.6)	6(3.7)	3(1.8)

Primary system organ classes are sorted in descending order of frequency, as reported in the agomelatine group. A subject with multiple adverse events within a primary system organ class is 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

Preferred Term	Agomelatine N=167 n(%)	Placebo N=163 n(%)	Paroxetine N=166 n(%)
Patients with AEs	120 (71.9)	130(79.8)	135(81.3)
Headache	22(13.2)	30(18.4)	31(18.7)
Dry mouth	16(9.6)	13(8.0)	16(9.6)
Upper respiratory tract infection	15(9.0)	9(5.5)	13(7.8)
Somnolence	13(7.8)	15(9.2)	15(9.0)
Nausea	10(6.0)	15(9.2)	27(16.3)
Fatigue	9(5.4)	7(4.3)	17(10.2)
Sedation	9(5.4)	5(3.1)	7(4.2)
Dizziness	8(4.8)	6(3.7)	10(6.0)
Nasopharyngitis	7(4.2)	9(5.5)	5(3.0)
Stomach discomfort	7(4.2)	0(0.0)	3(1.8)

Preferred terms are sorted in descending order of frequency as reported in the agomelatine group.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Deaths and other serious or clinically significant events or adverse events leading to discontinuation – Safety population

	Agomelatine	Placebo	Paroxetine
No. (%) of patients studied	**N = 167**	**N = 163**	**N = 166**
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
SAEs*	3(1.8)	1 (0.6)	1 (0.6)
Discontinuation due to AEs	4 (2.4)	9(5.5)	8(4.8)
Sexual dysfunction AEs	3 (1.8)	2(1.2)	21(12.7)

*SAEs = Anemia, swelling of benign goiter, abdominal pain and musculoskeletal chest pain (One event each in agomelatine group), worsening depression (one event in placebo group), severe costochondritis (one event in paroxetine group).

Other Relevant Findings

No significant differences in ECG or vital signs findings were observed between the 3 groups of patients. There were no clinically relevant findings in urinalysis, hematology and biochemistry.

Overall, three patients treated with agomelatine (3/158, 1.9%) experienced newly occurring clini-

cally notable elevations (≥3 x ULN) in aminotransferases (ALT or AST); two on 25 mg /day dose and one on 50 mg /day dose; one patient treated with paroxetine (1/160, 0.6%) 20 mg/day dose. No placebo-treated patients had clinically notable increases. One patient receiving 25 mg/day agomelatine, discontinued the study treatment and was reported to have taken alcohol the day prior to when the elevated AST was reported. In this patient AST completely resolved one day after discontinuation of the drug.

In the other two patients receiving agomelatine, the transaminase levels returned to normal values while continuing agomelatine treatment. Patient receiving paroxetine had entered open label extension receiving agomelatine (25 mg. /day) and the transaminase levels returned to normal values while continuing agomelatine treatment.

Date of Clinical Trial Report

03 Feb 2009

Date Inclusion on Novartis Clinical Trial Results Database

31 Jul 2009

Date of Latest Update

28 May 2009