Sponsor Novartis
Generic Drug Name Agomelatine
Therapeutic Area of Trial Major Depressive Disorder (MDD)
Approved Indication Investigational

Protocol Number

CAGO178C2302

Title

An 8-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study of the efficacy and safety of agomelatine 0.5 mg and 1 mg sublingual tablets administered once daily in patients with Major Depressive Disorder (MDD).

Phase of Development

Phase III

Study Start/End Dates

26-May-2010 to 01-Jul-2011

Study Design/Methodology

This was an 8-week randomized, double-blind, parallel-group, multi-center study using a placebo control and 2 doses of agomelatine sublingual tablets (0.5 mg and 1 mg) administered once daily in patients with MDD. Visits to assess safety and efficacy were scheduled at 1-week intervals for the first 2 weeks and then at 2-week intervals for the next 6 weeks. The primary objective was assessed at the end of the double-blind treatment period (Week 8). Patients who completed all visits of the study were eligible to enter a 52-week, long-term, open-label study of agomelatine sublingual tablets if: 1) the site was participating in the 52-week open-label study and 2) the patient met the entry criteria for the 52-week open-label study.

Centers

48 investigative centers in the United States.

Publication

None

Outcome Measures

Change from baseline to Week 8 in the total score of the 17-item Hamilton Depression Rating Scale (HAM-D_{17}).

Secondary outcome measure(s)

Key secondary outcome measure

Patients' improvement relative to baseline, as measured by The Global Improvement rating of the Clinical Global Impression of Improvement (CGI-I) at Week 8 (last observation carried forward, LOCF).

Other secondary outcome measures

- Proportion of patients who demonstrated clinical response, where response was defined by a reduction of at least 50% in the Baseline clinician-rated HAM-D_{17} total score at Week 8 endpoint.
- Proportion of patients who demonstrated clinical improvement, whereby improvement was defined by a CGI-I score of 1 or 2 at Week 8 endpoint.
- Proportion of patients with MDD who achieved remission.
- Aspects of sleep behavior, as measured by the score on the Leeds Sleep Evaluation Questionnaire (LSEQ) domains of "quality of sleep," "getting off to sleep," "ease of awakening," and "alertness following awakening" at Week 8 endpoint.
- Patients' functioning in daily life, as measured by the change from baseline to endpoint at Week 8 on the total score and subscales of the Sheehan Disability Scale (SDS)
- Safety and tolerability by adverse events (AEs), serious adverse events (SAEs) and assessment of suicidal ideation and behavior by Columbia Suicide Severity Rating Scale. Other safety assessments included vital signs, electrocardiograms (ECGs), laboratory, liver function tests (LFTs), and bilirubin monitoring.

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

Sublingual tablets of agomelatine 0.5 mg and 1 mg were supplied by Novartis Drug Supply Management (DSM).

During the 8-week treatment period, the agomelatine sublingual tablets were to be taken sublingually once a day (o.d.) at bedtime, preferably before 11 p.m. The patient placed one tablet of study drug under his/her tongue and let it dissolve and disappear completely without swallowing. A drink of water was allowed after complete dissolution and disappearance of the tablet.

Agomelatine matching placebo sublingual tablets were supplied by Novartis DSM. Placebo was to be administered following the same conditions as those specified for agomelatine.

Statistical Methods

The primary efficacy variable was the change from baseline to endpoint at Week 8 on the total score of the 17-item clinician-rated HAM-D_{17}.

For each of the two agomelatine doses (0.5 mg and 1 mg), the following null hypotheses were tested: no difference between the agomelatine dose group and placebo in the change from

baseline to Week 8 on HAM-D_{17} total score. The corresponding alternative hypothesis was that the agomelatine dose group differed from placebo in the change from baseline to Week 8 on HAM-D_{17} total score. Since the two null hypotheses were tested simultaneously, the step-down Dunnett procedure was used to adjust for multiplicity. The treatment groups were compared using least square means derived from a Mixed Effect Repeated Measures Model (MMRM) including terms for treatment group, pooled center, visit, and treatment group by visit interaction as fixed effects and baseline HAM-D_{17} total score as a covariate, using an unstructured covariance structure. Visit was included as a discrete variable. The primary comparison was the contrast between each agomelatine dose and placebo at Week 8, and was estimated and presented with a two-sided 95% confidence interval and p-values (both unadjusted p-values and adjusted p-values were presented).

The primary efficacy analysis was performed on the full analysis set (FAS).

The key secondary efficacy variable was CGI-I score at Week 8 (LOCF).

To control for family-wise error rate, the key secondary efficacy variable was tested to compare the two dose groups to placebo, only if the primary efficacy variable tested significantly different from placebo for both dose groups. Tests of hypotheses were two-sided with type I error rate of 5%. The Hochberg procedure was used to adjust for multiplicity for the simultaneous testing of two dose groups versus placebo.

The rating of the CGI-I at Week 8 (LOCF) was analyzed by the Cochran-Mantel-Haenszel test blocking on pooled center, using the modified ridit score statistic of the ordinal response. Both unadjusted and adjusted p-values were presented in the summary tables.

These analyses were performed on the FAS.

Study Population: Inclusion/Exclusion Criteria and Demographics

Main inclusion criteria:

- Male and female adults (18 to 70 years of age inclusive)
- Diagnosis of MDD with a single or recurrent episode according to the Diagnostic and Statistical Manual of Mental Disorders – 4th Edition criteria,
- Current episode ≥ 4 weeks
- Clinician-rated HAM-D_{17} total score ≥ 22 at screening and baseline,
- Clinical Global Impression – Severity score ≥ 4 at screening and baseline.

Main exclusion criteria:

- History of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, eating disorder (current or during previous one year), 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 6 months, or dependence within the last 12 months
- Female patients of childbearing potential who were not using acceptable methods of contraception
- Psychotherapy of any type
- Concomitant psychotropic medication, including herbal preparations and melatonin.

- Prior exposure to agomelatine

Other protocol-defined Inclusion/Exclusion criteria were used.

Participant Flow

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

Disposition Reason	Agomelatine 0.5 mg (N = 192) n (%)	Agomelatine 1 mg (N = 195) n (%)	All Agomelatine (N = 387) n (%)	Placebo (N = 203) n (%)	All (N = 590) n (%)
Completed	159 (82.8)	153 (78.5)	312 (80.6)	167 (82.3)	479 (81.2)
Discontinued	33 (17.2)	42 (21.5)	75 (19.4)	36 (17.7)	111 (18.8)
Adverse event(s)	6 (3.1)	6 (3.1)	12 (3.1)	2 (1.0)	14 (2.4)
Abnormal laboratory value(s)	0	0	0	0	0
Abnormal test procedure result(s)	0	0	0	0	0
Unsatisfactory therapeutic effect	2 (1.0)	6 (3.1)	8 (2.1)	2 (1.0)	10 (1.7)
Subject's condition no longer requires study drug	0	0	0	0	0
Subject withdrew consent	7 (3.6)	14 (7.2)	21 (5.4)	12 (5.9)	33 (5.6)
Lost to follow-up	13 (6.8)	13 (6.7)	26 (6.7)	15 (7.4)	41 (6.9)
Administrative problem	2 (1.0)	0	2 (0.5)	1 (0.5)	3 (0.5)
Death	0	0	0	0	0
Protocol deviation	3 (1.6)	3 (1.5)	6 (1.6)	4 (2.0)	10 (1.7)

Baseline Characteristics

Demographics, by treatment — All randomized patients

Demographic Variable	Agomelatine 0.5 mg N = 192 n (%)	Agomelatine 1 mg N = 195 n (%)	All Agomelatine N = 387 n (%)	Placebo N = 203 n (%)	All N = 590 n (%)
Baseline Age (Years)					
< 45	105 (54.7)	112 (57.4)	217 (56.1)	102 (50.2)	319 (54.1)
45 - < 65	83 (43.2)	78 (40.0)	161 (41.6)	92 (45.3)	253 (42.9)
≥ 65	4 (2.1)	5 (2.6)	9 (2.3)	9 (4.4)	18 (3.1)
Age (Years)					
n	192	195	387	203	590
Mean	41.6	41.1	41.3	43.6	42.1
SD	12.83	12.57	12.69	12.70	12.7
Median	42.5	42.0	42.0	44.0	43.0
Min	18	18	18	18	18
Max	70	67	70	70	70
Sex					
Male	67 (34.9)	68 (34.9)	135 (34.9)	64 (31.5)	199 (33.7)
Female	125 (65.1)	127 (65.1)	252 (65.1)	139 (68.5)	391 (66.3)
Race					
Caucasian	131 (68.2)	126 (64.6)	257 (66.4)	140 (69.0)	397 (67.3)
Black	50 (26.0)	53 (27.2)	103 (26.6)	44 (21.7)	147 (24.9)
Asian	6 (3.1)	3 (1.5)	9 (2.3)	5 (2.5)	14 (2.4)

Native American	1	(0.5)	1	(0.5)	2	(0.5)	2	(1.0)	4	(0.7)
Pacific islander	0		2	(1.0)	2	(0.5)	0		2	(0.3)
Other	4	(2.1)	10	(5.1)	14	(3.6)	12	(5.9)	26	(4.4)

Outcome Measures

Primary Outcome Result(s)

Change from baseline to Week 8 in the HAM-D_{17} total score — FAS

					Treatment group vs. placebo ---Difference in LS Mean Change---			
Treatment	n	Baseline Mean (SE)	Endpoint Mean (SE)	Change LS Mean (SE)	Mean (SE)	95% CI	p-value	Adj. p-value
Agomelatine 0.5 mg (N = 185)	160	26.0 (0.24)	15.7 (0.59)	10.61 (0.527)	0.46 (0.732)	(-0.98, 1.90)	0.5286	0.7537
Agomelatine 1 mg (N = 192)	154	26.2 (0.25)	15.8 (0.62)	10.57 (0.530)	0.42 (0.733)	(-1.02, 1.86)	0.5691	0.7537
Placebo (N = 198)	164	26.4 (0.25)	16.3 (0.57)	10.15 (0.518)				

SE = Standard error, CI = confidence interval, LS = least square.
N is the number of FAS patients; n is the number of patients with a value at both baseline and at Week 8. Baseline is the last pre-randomization value.
Least square means, confidence intervals and p-values are derived from MMRM model with treatment group, pooled center, baseline HAM-D_{17} total score, visit (in weeks) and treatment*visit interaction as explanatory variables.
A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.
The Kenward-Roger approximation is used to estimate denominator degrees of freedom.
Adjusted p-values are based on the step-down Dunnett procedure.

Secondary Outcome Result(s)

Key secondary outcome results

Rating of the CGI-I at Week 8 (LOCF) — FAS

	Agomelatine 0.5 mg N = 185		Agomelatine 1 mg N = 192		Placebo N = 198	
Score	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**
1 - Very much improved	185	27 (14.6)	192	29 (15.1)	198	23 (11.6)
2 - Much improved	185	61 (33.0)	192	56 (29.2)	198	51 (25.8)
3 - Minimally improved	185	44 (23.8)	192	58 (30.2)	198	65 (32.8)
4 - No change	185	53 (28.6)	192	39 (20.3)	198	54 (27.3)
5 - Minimally worse	185	0	192	10 (5.2)	198	5 (2.5)
6 - Much worse	185	0	192	0	198	0
7 - Very much worse	185	0	192	0	198	0
p-value	0.1664		0.2777			
Adj. p-value	0.2777		0.2777			

* Indicating statistical significance at the 0.05 level.
N is the number of FAS patients; Total is the number of patients with a value at Week 8 using LOCF.
CGI-I is the Clinical Global Impression – Improvement scale.
p-value is from the Cochran-Mantel-Haenszel test blocking on pooled center.
The Hochberg procedure is used to adjust for multiplicity for the simultaneous testing of two dose groups versus placebo.

Other secondary outcome results

Proportion of patients with clinical response at Week 8 (LOCF) — FAS

Treatment	Total	Clinical response n (%)	Odds ratio	95% CI for odds ratio	p-value
Agomelatine 0.5 mg (N = 185)	185	63 (34.1)	1.31	(0.82, 2.10)	0.2595
Agomelatine 1 mg (N = 192)	192	70 (36.5)	1.46	(0.92, 2.32)	0.1107
Placebo (N = 198)	198	58 (29.3)			

* Indicates statistical significance at the 0.05 level. CI = Confidence Interval.
Clinical response = reduction ≥ 50% in the HAM-D_{17} total score from baseline.
N is the number of FAS patients; Total is the number of patients with a value at both baseline and Week 8 using LOCF.
Odds-ratio represents the odds of an agomelatine-treated patient having clinical response relative to the odds of a placebo-treated patient, based on a logistic regression model with treatment, pooled center and baseline HAM-D_{17} total score as explanatory variables. P-value is from the logistic regression model.

Proportion of patients with CGI-I clinical improvement at Week 8 (LOCF) — FAS

Treatment	Total	Clinical Improvement n (%)	Odds ratio	95% CI for odds ratio	p-value
Agomelatine 0.5 mg (N = 185)	185	88 (47.6)	1.57	(1.01, 2.44)	0.0428*
Agomelatine 1 mg (N = 192)	192	85 (44.3)	1.35	(0.88, 2.09)	0.1707
Placebo (N = 198)	198	74 (37.4)			

* Indicates statistical significance at the 0.05 level. CI = Confidence Interval.
N is the number of FAS patients; Total is the number of patients with a value at Week 8 using LOCF.
Clinical improvement is defined by a score of 1 “very much improved” or 2 “much improved” on the CGI-I scale.
Odds-ratio represents the odds of an agomelatine-treated patient having clinical improvement relative to the odds of a placebo-treated patient, based on a logistic regression model with treatment, pooled center and baseline HAM-D_{17} total score as explanatory variables. P-value is from the logistic regression model.

Proportion of patients with clinical remission at Week 8 (LOCF) — FAS

Treatment	Total	Clinical remission n (%)	Odds ratio	95% CI for odds ratio	p-value
Agomelatine 0.5 mg (N = 185)	185	30 (16.2)	1.32	(0.73, 2.37)	0.3604
Agomelatine 1 mg (N = 192)	192	26 (13.5)	1.01	(0.55, 1.82)	0.9844
Placebo (N = 198)	198	25 (12.6)			

* Indicates statistical significance at the 0.05 level. CI = Confidence Interval.
Clinical remission = HAM-D_{17} total score ≤ 7.
N is the number of FAS patients; Total is the number of patients with a value at Week 8 using LOCF.
Odds-ratio represents the odds of an agomelatine-treated patient having clinical remission relative to the odds of a placebo-treated patient, based on a logistic regression model with treatment, pooled center and baseline HAM-D_{17} total score as explanatory variables. P-value is from the logistic regression model.

LSEQ “'Sleep Quality” domain score at Week 8 (MMRM) — FAS

Treatment	n	LS Mean (SE) at endpoint	Treatment Group vs. Placebo ---Difference in LS Mean Change--- Mean (SE)	95% CI	p-value
Agomelatine 0.5 mg (N = 185)	159	61.00 (1.607)	2.32 (2.206)	(-2.01, 6.66)	0.2930
Agomelatine 1 mg (N = 192)	153	61.07 (1.616)	2.40 (2.209)	(-1.94, 6.74)	0.2785
Placebo (N = 198)	167	58.68 (1.565)			

LSEQ is the Leeds Sleep Evaluations Questionnaire.
* Indicating statistical significance at the 0.05 level.
N is the number of FAS patients; n is the number of patients with a value at both baseline and at Week 8. Baseline is the last pre-randomization value.
Least square means, confidence intervals and p-values are derived from MMRM model with treatment group, pooled center, baseline HAM-D_{17} total score, visit (in weeks) and treatment*visit interaction as explanatory variables.
A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.
The Kenward-Roger approximation is used to estimate denominator degrees of freedom.

LSEQ "Getting to Sleep" domain score at Week 8 (MMRM) — FAS

			Treatment Group vs. Placebo		
		LS Mean (SE) at endpoint	---Difference in LS Mean Change---		
Treatment	**n**		**Mean (SE)**	**95% CI**	**p-value**
Agomelatine 0.5 mg (N = 185)	159	61.62 (1.350)	6.25 (1.852)	(2.61, 9.88)	0.0008*
Agomelatine 1 mg (N = 192)	153	59.96 (1.360)	4.58 (1.856)	(0.94, 8.23)	0.0139*
Placebo (N = 198)	167	55.37 (1.315)			

LSEQ is the Leeds Sleep Evaluations Questionnaire.
* Indicating statistical significance at the 0.05 level.
N is the number of FAS patients; n is the number of patients with a value at both baseline and at Week 8. Baseline is the last pre-randomization value.
Least square means, confidence intervals and p-values are derived from MMRM model with treatment group, pooled center, baseline HAM-D_{17} total score, visit (in weeks) and treatment*visit interaction as explanatory variables.
A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.
The Kenward-Roger approximation is used to estimate denominator degrees of freedom.

LSEQ "Ease of Wakening" domain score at Week 8 (MMRM) — FAS

			Treatment Group vs. Placebo		
		LS Mean (SE) at endpoint	---Difference in LS Mean Change---		
Treatment	**n**		**Mean (SE)**	**95% CI**	**p-value**
Agomelatine 0.5 mg (N = 185)	159	58.20 (1.648)	1.90 (2.273)	(-2.57, 6.36)	0.4040
Agomelatine 1 mg (N = 192)	153	57.66 (1.659)	1.35 (2.278)	(-3.12, 5.83)	0.5528
Placebo (N = 198)	167	56.31 (1.611)			

LSEQ is the Leeds Sleep Evaluations Questionnaire.
* Indicating statistical significance at the 0.05 level.
N is the number of FAS patients; n is the number of patients with a value at both baseline and at Week 8. Baseline is the last pre-randomization value.
Least square means, confidence intervals and p-values are derived from MMRM model with treatment group, pooled center, baseline HAM-D_{17} total score, visit (in weeks) and treatment*visit interaction as explanatory variables.
A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.
The Kenward-Roger approximation is used to estimate denominator degrees of freedom.

LSEQ "Alertness following Awakening" domain score at Week 8 (MMRM) — FAS

			Treatment Group vs. Placebo		
		LS Mean (SE) at endpoint	---Difference in LS Mean Change---		
Treatment	n		Mean (SE)	95% CI	p-value
Agomelatine 0.5 mg (N = 185)	159	55.07 (1.648)	1.00 (2.262)	(-3.45, 5.44)	0.6601
Agomelatine 1 mg (N = 192)	153	54.12 (1.653)	0.05 (2.262)	(-4.39, 4.50)	0.9823
Placebo (N = 198)	167	54.07 (1.605)			

LSEQ is the Leeds Sleep Evaluations Questionnaire.
* Indicating statistical significance at the 0.05 level.
N is the number of FAS patients; n is the number of patients with a value at both baseline and at Week 8. Baseline is the last pre-randomization value.
Least square means, confidence intervals and p-values are derived from MMRM model with treatment group, pooled center, baseline HAM-D_{17} total score, visit (in weeks) and treatment*visit interaction as explanatory variables.
A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.
The Kenward-Roger approximation is used to estimate denominator degrees of freedom

Change from baseline to Week 8 (MMRM) in the SDS total score — FAS

					Treatment Group vs. Placebo		
		Baseline	Mean (SE)	LS Mean	---Difference in LS Mean Change---		
Treatment	n	Mean (SE)	at endpoint	Change (SE)	Mean (SE)	95% CI	p-value
Agomelatine 0.5 mg (N = 185)	130	21.2 (0.43)	13.6 (0.61)	7.04 (0.583)	0.78 (0.789)	(-0.77, 2.33)	0.3221
Agomelatine 1 mg (N = 192)	123	21.9 (0.47)	13.6 (0.62)	7.46 (0.611)	1.21 (0.803)	(-0.37, 2.78)	0.1343
Placebo (N = 198)	140	21.5 (0.40)	14.6 (0.57)	6.26 (0.566)			

SDS is the Sheehan Disability Scale.
* Indicating statistical significance at the 0.05 level.
N is the number of FAS patients; n is the number of patients with a value at both baseline and at Week 8. Baseline is the last pre-randomization value.
Least square means, confidence intervals and p-values are derived from MMRM model with treatment group, pooled center, baseline SDS total score, visit (in weeks) and treatment*visit interaction as explanatory variables.
A higher SDS score indicates greater disability.
A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.
The Kenward-Roger approximation is used to estimate denominator degrees of freedom.

Change from baseline to Week 8 (MMRM) in the SDS work sub-scale score — FAS

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 0.5 mg (N = 185)	130	6.9 (0.17)	4.3 (0.21)	2.35 (0.210)	0.41 (0.283)	(-0.15, 0.96)	0.1520
Agomelatine 1 mg (N = 192)	123	6.9 (0.19)	4.3 (0.22)	2.33 (0.219)	0.39 (0.288)	(-0.18, 0.95)	0.1814
Placebo (N = 198)	140	6.7 (0.18)	4.6 (0.20)	1.95 (0.203)			

SDS is the Sheehan Disability Scale.
* Indicating statistical significance at the 0.05 level.
N is the number of FAS patients; n is the number of patients with a value at both baseline and at Week 8. Baseline is the last pre-randomization value.
Least square means, confidence intervals and p-values are derived from MMRM model with treatment group, pooled center, baseline SDS work sub-scale score, visit (in weeks) and treatment*visit interaction as explanatory variables.
A higher SDS score indicates greater disability.
A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.
The Kenward-Roger approximation is used to estimate denominator degrees of freedom.

Change from baseline to Week 8 (MMRM) in the SDS social life sub-scale score — FAS

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 0.5 mg (N = 185)	160	7.4 (0.14)	4.9 (0.19)	2.45 (0.190)	0.16 (0.259)	(-0.35, 0.67)	0.5418
Agomelatine 1 mg (N = 192)	157	7.7 (0.15)	4.9 (0.20)	2.65 (0.191)	0.37 (0.260)	(-0.15, 0.88)	0.1602
Placebo (N = 198)	169	7.5 (0.13)	5.1 (0.19)	2.29 (0.184)			

SDS is the Sheehan Disability Scale.
* Indicating statistical significance at the 0.05 level.
N is the number of FAS patients; n is the number of patients with a value at both baseline and at Week 8. Baseline is the last pre-randomization value.
Least square means, confidence intervals and p-values are derived from MMRM model with treatment group, pooled center, baseline SDS social life sub-scale score, visit (in weeks) and treatment*visit interaction as explanatory variables.
A higher SDS score indicates greater disability.
A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.
The Kenward-Roger approximation is used to estimate denominator degrees of freedom.

Change from baseline to Week 8 (MMRM) in the SDS family life/home responsibilities sub-scale score — FAS

					Treatment Group vs. Placebo		
		Baseline	Mean (SE)	LS Mean	---Difference in LS Mean Change---		
Treatment	n	Mean (SE)	at end-point	Change (SE)	Mean (SE)	95% CI	p-value
Agomelatine 0.5 mg (N = 185)	160	7.1 (0.15)	4.8 (0.19)	2.24 (0.184)	0.24 (0.250)	(-0.25, 0.74)	0.3304
Agomelatine 1 mg (N = 192)	157	7.3 (0.15)	4.8 (0.19)	2.41 (0.185)	0.41 (0.251)	(-0.08, 0.91)	0.0987
Placebo (N = 198)	169	7.4 (0.14)	5.2 (0.18)	1.99 (0.178)			

SDS is the Sheehan Disability Scale.
* Indicating statistical significance at the 0.05 level.
N is the number of FAS patients; n is the number of patients with a value at both baseline and at Week 8. Baseline is the last pre-randomization value.
Least square means, confidence intervals and p-values are derived from MMRM model with treatment group, pooled center, baseline SDS family life/home sub-scale score, visit (in weeks) and treatment*visit interaction as explanatory variables.
A higher SDS score indicates greater disability.
A positive treatment difference indicates greater improvement in Agomelatine group as compared to placebo.
The Kenward-Roger approximation is used to estimate denominator degrees of freedom.

Safety Results

Adverse Events by System Organ Class

Adverse events by primary system organ class and treatment — Safety set

Primary system organ class	Agomelatine 0.5 mg N = 185 n (%)	Agomelatine 1 mg N = 192 n (%)	All Agomelatine N = 377 n (%)	Placebo N = 199 n (%)
Patients with any AE(s)	114 (61.6)	106 (55.2)	220 (58.4)	102 (51.3)
Nervous system disorders	40 (21.6)	37 (19.3)	77 (20.4)	40 (20.1)
Gastrointestinal disorders	36 (19.5)	38 (19.8)	74 (19.6)	26 (13.1)
Infections & infestations	32 (17.3)	19 (9.9)	51 (13.5)	32 (16.1)
Psychiatric disorders	19 (10.3)	21 (10.9)	40 (10.6)	14 (7.0)
General disorders & administration site conditions	15 (8.1)	12 (6.3)	27 (7.2)	9 (4.5)
Musculoskeletal & connective tissue disorders	16 (8.6)	10 (5.2)	26 (6.9)	14 (7.0)
Respiratory, thoracic & mediastinal disorders	8 (4.3)	8 (4.2)	16 (4.2)	6 (3.0)
Skin and subcutaneous tissue disorders	10 (5.4)	6 (3.1)	16 (4.2)	6 (3.0)
Injury, poisoning & procedural complications	5 (2.7)	7 (3.6)	12 (3.2)	6 (3.0)
Investigations	7 (3.8)	3 (1.6)	10 (2.7)	3 (1.5)
Metabolism & nutrition disorders	4 (2.2)	5 (2.6)	9 (2.4)	2 (1.0)
Eye disorders	5 (2.7)	2 (1.0)	7 (1.9)	2 (1.0)
Cardiac disorders	2 (1.1)	3 (1.6)	5 (1.3)	2 (1.0)
Ear & labyrinth disorders	1 (0.5)	4 (2.1)	5 (1.3)	0
Renal & urinary disorders	2 (1.1)	3 (1.6)	5 (1.3)	7 (3.5)
Reproductive system & breast disorders	2 (1.1)	1 (0.5)	3 (0.8)	2 (1.0)
Vascular disorders	2 (1.1)	1 (0.5)	3 (0.8)	3 (1.5)
Blood & lymphatic system disorders	2 (1.1)	0	2 (0.5)	0
Endocrine disorders	1 (0.5)	0	1 (0.3)	0
Immune system disorders	1 (0.5)	0	1 (0.3)	1 (0.5)
Neoplasms benign, malignant & unspecified (incl cysts and polyps)	1 (0.5)	0	1 (0.3)	1 (0.5)
Hepatobiliary disorders	0	0	0	1 (0.5)

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

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

Frequent adverse events (at least 2% in any group) by preferred term and treatment — Safety set

Preferred term	Agomelatine 0.5 mg N = 185 n (%)	Agomelatine 1 mg N = 192 n (%)	All Agomelatine N = 377 n (%)	Placebo N = 199 n (%)
Patients with any AE(s)	114 (61.6)	106 (55.2)	220 (58.4)	102 (51.3)
Preferred term				
Headache	21 (11.4)	23 (12.0)	44 (11.7)	22 (11.1)
Upper respiratory tract infection	20 (10.8)	5 (2.6)	25 (6.6)	11 (5.5)
Nausea	10 (5.4)	9 (4.7)	19 (5.0)	12 (6.0)
Dry mouth	8 (4.3)	10 (5.2)	18 (4.8)	5 (2.5)
Diarrhea	10 (5.4)	7 (3.6)	17 (4.5)	6 (3.0)
Somnolence	10 (5.4)	6 (3.1)	16 (4.2)	10 (5.0)
Dizziness	8 (4.3)	6 (3.1)	14 (3.7)	9 (4.5)
Anxiety	6 (3.2)	3 (1.6)	9 (2.4)	1 (0.5)
Nasopharyngitis	5 (2.7)	4 (2.1)	9 (2.4)	6 (3.0)
Sedation	4 (2.2)	5 (2.6)	9 (2.4)	2 (1.0)
Fatigue	5 (2.7)	2 (1.0)	7 (1.9)	3 (1.5)
Insomnia	4 (2.2)	2 (1.0)	6 (1.6)	5 (2.5)
Irritability	2 (1.1)	4 (2.1)	6 (1.6)	1 (0.5)
Myalgia	4 (2.2)	2 (1.0)	6 (1.6)	0
Abnormal dreams	3 (1.6)	2 (1.0)	5 (1.3)	4 (2.0)
Arthralgia	4 (2.2)	1 (0.5)	5 (1.3)	1 (0.5)
Depression	0	5 (2.6)	5 (1.3)	0
Nightmare	0	5 (2.6)	5 (1.3)	0
Suicidal ideation	1 (0.5)	4 (2.1)	5 (1.3)	2 (1.0)
Back pain	1 (0.5)	1 (0.5)	2 (0.5)	4 (2.0)

Preferred terms (PT) 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 and Deaths

Deaths, other serious or adverse events leading to discontinuation, by treatment – Safety set

	Agomelatine 0.5 mg N = 185 n (%)	Agomelatine 1 mg N = 192 n (%)	All Agomelatine N = 377 n (%)	Placebo N = 199 n (%)
Deaths	0	0	0	0
SAEs	2 (1.1)	5 (2.6)	7 (1.9)	2 (1.0)
Discontinuations due to AEs	6 (3.2)	9 (4.7)	15 (4.0)	2 (1.0)

SAEs = Serious adverse events, AEs = Adverse events

Serious adverse events regardless of study drug relationship, by primary system organ class, preferred term and treatment — Safety set

Primary system organ class Preferred term	Agomelatine 0.5 mg N = 185 n (%)	Agomelatine 1 mg N = 192 n (%)	All Agomelatine N = 377 n (%)	Placebo N = 199 n (%)
Patients with any SAE - Total	2 (1.1)	5 (2.6)	7 (1.9)	2 (1.0)
Gastrointestinal disorders - Total	0	1 (0.5)	1 (0.3)	0
Dyspepsia	0	1 (0.5)	1 (0.3)	0
Injury, poisoning & procedural complications - Total	0	0	0	1 (0.5)
Alcohol poisoning	0	0	0	1 (0.5)
Musculoskeletal & connective tissue disorders - Total	0	0	0	1 (0.5)
Osteoarthritis	0	0	0	1 (0.5)
Nervous system disorders - Total	1 (0.5)	0	1 (0.3)	0
Syncope	1 (0.5)	0	1 (0.3)	0
Psychiatric disorders - Total	1 (0.5)	3 (1.6)	4 (1.1)	0
Suicidal ideation	1 (0.5)	2 (1.0)	3 (0.8)	0
Anxiety	0	1 (0.5)	1 (0.3)	0
Depression	0	1 (0.5)	1 (0.3)	0
Suicide attempt	0	1 (0.5)	1 (0.3)	0
Respiratory, thoracic & mediastinal disorders - Total	0	1 (0.5)	1 (0.3)	0
Dyspnea	0	1 (0.5)	1 (0.3)	0

Primary system organ classes (SOC) are presented alphabetically; preferred terms are sorted within primary system organ class 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. A patient with multiple AEs within a primary SOC was counted only once in the total row.

Overall assessment of suicidality: Columbia-Suicide Severity Rating Scale (C-SSRS) by treatment (Double-blind Treatment Phase) — Safety set

Suicidality Category	Agomelatine 0.5 mg N = 185 n (%)	Agomelatine 1 mg N = 192 n (%)	All Agomelatine N = 377 n (%)	Placebo N = 199 n (%)
C-CASA code/category				
1 Completed suicide	0	0	0	0
2 Suicide attempt	1 (0.5)	1 (0.5)	2 (0.5)	0
3 Preparatory actions toward imminent Suicidal behavior	4 (2.2)	1 (0.5)	5 (1.3)	3 (1.5)
4 Suicidal Ideation	57 (30.8)	59 (30.7)	116 (30.8)	68 (34.2)
7 Self-injurious behaviors without Suicidal intent	3 (1.6)	2 (1.0)	5 (1.3)	1 (0.5)
Suicidal behavior	4 (2.2)	2 (1.0)	6 (1.6)	3 (1.5)
Suicidality	57 (30.8)	61 (31.8)	118 (31.3)	69 (34.7)

Suicidal behavior is defined as response ‘Yes’ for actual, interrupted, or aborted suicidal attempts or any preparatory actions toward imminent suicidal behavior.
Suicidality is defined as response “yes” for any suicidal behavior and/or response “yes” for any ideation at least once during the study.

Other Relevant Findings

There were no clinically significant findings on the assessment of laboratory values (including measures of liver function), suicidality, vital signs and ECGs. Three patients had newly occurring clinically notable LFT elevations (alanine aminotransferase, aspartate aminotransferase [AST], or gamma-glutamyl transferase [GGT]); one patient in the agomelatine 0.5 mg group (transient AST elevation) and two patients in the placebo group (GGT elevation each). None of these patients had SAEs or AEs leading to permanent discontinuation of study drug.

Date of Clinical Trial Report

21-Mar-2012

Date Inclusion on Novartis Clinical Trial Results Database

21 June 2012

Date of Latest Update