Sponsor

Novartis

Generic Drug Name

Agomelatine

Therapeutic Area of Trial

Major Depressive Disorder (MDD)

Approved Indication

Investigational

Protocol Number

CAGO178C2301

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

21-May-2010 to 21-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 [ratio 1:1:1]. 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

47 investigative centers in the United States.

Publication

None

Outcome Measures

Change from baseline to Week 8 (last observation carried forward, LOCF) in the total score of the 17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$).

Secondary outcome measure(s)

Key secondary outcome measure

Patients' improvement 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 $HAM\text{-}D_{17}$ 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 Week 8 (LOCF) on the total score of the 17-item clinician-rated $HAM\text{-}D_{17}$.

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 $HAM\text{-}D_{17}$ 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 = 200) n (%)	Agomelatine 1 mg (N = 191) n (%)	All Agomelatine (N = 391) n (%)	Placebo (N = 195) n (%)	All (N = 586) n (%)
Completed	168 (84.0)	162 (84.8)	330 (84.4)	166 (85.1)	496 (84.6)
Discontinued	32 (16.0)	29 (15.2)	61 (15.6)	29 (14.9)	90 (15.4)
Adverse event(s)	5 (2.5)	9 (4.7)	14 (3.6)	6 (3.1)	20 (3.4)
Abnormal laboratory value(s)	0	0	0	0	0
Abnormal test procedure result(s)	0	0	0	0	0
Unsatisfactory therapeutic effect	4 (2.0)	3 (1.6)	7 (1.8)	1 (0.5)	8 (1.4)
Subject's condition no longer requires study drug	0	0	0	0	0
Subject withdrew consent	7 (3.5)	7 (3.7)	14 (3.6)	8 (4.1)	22 (3.8)
Lost to follow-up	11 (5.5)	7 (3.7)	18 (4.6)	11 (5.6)	29 (4.9)
Administrative problem	0	1 (0.5)	1 (0.3)	1 (0.5)	2 (0.3)
Death	0	0	0	0	0
Protocol deviation	5 (2.5)	2 (1.0)	7 (1.8)	2 (1.0)	9 (1.5)

Baseline Characteristics

Demographics, by treatment — All randomized patients

Demographic Variable	Agomelatine 0.5 mg N = 200 n (%)	Agomelatine 1 mg N = 191 n (%)	All Agomelatine N = 391 n (%)	Placebo N = 195 n (%)	All N = 586 n (%)
Baseline Age (Years)					
< 45	109 (54.5)	98 (51.3)	207 (52.9)	104 (53.3)	311 (53.1)
45 - < 65	87 (43.5)	87 (45.5)	174 (44.5)	88 (45.1)	262 (44.7)
≥ 65	4 (2.0)	6 (3.1)	10 (2.6)	3 (1.5)	13 (2.2)
Age (Years)					
n	200	191	391	195	586
Mean	42.4	43.2	42.8	42.1	42.6
SD	12.12	12.93	12.51	12.35	12.45
Median	43.5	44.0	44.0	42.0	43.0
Min	18	18	18	18	18
Max	70	70	70	70	70
Sex					
Male	82 (41.0)	64 (33.5)	146 (37.3)	75 (38.5)	221 (37.7)
Female	118 (59.0)	127 (66.5)	245 (62.7)	120 (61.5)	365 (62.3)
Race					
Caucasian	132 (66.0)	130 (68.1)	262 (67.0)	133 (68.2)	395 (67.4)
Black	59 (29.5)	45 (23.6)	104 (26.6)	47 (24.1)	151 (25.8)
Asian	4 (2.0)	4 (2.1)	8 (2.0)	3 (1.5)	11 (1.9)
Native American	0	3 (1.6)	3 (0.8)	0	3 (0.5)

Pacific islander	0		0		0		1	(0.5)	1	(0.2)
Other	5	(2.5)	9	(4.7)	14	(3.6)	11	(5.6)	25	(4.3)

Outcome Measures

Primary Outcome Result(s)

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

		Baseline	Endpoint	Change LS	Treatment Group vs. Placebo ---Difference in LS Mean Change---			
Treatment	**n**	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**	**95% CI**	**p-value**	**Adj. p-value**
Agomelatine 0.5 mg (N = 197)	168	26.3 (0.23)	13.8 (0.57)	12.50 (0.567)	1.25 (0.798)	(-0.31, 2.82)	0.1165	0.2016
Agomelatine 1 mg (N = 187)	162	25.6 (0.24)	14.0 (0.60)	11.91 (0.577)	0.66 (0.807)	(-0.93, 2.25)	0.4134	0.4134
Placebo (N = 191)	165	26.2 (0.23)	15.2 (0.61)	11.25 (0.574)				

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-D17 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.
Adj. 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— FAS

	Agomelatine 0.5 mg N = 197		Agomelatine 1 mg N = 187		Placebo N = 191	
Score	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**
1 - Very much improved	197	43 (21.8)	187	31 (16.6)	191	31 (16.2)
2 - Much improved	197	57 (28.9)	187	70 (37.4)	191	57 (29.8)
3 - Minimally improved	197	48 (24.4)	187	51 (27.3)	191	56 (29.3)
4 - No change	197	46 (23.4)	187	32 (17.1)	191	43 (22.5)
5 - Minimally worse	197	3 (1.5)	187	3 (1.6)	191	3 (1.6)
6 - Much worse	197	0	187	0	191	1 (0.5)
7 - Very much worse	197	0	187	0	191	0
p-value	0.3362		0.1288			
Adj. p-value	0.3362		0.2576			

* 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 (CMH) 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 (HAM-D_{17}) at Week 8 (LOCF) — FAS

		Clinical response	Odds ratio	95% CI for odds ratio	p-value
Treatment	**Total**	**n (%)**			
Agomelatine 0.5 mg (N = 197)	197	90 (45.7)	1.44	(0.94, 2.22)	0.0965
Agomelatine 1 mg (N = 187)	187	85 (45.5)	1.38	(0.89, 2.14)	0.1532
Placebo (N = 191)	191	75 (39.3)			

* 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. Baseline is the last pre-randomization value.
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

		Clinical Improvement	Odds ratio	95% CI for odds ratio	p-value
Treatment	**Total**	**n (%)**			
Agomelatine 0.5 mg (N = 197)	197	100 (50.8)	1.26	(0.82, 1.92)	0.2897
Agomelatine 1 mg (N = 187)	187	101 (54.0)	1.42	(0.92, 2.18)	0.1139
Placebo (N = 191)	191	88 (46.1)			

* 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 (HAM-D_{17}) at Week 8 (LOCF) — FAS

Treatment	Total	Clinical remission n (%)	Odds ratio	95% CI for odds ratio	p-value
Agomelatine 0.5 mg (N = 197)	197	39 (19.8)	1.11	(0.66, 1.85)	0.6912
Agomelatine 1 mg (N = 187)	187	39 (20.9)	1.15	(0.69, 1.93)	0.5946
Placebo (N = 191)	191	37 (19.4)			

* 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 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 = 197)	168	62.33 (1.610)	-0.14 (2.251)	(-4.56, 4.28)	0.9501
Agomelatine 1 mg (N = 187)	161	59.36 (1.639)	-3.11 (2.281)	(-7.59, 1.37)	0.1729
Placebo (N = 191)	165	62.47 (1.630)			

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 = 197)	168	60.51 (1.354)	1.36 (1.889)	(-2.36, 5.07)	0.4735
Agomelatine 1 mg (N = 187)	161	59.63 (1.377)	0.47 (1.914)	(-3.29, 4.23)	0.8048
Placebo (N = 191)	165	59.16 (1.369)			

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 = 197)	168	58.90 (1.586)	-0.67 (2.219)	(-5.03, 3.69)	0.7624
Agomelatine 1 mg (N = 187)	161	55.35 (1.616)	-4.22 (2.249)	(-8.64, 0.20)	0.0610
Placebo (N = 191)	165	59.57 (1.606)			

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 = 197)	168	56.47 (1.657)	0.53 (2.319)	(-4.02, 5.09)	0.8184
Agomelatine 1 mg (N = 187)	161	53.93 (1.687)	-2.00 (2.350)	(-6.62, 2.61)	0.3941
Placebo (N = 191)	165	55.93 (1.680)			

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
(N = 197)	133	21.9 (0.39)	13.2 (0.65)	8.10 (0.623)	-0.12 (0.830)	(-1.75, 1.51)	0.8889
(N = 187)	132	21.7 (0.42)	13.8 (0.59)	7.92 (0.626)	-0.30 (0.835)	(-1.94, 1.35)	0.7224
(N = 191)	141	21.5 (0.38)	13.1 (0.58)	8.21 (0.604)			

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 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
(N = 197)	133	7.0 (0.17)	4.1 (0.23)	2.61 (0.216)	0.17 (0.287)	(-0.39, 0.74)	0.5432
(N = 187)	132	6.8 (0.18)	4.3 (0.20)	2.46 (0.216)	0.03 (0.288)	(-0.53, 0.60)	0.9057
(N = 191)	141	6.8 (0.16)	4.3 (0.21)	2.43 (0.209)			

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 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
(N = 197)	171	7.6 (0.14)	4.6 (0.20)	2.85 (0.194)	-0.00 (0.272)	(-0.54, 0.53)	0.9866
(N = 187)	166	7.7 (0.13)	4.8 (0.20)	2.85 (0.198)	-0.00 (0.275)	(-0.54, 0.54)	0.9880
(N = 191)	167	7.5 (0.13)	4.6 (0.19)	2.86 (0.198)			

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 endpoint	Change (SE)	Mean (SE)	95% CI	p-value
Agomelatine 0.5 mg (N = 197)	171	7.4 (0.14)	4.6 (0.20)	2.73 (0.196)	-0.15 (0.274)	(-0.68, 0.39)	0.5917
Agomelatine 1 mg (N = 187)	166	7.3 (0.13)	4.8 (0.20)	2.62 (0.199)	-0.26 (0.276)	(-0.81, 0.28)	0.3416
Placebo (N = 191)	167	7.4 (0.14)	4.5 (0.19)	2.88 (0.199)			

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 = 196 n (%)	Agomelatine 1 mg N = 188 n (%)	All Agomelatine N = 384 n (%)	Placebo N = 191 n (%)
Patients with any AE(s)	104 (53.1)	101 (53.7)	205 (53.4)	106 (55.5)
Gastrointestinal disorders	31 (15.8)	43 (22.9)	74 (19.3)	41 (21.5)
Nervous system disorders	32 (16.3)	35 (18.6)	67 (17.4)	42 (22.0)
Infections & infestations	25 (12.8)	27 (14.4)	52 (13.5)	33 (17.3)
Psychiatric disorders	20 (10.2)	19 (10.1)	39 (10.2)	25 (13.1)
General disorders & administration site conditions	8 (4.1)	9 (4.8)	17 (4.4)	14 (7.3)
Respiratory, thoracic & mediastinal disorders	9 (4.6)	5 (2.7)	14 (3.6)	12 (6.3)
Musculoskeletal & connective tissue disorders	7 (3.6)	6 (3.2)	13 (3.4)	14 (7.3)
Investigations	6 (3.1)	4 (2.1)	10 (2.6)	7 (3.7)
Renal & urinary disorders	5 (2.6)	5 (2.7)	10 (2.6)	3 (1.6)
Injury, poisoning & procedural complications	6 (3.1)	3 (1.6)	9 (2.3)	4 (2.1)
Ear & labyrinth disorders	3 (1.5)	2 (1.1)	5 (1.3)	0
Immune system disorders	4 (2.0)	1 (0.5)	5 (1.3)	0
Metabolism & nutrition disorders	2 (1.0)	3 (1.6)	5 (1.3)	1 (0.5)
Vascular disorders	2 (1.0)	3 (1.6)	5 (1.3)	2 (1.0)
Reproductive system & breast disorders	2 (1.0)	2 (1.1)	4 (1.0)	3 (1.6)
Skin & subcutaneous tissue disorders	3 (1.5)	1 (0.5)	4 (1.0)	9 (4.7)
Blood & lymphatic system disorders	1 (0.5)	1 (0.5)	2 (0.5)	2 (1.0)
Cardiac disorders	1 (0.5)	1 (0.5)	2 (0.5)	3 (1.6)
Endocrine disorders	1 (0.5)	1 (0.5)	2 (0.5)	0
Eye disorders	1 (0.5)	1 (0.5)	2 (0.5)	2 (1.0)
Pregnancy, puerperium & perinatal conditions	1 (0.5)	1 (0.5)	2 (0.5)	0
Surgical & medical procedures	0	1 (0.5)	1 (0.3)	2 (1.0)

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 in the total row.

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 = 196 n (%)	Agomelatine 1 mg N = 188 n (%)	All Agomelatine N = 384 n (%)	Placebo N = 191 n (%)
Patients with any AE(s)	104 (53.1)	101 (53.7)	205 (53.4)	106 (55.5)
Preferred term				
Headache	13 (6.6)	15 (8.0)	28 (7.3)	25 (13.1)
Dry mouth	12 (6.1)	9 (4.8)	21 (5.5)	9 (4.7)
Upper respiratory tract infection	9 (4.6)	11 (5.9)	20 (5.2)	4 (2.1)
Somnolence	11 (5.6)	7 (3.7)	18 (4.7)	6 (3.1)
Diarrhea	4 (2.0)	10 (5.3)	14 (3.6)	10 (5.2)
Abnormal dreams	8 (4.1)	4 (2.1)	12 (3.1)	6 (3.1)
Nausea	6 (3.1)	6 (3.2)	12 (3.1)	7 (3.7)
Insomnia	2 (1.0)	9 (4.8)	11 (2.9)	6 (3.1)
Vomiting	4 (2.0)	6 (3.2)	10 (2.6)	4 (2.1)
Dysgeusia	3 (1.5)	6 (3.2)	9 (2.3)	2 (1.0)
Anxiety	5 (2.6)	3 (1.6)	8 (2.1)	2 (1.0)
Fatigue	2 (1.0)	5 (2.7)	7 (1.8)	8 (4.2)
Influenza	5 (2.6)	2 (1.1)	7 (1.8)	0
Constipation	4 (2.0)	2 (1.1)	6 (1.6)	3 (1.6)
Depression	2 (1.0)	4 (2.1)	6 (1.6)	2 (1.0)
Dyspepsia	1 (0.5)	5 (2.7)	6 (1.6)	3 (1.6)
Nasopharyngitis	1 (0.5)	5 (2.7)	6 (1.6)	8 (4.2)
Sinusitis	1 (0.5)	5 (2.7)	6 (1.6)	6 (3.1)
Dizziness	1 (0.5)	4 (2.1)	5 (1.3)	4 (2.1)
Back pain	0	3 (1.6)	3 (0.8)	4 (2.1)

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 = 196 n (%)	Agomelatine 1 mg N = 188 n (%)	All Agomelatine N = 384 n (%)	Placebo N = 191 n (%)
Deaths	0	0	0	0
SAEs	4 (2.0)	2 (1.1)	6 (1.6)	3 (1.6)
Discontinuations due to AEs	5 (2.6)	10 (5.3)	15 (3.9)	6 (3.1)

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 = 196 n (%)	Agomelatine 1 mg N = 188 n (%)	All Agomelatine N = 384 n (%)	Placebo N = 191 n (%)
Patients with any SAE - Total	4 (2.0)	2 (1.1)	6 (1.6)	3 (1.6)
Gastrointestinal disorders - Total	1 (0.5)	0	1 (0.3)	0
Gastric ulcer	1 (0.5)	0	1 (0.3)	0
Infections & infestations - Total	0	0	0	1 (0.5)
Pneumonia	0	0	0	1 (0.5)
Investigations - Total	1 (0.5)	0	1 (0.3)	1 (0.5)
Aspartate aminotransferase increased	1 (0.5)	0	1 (0.3)	0
Hepatic enzyme increased	0	0	0	1 (0.5)
Metabolism & nutrition disorders - Total	1 (0.5)	0	1 (0.3)	0
Hypoglycemia	1 (0.5)	0	1 (0.3)	0
Nervous system disorders - Total	1 (0.5)	1 (0.5)	2 (0.5)	0
Cervicobrachial syndrome	0	1 (0.5)	1 (0.3)	0
Transient ischemic attack	1 (0.5)	0	1 (0.3)	0
Pregnancy, puerperium & perinatal conditions - Total	1 (0.5)	1 (0.5)	2 (0.5)	0
Abortion	1 (0.5)	0	1 (0.3)	0
Abortion spontaneous	0	1 (0.5)	1 (0.3)	0
Psychiatric disorders - Total	0	0	0	1 (0.5)
Suicide attempt	0	0	0	1 (0.5)

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 = 196 n (%)	Agomelatine 1 mg N = 188 n (%)	All Agomelatine N = 384 n (%)	Placebo N = 191 n (%)
C-CASA code/category				
1 Completed suicide	0	0	0	0
2 Suicide attempt	0	0	0	1 (0.5)
3 Preparatory actions toward imminent Suicidal behavior	0	0	0	0
4 Suicidal Ideation	53 (27.0)	53 (28.2)	106 (27.6)	57 (29.8)
7 Self-injurious behaviors without Suicidal intent	1 (0.5)	3 (1.6)	4 (1.0)	2 (1.0)
Suicidal behavior	0	0	0	1 (0.5)
Suicidality	53 (27.0)	53 (28.2)	106 (27.6)	57 (29.8)

Suicidal behavior is a 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 few clinically significant findings on the assessment of laboratory values (including measures of liver function), suicidality, vital signs and ECGs.

In total, 13 patients had elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transferase (GGT) (≥ 3 x ULN each) during the double-blind treatment phase of the study (3 patients in agomelatine 0.5 mg, 5 patients in agomelatine 1 mg and 5 patients in placebo). Two patients had AST elevations (one in each agomelatine group), 5 patients had ALT elevations (one patient in each agomelatine 0.5 mg and placebo, and three patients in agomelatine 1 mg), 4 patients had GGT elevations (one patient in each agomelatine group, and 2 patients in the placebo group), and 2 patients had both, ALT and AST elevations (placebo group). With the exception of one patient with GGT elevation (agomelatine 0.5 mg group), all elevations were transient.

Date of Clinical Trial Report

03 July 2012

Date Inclusion on Novartis Clinical Trial Results Database

19 July 2012

Date of Latest Update