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Full Novartis CTRD Results Template

Sponsor Novartis
Generic Drug Name Agomelatine
Therapeutic Area of Trial Major Depressive Disorder (MDD)
Approved Indication Investigational
Protocol Number CAGO178C2399
Title A 52-week, multi-center, open-label study of the safety and tolerability of agomelatine sublingual tablets in patients with Major Depressive Disorder (MDD).
Phase of Development Phase III
Study Start/End Dates 22-Jun-2010 (first patient enrolled) to 02-Nov-2011 (last patient completed) This ongoing 52-week long-term safety study was terminated early based upon the finding of no statistical separation between agomelatine and placebo on the primary efficacy variable in studies CAGO178C2301 and CAGO178C2302. Investigators were instructed to schedule final termination visits for patients still continuing on study at the time of notification of early study termination. Patients who had completed at least a 52-week period in the study were considered completed patients. All other patients were prematurely discontinued for administrative reasons. Follow-up of any SAEs, pregnancies, or patients who experienced elevated liver enzyme values was to be conducted as per study protocol.
Study Design/Methodology This 52-week open-label study was an extension of completed Novartis AGO178C core double-blind studies (Cohort I) and also enrolled de-novo patients (Cohort II). Cohort II was required to have a sufficient number of patients to meet the ICH requirements for long-term exposure.

Cohort I: Patients who completed a Novartis AGO178C double-blind study in MDD patients were eligible to enter the 52-week open-label study. Patients who prematurely discontinued from a double-blind study for any reason were not eligible to participate in the open-label study. The baseline visit of this study was to be performed between 3 to a maximum of 5 days after completion of a double-blind study. These patients received doses of either 0.5 or 1 mg/day according to investigator judgment to optimize efficacy and tolerability. Cohort II: Patients with MDD who had not been previously exposed to agomelatine were also eligible to participate in the 52-week open-label study. These patients received a fixed-dose of 1 mg/day as de-novo patients, but could be down-titrated to 0.5 mg if 1 mg dose was not tolerated.
Centers 99 investigative centers in the United States
Publication None

Outcome measures

Primary outcome measures(s)

Evaluate the safety and tolerability of agomelatine administered as sublingual tablets in patients with MDD as measured by reports of adverse events and serious adverse events, changes in laboratory values, electrocardiograms (ECGs), physical examination, vital signs and suicidality assessments during the 52-week treatment period.

Secondary outcome measures(s)

- Evaluate the antidepressant effect of long-term treatment with agomelatine from baseline of open-label study (Visit 102) to Weeks 6, 8, 12, 28, 36, 52 or premature patient withdrawal (PPW), as measured by the change from baseline (Visit 102) on the HAM-D_{17} total score.
- Evaluate the proportion of patients demonstrating clinical improvement after long-term treatment with agomelatine at Weeks 6, 8, 12, 28, 36, 52 or PPW, whereby improvement was defined by a (Clinical Global Impression - Improvement) CGI-I score of 1 or 2.
- Evaluate the overall illness severity after long-term treatment with agomelatine, at Week 52 or PPW on CGI-S (Clinical Global Impression – Severity), a 7-point scale. A rating of 1 was equivalent to "normal, not ill", and a rating of 7 was equivalent to "very severely ill".
- Assess the effects of agomelatine on the patient's functioning in daily life, as measured by the change from baseline (Visit 102) to Week 52 or PPW on the total score of the Sheehan Disability Scale (SDS).

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.

During the 52-week treatment period, the daily agomelatine tablet was taken sublingually at bedtime, preferably before 11 p.m. The patient placed one tablet of agomelatine under his/her tongue and let it dissolve and disappear completely without swallowing. A drink of water was allowed, but only after complete dissolution and disappearance of the tablet. The patient was informed that the tablet has a distinctive taste.

Statistical Methods

The primary safety assessment was based mainly on the frequency of adverse events and on the number of laboratory values that fell outside of pre-determined ranges. Other safety data included vital signs, ECG and suicidality assessments during the open-label treatment period.

The number and percentage of patients reporting AEs during the open-label treatment period were summarized, by cohort and maximum dose taken.

Tables were summarized by cohort and treatment. Summary data for Cohort I was presented by core study double-blind treatment taken for efficacy analysis and by maximum dose taken for safety analysis.

All safety and efficacy analyses were performed on the safety analysis set.

Study Population: Inclusion/Exclusion Criteria and Demographics

Main inclusion criteria:

Cohort I:

- Documentation of completion of a Novartis AGO178C double-blind study in MDD patients;
- Male and female adults, 18 through 71 years of age, inclusive (i.e., same age range as for double-blind study, but with upper age limit increased by 1 year to accommodate patients whose age increased during the double-blind study);

Cohort II:

- Male and female adults, 18 through 70 years of age, inclusive;
- Diagnosis of Major Depressive Disorder, single or recurrent episode, according to Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (DSM-IV) criteria;
- Current episode $\geq$ 4 weeks;
- 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:

Cohort I:

- Concomitant use of fluvoxamine;
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (>5 mIU/mL).
- Any significant medical condition that emerged during the Double-blind Phase of a previous study, which may interfere with study participation and/or study assessments as assessed by the investigator;

Cohort II:

- History of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, eating disorder (current or past one year), obsessive-compulsive disorder;
- Dysthymia (DSM code 300.40), depressive episode of mild intensity;
- Any other current Axis I disorder other than major depressive disorder which is the focus of treatment;
- Improvement of more than 20% in HAM-D_{17} score at Baseline (clinician-rated);
- Substance or alcohol abuse within the last six (6) months, or dependence within the last twelve (12) months;
- Female patients who are not using effective contraception.

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Participant Flow

Subject disposition by cohort and maximum dose – Treated patients

Disposition Reason	Cohort I Agomelatine 0.5 mg N = 87 n (%)	Cohort I Agomelatine 1 mg N = 492 n (%)	Cohort I Total N = 579 n (%)	Cohort II Agomelatine 1 mg N = 291 n (%)	Overall Total N = 870 n (%)
Completed	1 (1.1)	26 (5.3)	27 (4.7)	146 (50.2)	173 (19.9)
Discontinued	86 (98.9)	466 (94.7)	552 (95.3)	145 (49.8)	697 (80.1)
Adverse event(s)	5 (5.7)	14 (2.8)	19 (3.3)	22 (7.6)	41 (4.7)
Abnormal laboratory value(s)	0	0	0	0	0
Abnormal test procedure result(s)	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Unsatisfactory therapeutic effect	0	41 (8.3)	41 (7.1)	27 (9.3)	68 (7.8)
Subject's condition no longer requires study drug	1 (1.1)	2 (0.4)	3 (0.5)	0	3 (0.3)
Subject withdrew consent	14 (16.1)	59 (12.0)	73 (12.6)	43 (14.8)	116 (13.3)
Lost to follow-up	23 (26.4)	44 (8.9)	67 (11.6)	36 (12.4)	103 (11.8)
Administrative problem	39 (44.8)	294 (59.8)	333 (57.5)	8 (2.7)	341 (39.2)
Death	0	0	0	1 (0.3)	1 (0.1)
Protocol deviation	3 (3.4)	12 (2.4)	15 (2.6)	8 (2.7)	23 (2.6)

Baseline Characteristics

Demographics by cohort and maximum dose – Treated patients

Demographic Variable	Cohort I Agomelatine 0.5 mg N = 87 n (%)	Cohort I Agomelatine 1 mg N = 492 n (%)	Cohort I Total N = 579 n (%)	Cohort II Agomelatine 1 mg N = 291 n (%)	Overall Total N = 870 n (%)
Baseline age (Years)					
<45	37 (42.5)	273 (55.5)	310 (53.5)	122 (41.9)	432 (49.7)
45 - <65	50 (57.5)	205 (41.7)	255 (44.0)	156 (53.6)	411 (47.2)
>=65	0	14 (2.8)	14 (2.4)	13 (4.5)	27 (3.1)
Age (Years)					
n	87	492	579	291	870
Mean	44.9	42.1	42.6	45.5	43.5
Min	20	18	18	19	18
Median	46.0	43.0	43.0	47.0	45.0
Max	64	70	70	70	70
SD	11.24	12.49	12.34	12.51	12.47
Sex					
Female	57 (65.5)	304 (61.8)	361 (62.3)	192 (66.0)	553 (63.6)
Male	30 (34.5)	188 (38.2)	218 (37.7)	99 (34.0)	317 (36.4)
Race					
Black	32 (36.8)	114 (23.2)	146 (25.2)	38 (13.1)	184 (21.1)
Asian	1 (1.1)	13 (2.6)	14 (2.4)	10 (3.4)	24 (2.8)

Caucasian	51 (58.6)	339 (68.9)	390 (67.4)	230 (79.0)	620 (71.3)
Native American	0	1 (0.2)	1 (0.2)	2 (0.7)	3 (0.3)
Pacific islander	0	2 (0.4)	2 (0.3)	0	2 (0.2)

Outcome measures

Primary Outcome Result(s)

This was primarily a safety study. Safety results are reported in the safety section.

Secondary Outcome Result(s)

Change from baseline in the HAM-D17 total score by visit, double-blind treatment and cohort – Safety set

	Cohort I				Cohort II	
Visit	DB Ago 0.5 mg N=190 Mean (SE)	DB Ago 1 mg N=181 Mean (SE)	DB Placebo N=197 Mean (SE)	Total N=568 Mean (SE)	Ago 1 mg N=287 Mean (SE)	Overall Total N=855 Mean (SE)
Baseline (n=855)	15.9 (0.52)	16.9 (0.52)	16.6 (0.52)	16.5 (0.30)	25.0 (0.15)	19.3 (0.25)
Week 6 (n=764)	11.1 (0.53)	12.5 (0.54)	11.9 (0.50)	11.8 (0.30)	14.2 (0.38)	12.6 (0.24)
Change from Baseline	4.4 (0.45)	4.5 (0.40)	4.5 (0.43)	4.5 (0.25)	10.8 (0.40)	6.6 (0.24)
Week 8 (n=733)	10.2 (0.48)	11.4 (0.54)	10.9 (0.51)	10.8 (0.30)	12.5 (0.40)	11.4 (0.24)
Change from Baseline	5.5 (0.44)	5.8 (0.41)	5.6 (0.45)	5.6 (0.25)	12.5 (0.43)	7.9 (0.25)
Week 12 (n=649)	9.4 (0.53)	10.8 (0.55)	10.3 (0.57)	10.2 (0.32)	10.9 (0.41)	10.4 (0.25)
Change from Baseline	6.1 (0.58)	6.6 (0.47)	6.6 (0.56)	6.4 (0.31)	14.1 (0.44)	9.2 (0.29)
Week 28 (n=368)	7.0 (0.68)	12.0 (0.82)	8.6 (0.72)	9.2 (0.45)	9.2 (0.42)	9.2 (0.31)
Change from Baseline	7.1 (0.71)	6.5 (0.73)	9.2 (0.71)	7.6 (0.42)	15.7 (0.47)	11.6 (0.38)
Week 36 (n=302)	6.0 (0.67)	10.1 (0.98)	8.6 (0.88)	8.1 (0.50)	9.0 (0.47)	8.6 (0.34)
Change from Baseline	8.0 (0.98)	8.1 (0.94)	9.6 (0.86)	8.6 (0.54)	16.0 (0.51)	12.8 (0.43)
End of Study (n=715)	10.4 (0.60)	11.9 (0.62)	11.2 (0.55)	11.2 (0.34)	11.4 (0.49)	11.2 (0.28)
Change from Baseline	5.4 (0.60)	5.0 (0.48)	5.6 (0.58)	5.3 (0.32)	13.5 (0.51)	7.9 (0.31)

- SE = Standard error
- N is the number of Safety set subjects; n is the number of subjects with a value at both baseline and endpoint. Baseline is the last measurement obtained immediately prior to first dose of open-label study drug
- A positive change from baseline indicates improvement in condition.

Proportion of subjects with CGI-I clinical improvement at end of study visit (OC) by cohort and double-blind treatment – Safety set

	Cohort I				Cohort II	
	DB Agomelatine 0.5 mg N=190 Total* n (%)	DB Agomelatine 1 mg N=181 Total* n (%)	DB Placebo N=197 Total* n (%)	Total N=568 Total* n (%)	Agomelatine 1 mg N=287 Total* n (%)	Overall Total N=855 Total* n (%)
Clinical Improvement	162 93 (57.4)	157 91 (58.0)	163 91 (55.8)	482 275 (57.1)	229 142 (62.0)	711 417 (58.6)

N is the number of Safety set subjects; Total* is the number of subjects with a value at the end of study visit using OC.
- Clinical improvement is defined by a score of 1 'very much improved' or 2 'much improved' on the CGI-I scale.

Safety Results

Adverse Events by System Organ Class

Number of subjects with Adverse events by primary system organ class, cohort and maximum dose – Safety set

Primary system organ class	Cohort I Agomelatine 0.5 mg N = 76 n (%)	Cohort I Agomelatine 1 mg N = 492 n (%)	Cohort I Total N = 568 n (%)	Cohort II Agomelatine 1 mg N = 287 n (%)	Overall Total N=855 n (%)
Subjects with any AE(s)	35 (46.1)	312 (63.4)	347 (61.1)	228 (79.4)	575 (67.3)
Gastrointestinal disorders	15 (19.7)	94 (19.1)	109 (19.2)	106 (36.9)	215 (25.1)
Nervous system disorders	13 (17.1)	110 (22.4)	123 (21.7)	91 (31.7)	214 (25.0)
Infections and infestations	7 (9.2)	92 (18.7)	99 (17.4)	86 (30.0)	185 (21.6)
Psychiatric disorders	4 (5.3)	66 (13.4)	70 (12.3)	53 (18.5)	123 (14.4)
Musculoskeletal and connective tissue disorders	4 (5.3)	36 (7.3)	40 (7.0)	48 (16.7)	88 (10.3)
General disorders and administration site conditions	2 (2.6)	48 (9.8)	50 (8.8)	31 (10.8)	81 (9.5)
Respiratory, thoracic and mediastinal disorders	4 (5.3)	28 (5.7)	32 (5.6)	34 (11.8)	66 (7.7)
Injury, poisoning and procedural complications	3 (3.9)	28 (5.7)	31 (5.5)	28 (9.8)	59 (6.9)
Investigations	0	27 (5.5)	27 (4.8)	19 (6.6)	46 (5.4)
Metabolism and nutrition disorders	0	11 (2.2)	11 (1.9)	22 (7.7)	33 (3.9)
Skin and subcutaneous tissue disorders	2 (2.6)	10 (2.0)	12 (2.1)	14 (4.9)	26 (3.0)
Reproductive system and breast disorders	1 (1.3)	8 (1.6)	9 (1.6)	8 (2.8)	17 (2.0)
Renal and urinary disorders	2 (2.6)	6 (1.2)	8 (1.4)	7 (2.4)	15 (1.8)
Vascular disorders	2 (2.6)	8 (1.6)	10 (1.8)	5 (1.7)	15 (1.8)
Eye disorders	0	7 (1.4)	7 (1.2)	7 (2.4)	14 (1.6)
Ear and labyrinth disorders	0	6 (1.2)	6 (1.1)	7 (2.4)	13 (1.5)
Cardiac disorders	0	6 (1.2)	6 (1.1)	6 (2.1)	12 (1.4)
Immune system disorders	0	5 (1.0)	5 (0.9)	4 (1.4)	9 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.3)	4 (0.8)	5 (0.9)	3 (1.0)	8 (0.9)
Blood and lymphatic system disorders	0	1 (0.2)	1 (0.2)	3 (1.0)	4 (0.5)
Hepatobiliary disorders	0	1 (0.2)	1 (0.2)	2 (0.7)	3 (0.4)
Endocrine disorders	0	0	0	1 (0.3)	1 (0.1)

- Primary System Organ Classes (SOCs) were sorted in descending order of frequency, as reported in the 'Overall total' column. 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.

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

Number of subjects with frequent adverse events (greater than or equal to 2% in any group) by preferred term, cohort and maximum dose

	Cohort I			Cohort II	
Preferred term	**Agomelatine 0.5 mg N = 76 n (%)**	**Agomelatine 1 mg N = 492 n (%)**	**Total N = 568 n (%)**	**Agomelatine 1 mg N = 287 n (%)**	**Overall Total N=855 n (%)**
Subjects with any AE(s)	35 (46.1)	312 (63.4)	347 (61.1)	228 (79.4)	575 (67.3)
Preferred term					
Headache	6 (7.9)	58 (11.8)	64 (11.3)	38 (13.2)	102 (11.9)
Dry mouth	2 (2.6)	22 (4.5)	24 (4.2)	28 (9.8)	52 (6.1)
Nasopharyngitis	0	21 (4.3)	21 (3.7)	30 (10.5)	51 (6.0)
Upper respiratory tract infection	1 (1.3)	29 (5.9)	30 (5.3)	21 (7.3)	51 (6.0)
Nausea	2 (2.6)	21 (4.3)	23 (4.0)	22 (7.7)	45 (5.3)
Somnolence	1 (1.3)	20 (4.1)	21 (3.7)	22 (7.7)	43 (5.0)
Dizziness	4 (5.3)	19 (3.9)	23 (4.0)	14 (4.9)	37 (4.3)
Anxiety	3 (3.9)	20 (4.1)	23 (4.0)	12 (4.2)	35 (4.1)
Diarrhoea	2 (2.6)	13 (2.6)	15 (2.6)	19 (6.6)	34 (4.0)
Insomnia	1 (1.3)	19 (3.9)	20 (3.5)	13 (4.5)	33 (3.9)
Fatigue	1 (1.3)	18 (3.7)	19 (3.3)	13 (4.5)	32 (3.7)
Back pain	2 (2.6)	13 (2.6)	15 (2.6)	16 (5.6)	31 (3.6)
Constipation	3 (3.9)	13 (2.6)	16 (2.8)	15 (5.2)	31 (3.6)
Irritability	0	15 (3.0)	15 (2.6)	7 (2.4)	22 (2.6)
Sinusitis	1 (1.3)	8 (1.6)	9 (1.6)	10 (3.5)	19 (2.2)
Dyspepsia	2 (2.6)	10 (2.0)	12 (2.1)	6 (2.1)	18 (2.1)
Abnormal dreams	0	5 (1.0)	5 (0.9)	11 (3.8)	16 (1.9)
Dysgeusia	0	3 (0.6)	3 (0.5)	13 (4.5)	16 (1.9)
Arthralgia	1 (1.3)	8 (1.6)	9 (1.6)	6 (2.1)	15 (1.8)
Cough	1 (1.3)	6 (1.2)	7 (1.2)	8 (2.8)	15 (1.8)
Weight increased	0	8 (1.6)	8 (1.4)	7 (2.4)	15 (1.8)
Pain in extremity	0	6 (1.2)	6 (1.1)	8 (2.8)	14 (1.6)
Increased appetite	0	3 (0.6)	3 (0.5)	9 (3.1)	12 (1.4)
Toothache	0	6 (1.2)	6 (1.1)	6 (2.1)	12 (1.4)
Abdominal pain upper	0	5 (1.0)	5 (0.9)	6 (2.1)	11 (1.3)
Neck pain	0	5 (1.0)	5 (0.9)	6 (2.1)	11 (1.3)
Urinary tract infection	2 (2.6)	7 (1.4)	9 (1.6)	2 (0.7)	11 (1.3)
Gastrooesophageal reflux disease	0	3 (0.6)	3 (0.5)	7 (2.4)	10 (1.2)
Musculoskeletal pain	0	4 (0.8)	4 (0.7)	6 (2.1)	10 (1.2)
Decreased appetite	0	1 (0.2)	1 (0.2)	7 (2.4)	8 (0.9)
Flatulence	0	2 (0.4)	2 (0.4)	6 (2.1)	8 (0.9)
Joint sprain	0	1 (0.2)	1 (0.2)	7 (2.4)	8 (0.9)
Pollakiuria	2 (2.6)	2 (0.4)	4 (0.7)	3 (1.0)	7 (0.8)
Hot flush	2 (2.6)	1 (0.2)	3 (0.5)	0	3 (0.4)

- Preferred terms (PT) are sorted in descending order of frequency, as reported in the 'Overall total' column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE

category for that treatment.

Serious Adverse Events and Deaths

Number of subjects with deaths, other serious or adverse events leading to discontinuation, by cohort and maximum dose – Safety set

	Cohort I			Cohort II	
	Agomelatine 0.5 mg N = 76 n (%)	Agomelatine 1 mg N = 492 n (%)	Total N = 568 n (%)	Agomelatine 1 mg N = 287 n (%)	Overall Total N=855 n (%)
Deaths	0	0	0	1 (0.3)	1 (0.1)
SAEs	2 (2.6)	19 (3.9)	21 (3.7)	11 (3.8)	32 (3.7)
Discontinuations due to AEs	5 (6.6)	11 (2.2)	16 (2.8)	24 (8.4)	40 (4.7)

- SAEs = Serious adverse events, AEs = Adverse events

Number of subjects with serious adverse events regardless of study drug relationship, by primary system organ class, preferred term, cohort and maximum dose – Safety set

	Cohort I			Cohort II	
Primary system organ class Preferred term	Agomelatine 0.5 mg N = 76 n (%)	Agomelatine 1 mg N = 492 n (%)	Total N = 568 n (%)	Agomelatine 1 mg N = 287 n (%)	Overall Total N=855 n (%)
-Subjects with any SAE					
-Total	**2 (2.6)**	**19 (3.9)**	**21 (3.7)**	**11 (3.8)**	**32 (3.7)**
Cardiac disorders					
-Total	0	1 (0.2)	1 (0.2)	1 (0.3)	2 (0.2)
Tachycardia	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Cardio-respiratory arrest	0	0	0	1 (0.3)	1 (0.1)
Gastrointestinal disorders					
-Total	0	0	0	2 (0.7)	2 (0.2)
Abdominal pain	0	0	0	1 (0.3)	1 (0.1)
Diverticulum	0	0	0	1 (0.3)	1 (0.1)
Nausea	0	0	0	1 (0.3)	1 (0.1)
Pancreatitis	0	0	0	1 (0.3)	1 (0.1)
Hepatobiliary disorders					
-Total	0	1 (0.2)	1 (0.2)	2 (0.7)	3 (0.4)
Hepatitis	0	1 (0.2)	1 (0.2)	1 (0.3)	2 (0.2)
Bile duct stone	0	0	0	1 (0.3)	1 (0.1)
Cholecystitis acute	0	0	0	1 (0.3)	1 (0.1)
Infections and infestations					
-Total	0	2 (0.4)	2 (0.4)	2 (0.7)	4 (0.5)
Gastrointestinal infection	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Kidney infection	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Pneumonia	0	0	0	1 (0.3)	1 (0.1)
Sepsis	0	0	0	1 (0.3)	1 (0.1)
Injury, poisoning and procedural complications					

-Total	1 (1.3)	2 (0.4)	3 (0.5)	1 (0.3)	4 (0.5)
Burns third degree	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Overdose	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Post procedural haemorrhage	1 (1.3)	0	1 (0.2)	0	1 (0.1)
Collapse of lung	0	0	0	1 (0.3)	1 (0.1)
Investigations					
-Total	1 (1.3)	2 (0.4)	3 (0.5)	1 (0.3)	4 (0.5)
Aspartate aminotransferase increased	0	2 (0.4)	2 (0.4)	1 (0.3)	3 (0.4)
Hepatic enzyme increased	1 (1.3)	0	1 (0.2)	0	1 (0.1)
Alanine aminotransferase increased	0	0	0	1 (0.3)	1 (0.1)
Metabolism and nutrition disorders					
-Total	0	1 (0.2)	1 (0.2)	1 (0.3)	2 (0.2)
Dehydration	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Diabetic ketoacidosis	0	0	0	1 (0.3)	1 (0.1)
Hyperglycaemia	0	0	0	1 (0.3)	1 (0.1)
Metabolic acidosis	0	0	0	1 (0.3)	1 (0.1)
Musculoskeletal and connective tissue disorders					
-Total	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Osteoarthritis	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
-Total	0	0	0	1 (0.3)	1 (0.1)
Prostate cancer	0	0	0	1 (0.3)	1 (0.1)
Nervous system disorders					
-Total	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Loss of consciousness	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Psychiatric disorders					
-Total	0	8 (1.6)	8 (1.4)	3 (1.0)	11 (1.3)
Suicide attempt	0	4 (0.8)	4 (0.7)	0	4 (0.5)
Suicidal ideation	0	3 (0.6)	3 (0.5)	3 (1.0)	6 (0.7)
Depression	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Suicidal behaviour	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Reproductive system and breast disorders					
-Total	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Endometrial hyperplasia	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders					
-Total	0	0	0	1 (0.3)	1 (0.1)
Nasal septum deviation	0	0	0	1 (0.3)	1 (0.1)
Nasal turbinate abnormality	0	0	0	1 (0.3)	1 (0.1)
Vascular disorders					
-Total	0	2 (0.4)	2 (0.4)	0	2 (0.2)
Deep vein thrombosis	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Thrombophlebitis	0	1 (0.2)	1 (0.2)	0	1 (0.1)

- 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 'Overall total' column.
- A subject with multiple occurrences of an 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.

Overall assessment of suicidality: Columbia-Suicide Severity Rating Scale (C-SSRS), by cohort and maximum dose – Safety set

	Cohort I			Cohort II	
Suicidality Category	**Ago 0.5 mg N = 76 n (%)**	**Ago 1 mg N = 492 n (%)**	**Total N = 568 n (%)**	**Ago 1 mg N = 287 n (%)**	**Overall Total N=855 n (%)**
1 Completed suicide	0	0	0	0	0
2 Suicide attempt	0	3 (0.6)	3 (0.5)	0	3 (0.4)
3 Preparatory actions toward imminent Suicidal behavior	1 (1.3)	2 (0.4)	3 (0.5)	2 (0.7)	5 (0.6)
4 Suicidal Ideation	7 (9.2)	109 (22.2)	116 (20.4)	86 (30.0)	202 (23.6)
7 Self-injurious behaviors without Suicidal intent	0	6 (1.2)	6 (1.1)	2 (0.7)	8 (0.9)
Suicidal behavior	1 (1.3)	5 (1.0)	6 (1.1)	2 (0.7)	8 (0.9)
Suicidality	7 (9.2)	109 (22.2)	116 (20.4)	86 (30.0)	202 (23.6)

- 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 no clinically significant findings on the assessment of laboratory values (including measures of liver function), suicidality, vital signs and ECG. Newly occurring clinically notable liver function test elevations occurred predominantly in the agomelatine 1 mg groups. A total of 4 patients overall (0.5%) had elevations in AST and/or ALT ≥ 3x ULN, and 3 (0.4%) had elevations in AST and/or ALT ≥ 5x ULN. Eight patients (0.9%) overall were reported to have elevations of GGT ≥ 3x ULN and 4 patients (0.5%) had isolated elevations of bilirubin ≥ 1.5x ULN.

Date of Clinical Trial Report

26-June-2012

Date Inclusion on Novartis Clinical Trial Results Database

October 10 2012

Date of Latest Update