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Data supplement

Online supplement DS1

Method

Additional exclusion criteria

Other exclusion criteria included patients who were considered to be treatment resistant/refractory to antipsychotic treatment by history. Patients were also excluded if they failed to respond to clozapine treatment or were responsive to clozapine treatment only. The use of CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers was also prohibited at screening and during the study. Adjunctive antipsychotics, antidepressants (including monoamine oxidase inhibitors), and mood stabilisers were not permitted during the study. Patients requiring more than one benzodiazepine beyond screening (e.g. lorazepam and oxazepam) were excluded.

Benzodiazepine use (lorazepam or equivalent) was allowed up to 6 mg/day, but not within 8 h of any rating scale assessment during any phase of the trial. For insomnia, zolpidem (5–10 mg, or equivalent) was permitted but not in addition to a benzodiazepine. The use of intramuscular lorazepam was permitted for emergent agitation. Other allowed concomitant medications were benzatropine (up to 4 mg/day, or equivalent) and propranolol (up to 60 mg/day).

Rationale for change in primary efficacy end-point

The primary efficacy end-point was changed from time to impending relapse to estimated proportion of participants experiencing impending relapse by end of 26 weeks from the date of randomisation in the double-blind, active-controlled phase (phase 3). This end-point was changed because of a lower-than-anticipated relapse rate. The lower-than-anticipated relapse rate was thought to have resulted from the requirement for 8 consecutive weeks of stabilisation prior to randomisation and the fact that participants randomised to the 50 mg aripiprazole once-monthly arm maintained stability of schizophrenic symptoms to a greater degree than anticipated. This change was discussed during a scientific advice procedure with the EMA (16 Dec 2010). The change in primary efficacy end-point was consistent with current EMA guidance on the development of medicinal products for the maintenance treatment of schizophrenia.

Results

Treatment exposure

The mean average daily dose of oral aripiprazole during the oral conversion phase was 13.7 mg (s.d. = 5.0) in all patients ($n = 709$) and 13.7 mg (s.d. = 4.7) in patients who continued treatment into the oral stabilisation phase ($n = 614$). For patients randomised to treatment ($n = 662$), the mean average daily dose of oral aripiprazole during the oral stabilisation phase was 19.2 mg (s.d. = 6.3) in patients who underwent oral conversion ($n = 474$) and 19.5 mg (s.d. = 7.0) in patients who entered directly into the oral stabilisation phase without oral conversion ($n = 188$). During the double-blind treatment phase, the mean dose of oral aripiprazole for patients randomised to oral aripiprazole 10–30 mg was 20.0 mg (s.d. = 6.9). During the 2-week period of oral overlap in the double-blind treatment phase, the mean daily dose of oral aripiprazole was 12.1 mg (s.d. = 2.9) for patients randomised to aripiprazole once-monthly 400 mg, 11.6 mg (s.d. = 2.4) for patients randomised to aripiprazole once-monthly 50 mg and 20.0 mg (s.d. = 7.0) for patients randomised to oral aripiprazole.

For patients randomised to an aripiprazole once-monthly treatment arm, the majority (92.8% receiving aripiprazole once-monthly 400 mg and 99.2% receiving aripiprazole once-monthly 50 mg) had no change in their injection dose during the randomised phase. A total of 18 patients in the aripiprazole once-monthly 400 mg group had a one-time dose decrease to 300 mg, of whom one patient returned to the 400 mg dose. One patient in the aripiprazole once-monthly 50 mg group had a one-time dose decrease to 25 mg.

Concomitant medication use

Concomitant medications were used by 78.4% (519/662) of patients in the randomised phase (phase 3). Of these, benzodiazepine derivatives were used by 38.9% ($n = 103/265$; mean daily dose 2.18 mg), 33.1% ($n = 88/266$; mean daily dose 1.93 mg) and 36.6% ($n = 48/131$; mean daily dose 2.29 mg) of patients receiving aripiprazole once-monthly 400 mg, oral aripiprazole and aripiprazole once-monthly 50 mg, respectively, during phase 3. Benzodiazepine equivalence was determined as follows: 1 mg lorazepam = 5 mg diazepam = 15 mg oxazepam = 15 mg clorazepate.

Table DS1 Other efficacy end-points (efficacy sample, observed cases)

Efficacy end-point	Aripiprazole once-monthly 400 mg	Oral aripiprazole 10–30 mg	Aripiprazole once-monthly 50 mg	*P*	
				Aripiprazole once-monthly 400 mg *v.* oral aripiprazole 10–30 mg	Aripiprazole once-monthly 400 mg *v.* aripiprazole once-monthly 50 mg
Positive and Negative Syndrome Scale, total score					
Baseline, *n*	263	266	131		
Baseline, least square mean (s.e).	57.94 (0.79)	56.57 (0.78)	56.08 (1.11)	0.2179	0.1751
Week 38, *n*	192	171	61		
Change from baseline at week 38, least square mean (s.e).	−3.91 (0.55)	−3.49 (0.58)	−5.31 (0.97)	0.5988	0.2059
Clinical Global Impression – Severity					
Baseline, *n*	259	263	129		
Baseline, least square mean (s.e).	3.12 (0.05)	3.09 (0.05)	2.95 (0.07)	0.7262	0.0605
Week 38, *n*	192	171	61		
Change from baseline at week 38, least square mean (s.e).	−0.28 (0.04)	−0.17 (0.04)	−0.16 (0.07)	0.0708	0.1498
Clinical Global Impression – Improvement					
Baseline, *n*	265	266	131		
Baseline, mean (s.d)	3.24 (0.91)	3.26 (0.90)	3.08 (1.02)	0.7830	0.1306
Week 38, *n*	192	171	61		
At week 38, mean (s.d.)	3.07 (0.97)	3.33 (0.89)	3.39 (0.92)	0.0085	0.0237

Table DS2 Metabolic and prolactin parameters during exposure to aripiprazole (safety sample, observed cases)

	Aripiprazole once-monthly 400 mg (*n* = 265)			Oral aripiprazole 10–30 mg (*n* = 266)			Aripiprazole once-monthly 50 mg (*n* = 131)		
		Baseline, mean	Change from baseline at week 38, mean (s.d.)		Baseline, mean	Change from baseline at week 38, mean (s.d.)		Baseline, mean	Change from baseline at week 38, mean (s.d.)
Metabolic parameters, mg/dl	*n*			*n*			*n*		
Fasting glucose	176	96.97	1.65 (31.31)	138	97.57	−1.07 (19.06)	48	96.79	0.19 (30.36)
Fasting total cholesterol	176	186.72	−0.38 (26.46)	141	187.57	−3.89 (27.15)	48	190.48	−4.56 (28.29)
Fasting LDL cholesterol	173	109.93	−2.28 (24.69)	138	110.57	−4.82 (25.07)	48	115.40	−6.35 (25.47)
Fasting HDL cholesterol	176	50.06	1.04 (9.84)	141	50.06	−0.13 (9.41)	48	51.56	1.17 (7.76)
Fasting triglycerides	176	133.07	5.99 (72.59)	141	133.40	5.33 (71.82)	48	118.42	2.77 (46.62)
Incidence of new-onset metabolic abnormalities[a]	*n/N* (%)			*n/N* (%)			*n/N* (%)		
Glucose	12/162 (7.4)			7/148 (4.7)			4/84 (4.8)		
Total cholesterol	3/158 (1.9)			2/137 (1.5)			1/73 (1.4)		
LDL cholesterol	1/102 (1.0)			0/88 (0.0)			1/45 (2.2)		
HDL cholesterol	29/183 (15.8)			33/187 (17.6)			14/103 (13.6)		
Triglycerides	15/158 (9.5)			13/160 (8.1)			6/89 (6.7)		
Prolactin, ng/ml	184	6.07	−0.41 (3.15)	159	5.73	0.63 (5.40)	57	5.63	0.43 (3.66)
Incidence of prolactin abnormalities[b]	14/260 (5.4)			9/260 (3.5)			6/128 (4.7)		

LDL, low-density lipoprotein; HDL, high-density lipoprotein.
a. Incidence of shift in metabolic parameters from normal at baseline to high at any time during randomised treatment. Shifts from normal to abnormal values in fasting metabolic parameters were defined as follows: glucose, <100 mg/dl to ⩾126 mg/dl; total cholesterol, <200 mg/dl to ⩾240 mg/dl; LDL cholesterol, <100 mg/dl to ⩾160 mg/dl; HDL cholesterol, <40 mg/dl to <40 mg/dl; triglycerides, <150 mg/dl to ⩾200 mg/dl.
b. Prolactin abnormality was predefined as >1 × upper limit of normal.

Table DS3 Extrapyramidal symptoms and suicidality (safety sample, last observation carried forward)

	Aripiprazole once-monthly 400 mg ($n = 265$)			Oral aripiprazole 10–30 mg ($n = 266$)			Aripiprazole once-monthly 50 mg ($n = 131$)			*P*	
	n	Baseline mean	Change from baseline at week 38	*n*	Baseline mean	Change from baseline at week 38	*n*	Baseline mean	Change from baseline at week 38	Aripiprazole once-monthly 400 mg *v.* oral aripiprazole 10–30 mg	Aripiprazole once-monthly 400 mg *v.* aripiprazole once-monthly 50 mg
Extrapyramidal symptoms			Least square mean (s.e.)			Least square mean (s.e.)			Least square mean (s.e.)		
SAS total score[a]	262	10.85	−0.04 (0.08)	260	11.03	−0.07 (0.08)	128	10.76	−0.09 (0.12)	0.8110	0.7438
AIMS movement rating score[b]	262	0.35	−0.01 (0.05)	260	0.44	−0.08 (0.05)	128	0.33	−0.06 (0.07)	0.3237	0.5551
BARS global score[c]	262	0.15	0.07 (0.03)	260	0.12	−0.01 (0.03)	128	0.13	−0.03 (0.04)	0.0472	0.0571
Suicidality			Mean (s.d.)			Mean (s.d.)			Mean (s.d.)		
CGI-SS[d]	263	1.01	−0.01 (0.09)	266	1.01	0.01 (0.09)	131	1.02	0.06 (0.35)	NA	NA

NA, not applicable.
a. Simpson-Angus Scale (SAS): sum of ten parkinsonian symptom items; each rated on a five-point scale (1, absence of symptoms; 5, severe condition).
b. Abnormal Involuntary Movement Scale (AIMS): sum of seven items related to facial, oral, extremity, or trunk movements; each item rated on a five-point scale (0, absence of symptoms; 4, severe condition).
c. Barnes Akathisia Rating Scale (BARS): derived from the global clinical assessment of akathisia; rated on a six-point scale (0, absence of symptoms; 5, severe akathisia).
d. Clinical Global Impression of Severity of Suicidality (CGI-SS): change from baseline was evaluated with a seven-point scale (1, very much improved; 7, very much worse).