Figure 1. HAM-D Total Score in Patients with Less Severe Depression (HAM-D<=27). Meta-Analysis of 3 Placebo-Controlled Studies.

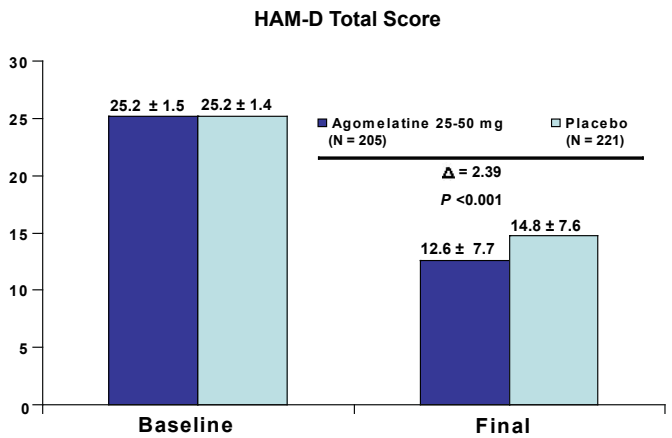
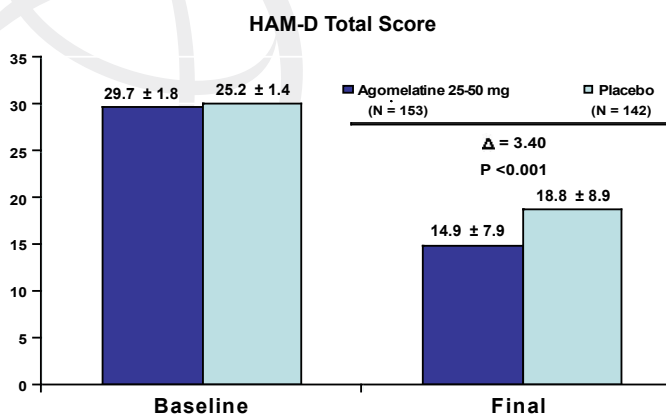


Figure 2. HAM-D Total Score in Patients with More Severe Depression (HAM-D>=27). Meta-Analysis of 3 Placebo-Controlled Studies.



those with greater symptom severity (both p<0.001; Figures 1 and 2). There was no significant difference in efficacy between the two severity groups; however, additional analyses revealed that the subgroup having the greatest difference from placebo were less depressed males, followed by more severely depressed females. This suggests that men and women may respond differently to the medication depending on their symptom severity. Agomelatine efficacy results were recently published online on May 4, 2007 by Pierre and Kasper, in the *International Journal of Neuropsychopharmacology.*

Safety of IM Aripiprazole in Acute Agitation Associated with Dementia

Aripiprazole is an atypical antipsychotic approved for the treatment of schizophrenia. Agitation is a common symptom experienced by patients with dementia, and medications with a rapid onset of action and appropriate tolerability in the elderly are desirable in these situations. This was a multicenter, double-blind, placebo-controlled pilot study to determine the tolerability of intramuscular (IM) aripiprazole in patients with acute agitation associated with dementia and to determine a maximum tolerated dose.

Eligible participants were aged 55-95 years with a diagnosis of Alzheimer's disease, vascular dementia, or mixed dementia. Eligible subjects had to have a PANSS Excited Component (PEC) score between 15 and 32 (inclusive) and a score ≥4 on at least one PEC component (hostility, extreme excitement, poor impulse control, uncooperativeness, tension). The study consisted of a 3 cohort design (Figure 1). Each cohort began with 15 patients, and within each cohort patients were randomized in a 4:1 ratio to receive either active medication or placebo by 2 injections separated by 2 hours. Once an MTD was determined from the 3 cohorts, additional patients were to be enrolled in the MTD cohort until a total of 125 subjects were enrolled. Safety assessments included adverse events, electrocardiograms, vital signs, the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and the Mini-Mental Status Exam (MMSE).

Figure 1. Cohort Study Design.

	Dose	# of injections	Maximum Dose
Cohort 1 15 Patients	2.5 mg aripiprazole or placebo	2	5 mg*
Cohort 2 15 Patients	5 mg aripiprazole or placebo	2	10 mg*
Cohort 3 15 Patients	10 mg aripiprazole or placebo 5 mg apripiprazole or placebo	1 1	15 mg*

*Actual doses:

IM aripiprazole 2.5 mg Cohort: Two injections of 2.475 mg = Maximum dose of 4.95 mg

IM aripiprazole 5 mg Cohort: Two injections of 5.025 mg = Maximum dose of 10.05 mg

IM aripiprazole 15 mg Cohort: One injection of 9.75 mg and one injection of 5.025 mg = Maximum dose of 14.775 mg

Exploratory analyses of efficacy were performed using the PEC, the Agitation-Calmness Evaluation Scale, Clinical Global Impression-Severity, and Clinical Global Impression-Improvement.

Because the tolerability of the 10 mg and 15 mg groups was similar, a maximum tolerated dose was not established. In order to be conservative, additional patients were enrolled in the 10 mg dose group. The only adverse event observed at a higher incidence than placebo in all 3 aripiprazole groups was somnolence, and there were no extrapyramidal symptom-related adverse events (Table 1). One patient from the IM aripiprazole 10 mg group was treated for a probable cerebrovascular event 16 days after taking study drug, but the adverse event was rated as not likely related to the study drug. There was no evidence of changes in vital signs, laboratory measures, or ECGs, and no decline in MMSE score post-dose. Exploratory analyses showed numeric improvement in the efficacy ratings over time although none reached statistical significance. Overall this pilot safety study showed that IM aripiprazole was generally well-tolerated at all 3 doses in acutely agitated subjects with dementia.

Table 1. Incidence of Treatment-Emergent Adverse Events that Occurred in at Least 5% of Patients in Any Treatment Group.

	IM Placebo (total from three cohorts)	IM aripiprazole 5 mg/day (Cohort 1)	IM aripiprazole 10 mg/day (Cohort 2)	IM aripiprazole 15 mg/day (Cohort 3)	IM aripiprazole (total from three cohorts)
N	25	12	76	15	103
Incidence, n (%)					
Any adverse event	8 (32.0)	6 (50.0)	41 (54.0)	9 (60.0)	56 (54.4)
Somnolence	2 (8.0)	2 (16.7)	30 (39.5)	5 (33.3)	37 (35.9)
Dementia	0	3 (25.0)	0	0	3 (2.9)
Lethargy	0	0	0	1 (6.7)	1 (1.0)
Vomiting	0	1 (8.3)	3 (4.0)	0	4 (3.9)
Pyrexia	0	0	0	1 (6.7)	1 (1.0)
Skin laceration	2 (8.0)	0	1 (1.3)	1 (6.7)	2 (1.94)
Fall	1 (4.0)			1 (6.7)	1 (1.0)
Femoral neck fracture	0	0	0	1 (6.7)	1 (1.0)
Electrocardiogram change	0	0	0	1 (6.7)	1 (1.0)
Irregular heart rate	0	0	0	1 (6.7)	1 (1.0)
Insomnia	0	0	2 (2.6)	1 (6.7)	3 (2.9)
Agitation	2 (8.0)	0	1 (1.3)	0	1 (1.0)