

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
21-866

STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Serial Number: 21-866 (N_000)
Drug Name: Aripiprazole
Indication: Agitation Associated with Schizophrenia and Bipolar Mania
Applicant: Otsuka Maryland Research Institute, Inc.
Dates: Date of Document: 11/29/2005
PDUFA Due Date: 9/30/2006
Review Priority: Standard
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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted three efficacy studies to seek the approval for the efficacy and safety of the IM injection formulation as a treatment of agitation in patients with schizophrenia or bipolar I disorder. After evaluation, this reviewer agreed with the sponsor that 10-mg IM aripiprazole was confirmed as effective in all three studies, in terms of the primary endpoint (PEC total score) and the key secondary endpoint (CGI-Improvement score) if it was determined that the CGI-Improvement was the pre-specified key secondary endpoint for the multiple dosed schizophrenia study (Study CN138050).

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted three efficacy studies to support the efficacy and safety of the IM injection formulation as a treatment of agitation in patients with schizophrenia or bipolar I disorder. Among these three studies, one was conducted in agitated patients with bipolar I disorder and two were conducted in agitated patients with schizophrenia, schizoaffective, or schizophreniform disorder. However, in this review patients with schizoaffective or schizophreniform disorder were excluded from the analysis data set since schizophrenia population was the only population that the oral formulation was approved and it is not clear what the other two diagnostic entities represent clinically.

Based on the sponsor's analysis results, they claimed that the proposed recommended dose of 10-mg IM aripiprazole was confirmed as effective in all 3 studies. The recommendation of 10-mg IM aripiprazole was supported by the efficacy on the PEC score and on the key secondary measure CGI-I, as well as on the other secondary measures of CGI-S, ACES, and CABS.

1.3 STATISTICAL ISSUES AND FINDINGS

For all three studies, this reviewer confirmed the sponsor's analysis results on the primary endpoint and all secondary endpoints. However, for two studies that patients' agitation due to schizophrenia, schizoaffective or schizophreniform disorder, the sponsor did not provide analysis results on other secondary endpoints for patients with only schizophrenia. The model they used to analyze for the primary endpoint also excluded the country factor, although this reviewer found that the results were consistent whether or not the factor of country was included in the model.

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2. INTRODUCTION

2.1 OVERVIEW

According to the sponsor, agitation is a common symptom that require immediate intervention to prevent patients from harming themselves or others in patients with schizophrenia and in patients with bipolar disorder. Because such patients may be unable or unwilling to take oral antipsychotic drugs, it may be necessary to use an alternative route of administration to treat them. The sponsor developed aripiprazole IM formulation to enable the appropriate treatment of acutely agitated patients who require an injection for rapid onset of action to relieve their symptoms. This is the first application making this formulation.

In this application, the sponsor submitted three efficacy studies of IM aripiprazole in the treatment of acutely agitated patients with schizophrenia or bipolar I disorder (manic or mixed). Among the three efficacy studies, one is for patients with bipolar I disorder (Study CN138013) and two are for patients with schizophrenia (Studies CN138012 and CN138050). However, in this review patients with schizoaffective or schizophreniform disorder were excluded from the analysis data set since schizophrenia population was the only population that the oral formulation was approved and it is not clear what the other two diagnostic entities represent clinically.

Table 2.1 shows the sponsor's analysis results for the primary endpoint, the mean change from baseline to 2 hours post first IM injection in the PEC Score for the LOCF data set. Based on the analysis results, the sponsor claimed that doses of 5-, 10-, and 15- mg IM aripiprazole were effective in treating agitation associated with schizophrenia or schizoaffective disorder. The 10- and 15- mg doses were effective in treating agitation associated with bipolar I disorder, manic or mixed. The proposed recommended dose of 10-mg IM aripiprazole was initially established as effective in one dose-ranging study in schizophrenia or schizoaffective disorder and was confirmed as effective in two subsequent studies: one in schizophrenia or schizoaffective disorder and the other in bipolar I disorder. No increase in efficacy over the 10-mg dose was seen with the 15-mg dose in the 2 clinical trials where it was studied.

Table 2.1 Summary of Sponsor's Efficacy Analysis Results for Primary Endpoint

Study CN138013	IM Placebo (N=73)	IM Lorazepam 2 mg (N=68)	IM Aripiprazole 10 mg (N=75)	IM Aripiprazole 15 mg (N=75)
LS Mean Change	-5.76	-9.57	-8.74	-8.67
P-Value* (vs. Placebo)		<0.001	<0.001	<0.001

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Study CN138012	IM Placebo		IM Haloperidol 6.5 mg		IM Aripiprazole 10 mg	
For the whole study population						
N	88		184		173	
LS Mean Change	-4.78		-7.75		-7.27	
P-Value* vs. Placebo			<0.001		<0.001	
For schizophrenia only subpopulation						
N	65		134		123	
LS Mean Change	-5.68		-8.25		-7.99	
P-Value* vs. Placebo			<0.001		0.003	
Study CN138050	IM Placebo	IM Haloperidol	IM Aripiprazole			
			1 mg	5 mg	10 mg	15 mg
For the whole study population						
N	61	57	56	62	56	58
LS Mean Change	-3.28	-6.38	-4.47	-5.65	-6.69	-5.72
P-Value* (vs. Placebo)		0.001	0.191	0.008	<0.001	0.007
For schizophrenia only subpopulation						
N	39	43	30	40	36	44
LS Mean Change	-4.78	-7.32	-4.87	-6.94	-7.82	-6.94
P-Value* (vs. Placebo)		0.020	0.935	0.050	0.008	0.045

* The reported p-values are nominal p-values.

2.2 DATA SOURCES

The sponsor's submission including clinical study reports and data is stored in the following link of the CDER's electronic document room (EDR):

\\CDSESUB1\N21866\N_000\2005-11-29

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The study description in this section is based on the sponsor's study report, any discrepancy between the study report and the study protocol will be discussed in the section of statistical reviewer's findings and comments.

3.1.1 Description of Study CN138013

This study was entitled "A Randomized, Double-Blind Comparison of the Efficacy and Safety of Aripiprazole Intramuscular Formula, Lorazepam, or Placebo in the Treatment of Acutely Agitated Patients Diagnosed with Bipolar Disorder, Manic or Mixed." There were 37 study centers (35 in USA, 1 in Latvia, and 1 in Poland) participating in the conduct of this study.

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3.1.1.1 Study Objectives

Primary Objective

The primary objective was to compare the efficacy of IM aripiprazole with placebo in the treatment of acutely agitated patients with a diagnosis of Bipolar I Disorder, manic or mixed.

Secondary Objectives

Secondary objectives were:

- 1) To compare the efficacy of IM aripiprazole with placebo in the treatment of acute agitation in patients with a diagnosis of Bipolar I Disorder, manic or mixed, as assessed by the Clinical Global Impressions Improvement Scale (CGI-I), Clinical Global Impressions Severity of Illness Scale (CGI-S), Agitation-Calmness Evaluation Scale (ACES), and Corrigan Agitated Behavior Scale (CABS).
- 2) To compare the effects of IM lorazepam (a known active therapy and standard of care in the treatment of acutely agitated patients with Bipolar I Disorder, manic or mixed) with placebo.
- 3) To determine the safety and tolerability of IM aripiprazole in the treatment of acutely agitated patients with Bipolar I Disorder, manic or mixed. This was assessed by the mean change from baseline to each specified observation time in the Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scale. Safety and tolerance was evaluated by reports of adverse events (AEs) and clinically significant changes in electrocardiograms (ECGs), vital signs, and laboratory tests.

3.1.1.2 Study Design

This was a randomized, double-blind, multicenter study comparing 2 doses of IM aripiprazole (10 mg and 15 mg) and 1 dose of IM lorazepam (2 mg) with placebo in the treatment of acute agitation in patients with a diagnosis of Bipolar I Disorder, manic or mixed.

After minimum 2-hour screening period and baseline assessment performed within 1 hour prior to initial injection, patients were randomly assigned to receive an initial injection of 1 of 4 treatments (i.e., placebo, 2-mg lorazepam, 10-mg aripiprazole, or 15-mg aripiprazole). A second injection was given, if needed, at least 2 hours after the initial injection, followed by a third injection, if needed at least 4 hours after the initial injection and at least 2 hours after the second injection. A second and/or third injection of study medication was given no more than 20 hours after the initial injection of study medication. The maximum lorazepam dose was 6 mg. For patients randomized to

placebo, the first and second injection contained placebo and the third injection contained 10-mg aripiprazole. The maximum aripiprazole doses were 30 mg and 45 mg for the 10-mg and 15-mg aripiprazole groups, respectively.

3.1.1.3 Efficacy Endpoints and Analyses

Efficacy Endpoints

The primary efficacy measure was the mean change from baseline to 2 hours post first IM injection in the PEC Score for the LOCF data set. Secondary efficacy measures were the mean change from baseline to 30, 45, 60, 90 minutes post first IM injection in the PEC score, the mean CGI-I score at 30, 45, 60, 90 minutes and 2 hours post first IM injection and the mean change from baseline to 30, 45, 60, 90 minutes and 2 hours post first IM injection in the CGI-S score, the ACES score, the CABS score, the mean change from baseline to 2 hours post first IM injection in PEC individual items scores, and PEC response rate at 30, 45, 60, 90 minutes and 2 hours post first IM injection (PEC response defined as a reduction of $\geq 40\%$ in PEC score compared with baseline).

Efficacy Analyses

Baseline data were evaluated by analysis of variance (ANOVA), with treatment and center as main effects when analyzing the LOCF data set; and with treatment as a main effect when analyzing the OC data set. The primary efficacy measure, the change from baseline to 2 hours after the first IM injection in the PEC score, was evaluated by analysis of covariance (ANCOVA) with baseline score as a covariate, and treatment and center as main effects. In order to control the overall type I error rate at 0.05 level when making two comparisons of IM aripiprazole doses (10 mg or 15 mg) with placebo, the statistical testing of the primary efficacy measure was carried out using the Hochberg sequentially rejective procedure. Therefore, superiority to placebo of both aripiprazole treatment groups were claimed if both pair-wise comparisons with placebo were significant at 5% level, or superiority to placebo of only 1 aripiprazole treatment group if the comparison of that aripiprazole treatment group with placebo was significant at the 2.5% level and the comparison with placebo of the other aripiprazole treatment group was not significant at the 5% level.

Regarding secondary efficacy measures, the changes from baseline in the PEC Score, PEC individual item scores, CGI-S Score, ACES Score and CABS Score, at each time point after the first IM injection were evaluated by ANCOVA with baseline score as a covariate, and treatment and center as main effects when using the LOCF data set, with center removed from ANCOVA model when using the OC data set. The CGI-I Score was analyzed using the Cochran-Mantel-Haenszel (CMH) Row Means test at each time point (30, 45, 60, 90 minutes, and 2, 4, 6, 12 and 24 hours) after the first IM injection, stratified by center when using the LOCF data set and not stratified by center when using the OC data set.

PEC response was defined as a reduction of $\geq 40\%$ in PEC Score compared with baseline. Numbers and percentages of PEC responders at 0.5, 0.75, 1, 1.5, and 2 hours after the first IM injection were provided by treatment group. Treatment differences from placebo with regard to PEC response were tested using the CMH general association test stratified by center when using the LOCF data set and not stratified by center when using the OC data set.

3.1.2 Efficacy Results for Study CN138013

3.1.2.1 Patient Disposition, Population and Baseline Demographic Characteristics

A total of 329 patients were enrolled in the study. Of these, 301 patients were randomized to double-blind treatment: 75 to the placebo group, 70 to the lorazepam group, 78 to the 10-mg aripiprazole group, and 78 to the 15-mg aripiprazole group. A total of 282 (94%) of the 301 patients completed the double-blind study. Nineteen (6%) patients discontinued from double-blind treatment, 10 of whom discontinued prior to receiving study medication. Overall, the primary reason for discontinuation from double-blind treatment was because of patient withdrawal of consent (8 patients [3%]). The detailed disposition of patients is presented in Table 3.2.1. Table 3.2.2 shows the distribution of all randomized patients within each of the patient samples. Table 3.2.3 shows demographic characteristics for the randomized sample by treatment group.

Table 3.2.1 Disposition of Patients for Study CN138013

Patient Status	Placebo	Lorazepam 2 mg	Aripiprazole 10 mg	Aripiprazole 15 mg	Total
Randomized	75	70	78	78	301
Discontinued	4 (5.3%)	4 (5.7%)	5 (6.4%)	6 (7.7%)	19 (6.3%)
Adverse Event	1 (1.3%)			1 (1.3%)	2 (0.7%)
Lack of Efficacy		1 (1.4%)			1 (0.3%)
Other	1 (1.3%)	1 (1.4%)	1 (1.3%)		3 (1.0%)
Poor/Non-Compliance			1 (1.3%)		1 (0.3%)
Subject no Longer Meet Study Criteria		1 (1.4%)	1 (1.3%)	2 (2.6%)	4 (1.3%)
Subject Withdrew Consent	2 (2.7%)	1 (1.4%)	2 (2.6%)	3 (3.8%)	8 (2.7%)
Completed Study	71 (94.7%)	66 (94.3%)	73 (93.6%)	72 (92.3%)	282 (93.7%)

Source: Table 8.1 from Sponsor's Clinical Study Report

Table 3.2.2 Number of Patients in Samples for Study CN138013

Sample	Placebo	Lorazepam 2 mg	Aripiprazole 10 mg	Aripiprazole 15 mg	Total
Randomized	75	70	78	78	301
Safety	72	69	75	75	291
Efficacy	73	68	75	75	291

Source: Table 8.2 from Sponsor's Clinical Study Report

Table 3.2.3 Demographic Characteristics in Randomized Sample for Study CN138013

Patient Status	Placebo (N=75)	Lorazepam 2 mg (N=70)	Aripiprazole 10 mg (N=78)	Aripiprazole 15 mg (N=78)	Total (N=301)
Age (years)					
Mean	40.56	41.61	38.49	42.64	40.81
Median	42.00	43.00	38.00	41.00	41.00
Min-Max	20.00-63.00	18.00-65.00	20.00-62.00	20.00-79.00	18.00-79.00
S.D.	9.44	10.37	11.17	10.78	10.54
Gender, N (%)					
Male	43 (57%)	30 (43%)	44 (56%)	39 (50%)	156 (52%)
Female	32 (43%)	40 (57%)	34 (44%)	39 (50%)	145 (48%)
Race, N (%)					
White	52 (69%)	52 (74%)	56 (72%)	57 (73%)	217 (72%)
Black/African American	18 (24%)	15 (21%)	20 (26%)	19 (24%)	72 (24%)
Asian	1 (1%)	0	0	0	1 (0%)
American Indian/Alaska Native	4 (5%)	2 (3%)	1 (1%)	0	7 (2%)
Other	0	1 (1%)	1 (1%)	2 (3%)	4 (1%)

Source: Table 8.3 from Sponsor's Clinical Study Report

3.1.2.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy measure was the mean change from baseline to 2 hours post first IM injection in the PEC Score. Table 3.2.4 shows the results of the model-based mean change from baseline in PEC Score for the LOCF data at different time points. According to the sponsor and as shown in the table, statistically significant differences between two separate aripiprazole treatment groups and placebo were observed for the primary efficacy measure by the Hochberg procedure at Hour 2. The sponsor's analysis results for OC data are shown in Table 3.2.5.

Table 3.2.4 Sponsor's Analysis Results of Mean Change from Baseline for LOCF data in PEC Score for Study CN138013

Visit	Placebo N = 73	Lor 2 mg N = 68	Ari 10 mg N = 75	Ari 15 mg N = 75	Nominal P-Values (vs. Placebo)		
					Lor 2 mg	Ari 10 mg	Ari 15 mg
Baseline	18.04	18.47	18.84	18.25	0.258	0.033	0.580
30 Min	-3.02	-3.57	-2.82	-2.70	0.358	0.738	0.578
45 Min	-4.14	-5.58	-5.14	-5.18	0.040	0.148	0.126
60 Min	-5.29	-7.07	-6.36	-6.87	0.016	0.140	0.028
90 Min	-6.08	-8.80	-8.09	-7.87	<0.001	0.008	0.017
120 Min	-5.76	-9.57	-8.74	-8.67	<0.001	<0.001	<0.001
4 Hrs	-6.11	-10.29	-9.44	-10.19	<0.001	<0.001	<0.001
6 Hrs	-7.92	-10.71	-10.96	-10.34	<0.001	<0.001	<0.001
12 Hrs	-10.38	-11.79	-11.55	-10.92	0.031	0.067	0.393
24 Hrs	-6.50	-7.43	-7.19	-7.05	0.226	0.356	0.457

Note: Lor and Ari are abbreviations for lorazepam and aripiprazole, respectively.

Source: Table 10.1A of the sponsor's clinical study report.

Table 3.2.5 Sponsor's Analysis Results of Mean Change from Baseline for OC data on PEC Score for Study CN138013

Visit	Placebo N = 73	Lor 2 mg N = 68	Ari 10 mg N = 75	Ari 15 mg N = 75	Nominal P-Values (vs. Placebo)		
					Lor 2 mg	Ari 10 mg	Ari 15 mg
Baseline	17.92	18.41	18.75	18.17	0.250	0.048	0.541
30 Min	-3.18	-3.71	-3.11	-2.87	0.422	0.912	0.637
45 Min	-4.07	-5.47	-5.22	-5.34	0.065	0.122	0.088
60 Min	(N=73) -5.16	(N=68) -6.95	(N=75) -6.44	(N=74) -7.01	0.021	0.094	0.015
90 Min	(N=73) -5.85	(N=68) -8.66	(N=75) -7.89	(N=74) -7.89	<0.001	0.009	0.008
120 Min	(N=73) -5.65	(N=68) -9.46	(N=74) -8.65	(N=74) -8.76	<0.001	<0.001	<0.001
4 Hrs	(N=72) -6.26	(N=68) -10.27	(N=75) -9.35	(N=74) -10.44	<0.001	<0.001	<0.001
6 Hrs	(N=72) -8.00	(N=68) -10.71	(N=74) -10.95	(N=74) -10.62	<0.001	<0.001	<0.001
12 Hrs	(N=72) -10.61	(N=68) -11.73	(N=74) -11.71	(N=74) -11.24	0.080	0.082	0.315
24 Hrs	(N=72) -6.64	(N=68) -7.27	(N=73) -6.99	(N=73) -7.15	0.436	0.664	0.518
	(N=71)	(N=68)	(N=74)	(N=74)			

Note: Lor and Ari are abbreviations for lorazepam and aripiprazole, respectively.
Source: Table S.10.1B of the sponsor's clinical study report.

Reviewer's Note: This reviewer noticed that for the baseline PEC Score, the comparison between the aripiprazole 10 mg arm and placebo arm had p-value 0.033, which is less than 0.05. It seems to show there is a concern about randomization failure, but there is not since the p-value from the overall F test for testing the treatment difference among the four treatment groups was 0.1681.

3.1.2.3 Sponsor's Efficacy Results for Secondary Endpoints

CGI Improvement Score

The sponsor's analysis results for CGI-I Score for the LOCF data set are shown in Table 3.2.6. As shown in the table, at 2 hours post first IM injection (LOCF data set), the results for CGI-I Score showed statistically significant differences when the 10-mg, 15-mg aripiprazole groups, and the lorazepam group and placebo were compared with placebo, respectively.

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Table 3.2.6 Sponsor's Analysis Results for LOCF data on CGI Improvement Score for Study CN138013

Visit	Placebo N = 73	Lor 2 mg N = 68	Ari 10 mg N = 75	Ari 15 mg N = 75	Nominal P-Values (vs. Placebo)		
					Lor 2 mg	Ari 10 mg	Ari 15 mg
30 Min	3.49	3.31	3.36	3.44	0.140	0.271	0.730
45 Min	3.37	2.88	2.91	2.99	<0.001	0.004	0.025
60 Min	3.08	2.53	2.64	2.73	<0.001	0.016	0.067
90 Min	2.97	2.22	2.44	2.53	<0.001	0.005	0.030
120 Min	3.05	2.10	2.17	2.33	<0.001	<0.001	<0.001
4 Hrs	2.92	1.85	2.01	1.92	<0.001	<0.001	<0.001
6 Hrs	2.49	1.74	1.76	1.99	<0.001	<0.001	0.021
12 Hrs	1.85	1.50	1.53	1.72	0.017	0.046	0.549
24 Hrs	2.67	2.35	2.35	2.49	0.060	0.123	0.562

Note: Lor and Ari are abbreviations for lorazepam and aripiprazole, respectively.
Source: Table 10.2.1.1 of the sponsor's clinical study report.

Clinical Severity of Illness Score

The sponsor's analysis results for CGI-S Score for the LOCF data set are shown in Table 3.2.7. As shown in the table, at 2 hours post first IM injection (LOCF data set), the results for CGI-S Score showed statistically significant differences when the 10-mg, 15-mg aripiprazole groups and the lorazepam group were compared with placebo, respectively.

Table 3.2.7 Sponsor's Analysis Results of Mean Change from Baseline for LOCF data on CGI Severity Score for Study CN138013

Visit	Placebo N = 73	Lor 2 mg N = 68	Ari 10 mg N = 75	Ari 15 mg N = 75	Nominal P-Values (vs. Placebo)		
					Lor 2 mg	Ari 10 mg	Ari 15 mg
Baseline	4.12	4.16	4.24	4.09	0.643	0.202	0.710
30 Min	-0.27	-0.45	-0.33	-0.24	0.133	0.599	0.805
45 Min	-0.55	-0.78	-0.77	-0.76	0.121	0.134	0.154
60 Min	-0.80	-1.06	-0.98	-0.97	0.096	0.239	0.257
90 Min	-0.88	-1.46	-1.22	-1.17	<0.001	0.035	0.074
120 Min	-0.94	-1.61	-1.48	-1.34	<0.001	0.001	0.015
4 Hrs	-0.88	-1.78	-1.66	-1.67	<0.001	<0.001	<0.001
6 Hrs	-1.16	-1.89	-1.89	-1.71	<0.001	<0.001	0.002
12 Hrs	-1.89	-2.28	-2.11	-1.98	0.024	0.184	0.584
24 Hrs	-1.10	-1.24	-1.23	-1.09	0.389	0.411	0.972

Note: Lor and Ari are abbreviations for lorazepam and aripiprazole, respectively.
Source: Table 10.2.1.2 of the sponsor's clinical study report.

Agitation-Calmness Evaluation Scale (ACES)

The sponsor's results for ACES for the LOCF data are shown in Table 3.2.8. As shown in the table, at 2 hours post first IM injection (LOCF data set), the results for ACES Score showed statistically significant differences when the 10-mg, 15-mg aripiprazole groups, and the lorazepam group were compared with placebo, respectively.

Table 3.2.8 Sponsor's Analysis Results of Mean Change from Baseline for LOCF data on ACES Score for Study CN138013

Visit	Placebo N = 73	Lor 2 mg N = 68	Ari 10 mg N = 75	Ari 15 mg N = 75	Nominal P-Values vs. Placebo		
					Lor 2 mg	Ari 10 mg	Ari15 mg
Baseline	2.38	2.38	2.28	2.41	0.948	0.154	0.723
30 Min	0.49	0.60	0.43	0.50	0.507	0.747	0.952
45 Min	0.69	0.96	1.01	1.08	0.200	0.124	0.057
60 Min	0.88	1.38	1.26	1.33	0.034	0.103	0.053
90 Min	1.06	1.98	1.64	1.74	0.001	0.041	0.015
120 Min	1.00	2.34	1.87	2.32	<0.001	0.003	<0.001
4 Hrs	1.06	2.90	2.50	2.78	<0.001	<0.001	<0.001
6 Hrs	1.22	2.91	2.52	2.48	<0.001	<0.001	<0.001
12 Hrs	3.31	3.79	3.46	3.35	0.114	0.622	0.899
24 Hrs	0.80	1.04	1.02	0.94	0.078	0.106	0.297

Note: Lor and Ari are abbreviations for lorazepam and aripiprazole, respectively.

Source: Table 10.2.2 of the sponsor's clinical study report.

Corrigan Agitated Behavior Scale (CABS)

The sponsor's results for CABS for the LOCF data are shown in Table 3.2.9. As shown in the table, at 2 hours post first IM injection, the results for CABS Score showed statistically significant differences when the 10-mg, 15-mg aripiprazole groups, and the lorazepam group were compared with placebo, respectively.

Table 3.2.8 Sponsor's Analysis Results of Mean Change from Baseline for LOCF data on CABS Score for Study CN138013

Visit	Placebo N = 73	Lor 2 mg N = 68	Ari 10 mg N = 75	Ari 15 mg N = 75	Nominal P-Values (vs. Placebo)		
					Lor 2 mg	Ari 10 mg	Ari15 mg
Baseline	28.38	28.96	29.36	28.00	0.389	0.137	0.555
30 Min	-3.67	-4.15	-4.02	-4.02	0.463	0.589	0.581
45 Min	-5.15	-6.80	-6.94	-6.24	0.035	0.020	0.150
60 Min	-6.38	-8.56	-8.07	-8.22	0.007	0.030	0.018
90 Min	-6.93	-10.00	-9.18	-8.65	<0.001	0.008	0.040
120 Min	-6.37	-10.35	-9.60	-9.08	<0.001	<0.001	0.002
4 Hrs	-6.87	-11.13	-10.29	-10.74	<0.001	<0.001	<0.001
6 Hrs	-8.10	-11.62	-12.18	-10.82	<0.001	<0.001	<0.001
12 Hrs	-11.51	-12.71	-12.52	-11.77	0.102	0.160	0.712
24 Hrs	-7.10	-7.82	-8.36	-7.32	0.398	0.131	0.787

Note: Lor and Ari are abbreviations for lorazepam and aripiprazole, respectively.

Source: Table 10.2.3 of the sponsor's clinical study report.

Number and Percentage of PEC Responders

A PEC responder was defined as a patient with a reduction of $\geq 40\%$ in the PEC Score compared with baseline. At 2 hours post first IM injection (LOCF data set), statistically significantly higher response rates were observed for 10-mg aripiprazole and 15 mg aripiprazole, as well as for lorazepam when compared with placebo. Table 3.2.9 shows the sponsor's analysis results of the number and percentage of responders for the LOCF data sets.

Table 3.2.9 Sponsor's Analysis Results for Number and Percentage of PEC-Responders for the LOCF Data for Study CN138013

Visit	Placebo N = 73	Lor 2 mg N = 68	Ari 10 mg N = 75	Ari 15 mg N = 75	Nominal P-Values (vs. Placebo)		
					Lor 2 mg	Ari 10 mg	Ari15 mg
30 Min	13 (18)	13 (19)	9 (12)	10 (13)	0.994	0.248	0.350
45 Min	19 (26)	20 (29)	28 (37)	26 (35)	0.775	0.148	0.226
60 Min	27 (37)	29 (43)	32 (43)	36 (48)	0.610	0.479	0.205
90 Min	30 (41)	42 (62)	43 (57)	39 (52)	0.023	0.046	0.195
120 Min	27 (37)	47 (69)	52 (69)	47 (63)	<0.001	<0.001	0.002

Note: Lor and Ari are abbreviations for lorazepam and aripiprazole, respectively.

Source: Table 10.2.4 of the sponsor's clinical study report.

PEC Individual Item Scores

Improvement in all PEC individual item scores was observed at 2 hours post first IM injection (LOCF data set) for the 10 mg and 15 mg aripiprazole groups, as well as for placebo and lorazepam. All active treatment groups were statistically superior to placebo in all PEC items.

3.1.2.4 Statistical Reviewer's Findings and Comments

1. This reviewer completely confirmed the sponsor's analysis results for the primary and secondary endpoints. Overall, this study is positive, where the data supported the efficacy of IM aripiprazole at 2 hours in the treatment of acutely agitated patients with a diagnosis of Bipolar I disorder, manic or mixed.

3.1.3 Description of Study CN138012

This study was entitled "A Randomized, Double-Blind Comparison of the Efficacy and Safety of Aripiprazole Intramuscular Formula, Haloperidol, or Placebo in the Treatment of Acutely Agitated Patients with a Diagnosis of Schizophrenia or Schizoaffective Disorder." There were 68 study centers (40 in USA, 6 in Czech Republic, 6 in France, 3 in Estomia, 3 in Latvia, 3 in Poland, 3 in Croatia, 1 in Italy, 1 in Puerto Rico, 1 in South Africa, and 1 in Spain) participating in the conduct of this study.

3.1.3.1 Study Objectives

Primary Objectives:

- To compare the efficacy of IM aripiprazole with placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia or schizoaffective disorders as assessed by the mean change from baseline to 2 hours post IM injection using the PEC scale.

- To determine if efficacy of IM aripiprazole is non-inferior to IM haloperidol in the treatment of acute agitation in patients with a diagnosis of schizophrenia or schizoaffective disorder as assessed by the mean change from baseline to 2 hours post-IM injection using the PEC scale.

Secondary Objectives:

- To compare the efficacy of IM aripiprazole with placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia or schizoaffective disorder as assessed by the Clinical Global Impressions-Improvement (CGI-I), Agitation-Calmness Evaluation Scale (ACES), Clinical Global Impression-Severity of Illness (CGI-S), Corrigan Agitated Behavior Scale (CABS).
- To compare the effects of IM haloperidol (a known active therapy, and standard of care in the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder) with placebo.
- To determine the safety and tolerability of IM aripiprazole in the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder. This was assessed by the mean change from baseline to each specified observation time in the Simpson-Angus Scale (SAS) and the Barnes Akathisia Rating Scale. Safety and tolerance was evaluated by reports of adverse events (AEs) and clinically significant changes in electrocardiograms (ECGs), vital signs, and laboratory tests.
- To measure the efficacy and safety of transition from IM aripiprazole to oral aripiprazole in the treatment of acute agitation in patients with schizophrenia.

Reviewer's Note:

- (1) Although the primary objective of this study was to assess the efficacy of 10 mg IM aripiprazole in the treatment of acutely agitated patients with a diagnosis of schizophrenia or schizoaffective disorder, this review only evaluated patients with schizophrenia since this is the population for which the oral formulation was approved. This comment had been conveyed to the sponsor during the meeting held on June 9, 2004.
- (2) The efficacy comparison between IM aripiprazole and IM haloperidol by using non-inferiority test is not for the purpose of approval in the US, so the sponsor's analysis results for this comparison were not evaluated by this reviewer and thus not reported in this review.

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3.1.3.2 Study Design

This was a double-blind, randomized, multicenter study comparing IM aripiprazole (10 mg) and IM haloperidol (6.5 mg) with IM placebo in the treatment of acute agitation in voluntarily hospitalized patients with a diagnosis of schizophrenia or schizoaffective disorder.

The study began with a 2-hour screening period (maximum 12 hours) prior to first IM injection. Baseline assessments, which were performed within 1 hour prior to the first IM injection of study drug, included the PANSS Excited Component (PEC), ACES, CGI-S, CABS, SAS, and Barnes Akathisia Rating Scale. Efficacy evaluations, for the IM Treatment Phase of the study, were performed at baseline (within 1 hour before the first injection), at time points 0.5, 0.75, 1.0, 1.5, 2.0, 4.0, 6.0, 12, and 24 hours after the first injection.

After completing the 24-Hour IM Phase, patients received blinded oral tablet and capsule study medication corresponding to their initial treatment arm for 4 days and were evaluated as inpatients.

3.1.3.3 Efficacy Endpoints and Analyses

The primary efficacy endpoint was the mean change from baseline to 2 hours post first IM injection in the PEC Score for the LOCF data set. The key secondary efficacy endpoint was the mean CGI-I Score at 2 hours post first IM injection. Other secondary efficacy endpoints were the mean change from baseline to 2 hours post first IM injection in the ACES Score, the CGI-S Score, the CABS Score, and the PEC Individual Items Score, and the PEC Responder Analysis (response defined as a patient with a reduction of $\geq 40\%$ in PEC Score compared with baseline) at 2 hours post first IM injection.

The primary efficacy endpoint was evaluated by the analysis of covariance (ANCOVA) model that included terms for treatment, country, and baseline score. Model-based mean change from baseline in the PEC Score by treatment group and the treatment differences with placebo (with 95% confidence intervals [CI]) were conducted.

In order to preserve the overall type I error rate at 0.05 level, the two research hypotheses involving the primary efficacy measure were tested sequentially. First, a 2-sided test to compare the 10-mg aripiprazole IM group with the placebo group was performed at the 0.05 significance level. Then, and only if the former test yielded a positive result favoring aripiprazole, the non-inferiority hypothesis of IM aripiprazole to IM haloperidol was then tested. The upper limit of the 95% confidence interval for the contrast of IM aripiprazole with IM haloperidol was compared to a non-inferiority bound that equaled 40% of the observed mean change from baseline to 2 hours post first IM injection in the haloperidol treatment group (LS Means) in order to show that IM aripiprazole retained 60% of IM haloperidol's efficacy.

In addition to the primary analysis, the change from baseline in the PEC Score at all timepoints, for both the IM and the Oral Phase, were evaluated by ANCOVA. Model-based mean change from baseline in the PEC Score by treatment group and all pairwise treatment differences (with 95% CI) were analyzed.

The treatment differences on the full scale of CGI-I was analyzed using the Cochran-Mantel-Haenszel (CMH) Row Means Score test for each timepoint 30, 45, 60, 90 minutes, and 2, 4, 6, 12, and 24 hours after the first IM injection using the LOCF and OC data sets.

The CGI-I was prospectively identified as a key secondary endpoint and thus a hierarchical testing procedure was planned so that the overall type I error rate was controlled. The CGI-I was tested only if, first, the aripiprazole treatment group was shown to be significantly different from placebo on the primary efficacy outcome measure, and second, the aripiprazole treatment group was shown to be statistically non-inferior to haloperidol on the primary efficacy outcome measure. The above test was performed at the 0.05 (2-sided) significance level. The outcome of the test for the key confirmatory endpoint did not affect the statistical significance achieved for the primary endpoint.

Mean change from baseline in CGI-S Score, ACES Score, and CABS Score, at each timepoint 30, 45, 60, 90 minutes, and 2, 4, 6, 12, and 24 hours after the first IM injection were analyzed by ANCOVA, using the LOCF and OC data sets.

Mean change from baseline to 2 hours after the first IM injection in each PEC individual item score was analyzed by ANCOVA, using the LOCF and OC data sets.

3.1.4 Efficacy Results for Study CN138012

3.1.4.1 Patient Disposition, Population and Baseline Demographic Characteristics

A total of 469 patients were enrolled in the study. Of these, 448 patients were randomized to double-blind treatment: 88 to placebo group, 185 to the 6.5-mg haloperidol group, and 175 to 10-mg aripiprazole group. A total of 435 (97%) of the 448 patients completed the IM Phase of the double-blind study. The primary reason for discontinuation from double-blind treatment was because of patient withdrawal of consent (5 patients [1%]). A total of 380 (85%) of the 448 patients transitioned from the double-blind IM Phase to the double-blind Oral Phase: 76 from the placebo group, 151 from the 6.5-mg haloperidol group, and 153 from 10-mg aripiprazole group. Thirty-nine (10%) patients discontinued from the Oral Phase. The primary reason for discontinuation from double-blind treatment was because of patient withdrawal of

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consent (20 patients [5%]). Table 3.4.1 shows the distribution of all randomized patients within each of the patient samples, Table 3.4.2 shows the psychiatric evaluation of patients in the randomized sample, Table 3.4.3 shows demographic characteristics for the randomized sample by treatment group, and Table 3.4.4 shows baseline ratings of the randomized sample.

Table 3.4.1 Number of Patients in Sample for Study CN138012

Sample	IM Placebo	IM Haloperidol	IM Aripiprazole	Total
		6.5 mg	10 mg	
Randomized	88	185	175	448
Safety	87	183	175	445
Efficacy	88	184	173	445

Source: Table 8.2A of the sponsor's clinical study report.

Table 3.4.2 Psychiatric Evaluation for Randomized Sample for Study CN138012

	IM Placebo	IM Haloperidol	IM Aripiprazole	Total
	N=88	6.5 mg N=185	10 mg N=175	N=448
Diagnosis N (%)				
Schizoaffective Disorder	23 (26)	50 (27)	50 (29)	123 (27)
Schizophrenia	65 (74)	135 (73)	125 (71)	325 (73)

Source: Table 8.4A of the sponsor's clinical study report.

Table 3.4.3 Demographic Characteristics for Randomized Sample for Study CN138012

	IM Placebo	IM Haloperidol	IM Aripiprazole	Total
	N=88	6.5 mg N=185	10 mg N=175	N=448
Age (years)				
Mean	40.33	41.77	41.90	41.54
SD	9.78	9.65	10.72	10.10
Gender N (%)				
Male	55 (63)	110 (59)	110 (63)	275 (61)
Female	33 (38)	75 (41)	65 (37)	173 (39)
Race N (%)				
White	60 (68)	113 (61)	122 (70)	295 (66)
Black/African American	27 (31)	65 (35)	47 (27)	139 (31)
Indian/Alaskan Native	1 (1)	1 (1)	2 (1)	4 (1)
Other	0	2 (1)	2 (1)	4 (1)
Ethnicity (US only) N %				
Hispanic/Latino	5 (6)	17 (9)	12 (7)	34 (8)
Not Hispanic/Latino	59 (67)	117 (63)	118 (67)	294 (66)
Non-US N %	24 (27)	51 (28)	45 (26)	120 (27)

Source: Table 8.3 of the sponsor's clinical study report.

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Table 3.4.4 Baseline Ratings for Randomized Sample for Study CN138012

	IM Placebo	IM Haloperidol 6.5 mg	IM Aripiprazole 10 mg	Total
	N=88	N=185	N=175	N=448
PANSS PEC TOTAL Mean (SD)	18.74 (2.71)	18.79 (2.59)	18.82 (2.67)	18.79 (2.64)
ACES SCORE Mean (SD)	2.23 (0.56)	2.21 (0.54)	2.19 (0.57)	2.21 (0.56)
CABS SCORE Mean (SD)	28.49 (4.64)	29.31 (5.03)	29.69 (5.22)	29.30 (5.04)
CGI-SEVERITY SCORE Mean (SD)	4.38 (0.75)	4.39 (0.72)	4.38 (0.75)	4.38 (0.74)
BPRS POSITIVE SCORE Mean (SD)	14.73 (3.83)	15.13 (3.15)	15.22 (3.54)	15.08 (3.45)
BPRS TOTAL Mean (SD)	54.90 (9.52)	55.75 (8.42)	56.86 (9.90)	56.02 (9.25)

Source: Table 8.4B of the sponsor's clinical study report.

3.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

As mentioned earlier, in this section this reviewer will focus on the evaluation of sponsor's analysis results on the comparisons between IM aripiprazole 10 mg and placebo for the subgroup of patients with schizophrenia only. The sponsor performed non-inferiority analysis for the comparison between aripiprazole and haloperidol was not reviewed, and therefore, not addressed.

Table 3.4.5 shows the sponsor's analysis results for the primary endpoint in schizophrenia subpopulation. As shown in the table, statistically significantly greater mean decreases from baseline to 2 hours post first IM injection with placebo for the LOCF data set were demonstrated in the schizophrenia subpopulation for the 10 mg aripiprazole group ($p=0.003$) and for the 6.5 mg haloperidol group ($p<0.001$).

Table 3.4.5 Mean Change from Baseline in PEC Total Score for Schizophrenia Sub-Population LOCF Data Set for Study CN138012

Visit	Mean Change from Baseline			Nominal P-values		
	IM Placebo	IM Halo 6.5 mg	IM Arip 10 mg	IM Halo vs Placebo	IM Arip vs Placebo	IM Arip vs IM Halo
	N=65	N=134	N=123			
Baseline	18.89	18.78	18.79	0.773	0.799	0.970
30 Min	-3.68	-3.63	-3.22	0.930	0.448	0.408
45 Min	-4.76	-5.84	-4.85	0.121	0.893	0.087
60 Min	-5.46	-7.31	-6.32	0.009	0.226	0.090
90 Min	-5.94	-8.40	-7.02	<0.001	0.147	0.024
120 Min	-5.68	-8.25	-7.99	<0.001	0.003	0.668
4 hrs	-6.10	-9.18	-9.08	<0.001	<0.001	0.866
6 hrs	-7.82	-9.75	-9.45	0.006	0.021	0.603
12 hrs	-10.49	-11.21	-10.95	0.290	0.508	0.639
24 hrs	-7.66	-7.63	-8.02	0.959	0.575	0.452

Source: Table 10.1C of the sponsor's clinical study report.

3.1.4.3 Sponsor's Efficacy Results for Key Secondary Endpoints

Table 3.4.6 shows the sponsor's analysis results for the key secondary endpoint, CGI-improvement score in the schizophrenia subpopulation. As shown in the table, the 10 mg aripiprazole group and the 6.5 haloperidol group had statistically significantly smaller CGI-I Score means than placebo at the 2 hour time point.

Table 3.4.6 Mean CGI-Improvement Score for Schizophrenia Sub-population LOCF Data Set for Study CN138012

Visit	Mean Change from Baseline			Nominal P-values		
	IM Placebo	IM Halo 6.5 mg	IM Arip 10 mg	IM Halo vs Placebo	IM Arip vs Placebo	IM Arip vs IM Halo
	N=65	N=134	N=123			
30 Min	3.26	3.30	3.35	0.781	0.508	0.609
45 Min	3.12	2.90	2.94	0.164	0.243	0.740
60 Min	2.98	2.63	2.68	0.033	0.063	0.697
90 Min	2.97	2.40	2.56	<0.001	0.015	0.226
120 Min	3.03	2.39	2.41	<0.001	<0.001	0.890
4 hrs	2.94	2.27	2.16	<0.001	<0.001	0.415
6 hrs	2.51	2.10	2.12	0.010	0.026	0.840
12 hrs	2.00	1.84	1.91	0.317	0.588	0.587
24 hrs	2.51	2.47	2.33	0.809	0.226	0.240

Source: Table 10.2.1.1B of the sponsor's clinical study report.

3.1.4.4 Reviewer's Efficacy Results for Other Secondary Endpoints

For other secondary endpoints, including the mean change from baseline to 2 hours post first IM injection in the CGI-S Score, the ACES Score, the CABS Score, and the PEC Individual Items Score, and the PEC Responder, the sponsor did not perform the analyses for schizophrenia sub-population. This reviewer performed the analyses by the ANCOVA model with factors treatment and country and the covariate, baseline values for the mean change from baseline endpoints and the unstratified CMH method for the responder endpoint. Table 3.4.7 shows this reviewer's analysis results.

Table 3.4.7 Reviewer's Analysis Results for Other Secondary Endpoints for Study CN138012

Variable	Mean Change from Baseline to 2 Hours			Nominal P-values		
	IM Placebo	IM Halo 6.5 mg	IM Arip 10 mg	IM Halo vs Placebo	IM Arip vs Placebo	IM Arip vs IM Halo
	N=65	N=134	N=123			
CGI-S	-0.67	-1.09	-1.08	0.023	0.03	0.933
ACES	0.92	1.65	1.42	0.007	0.0661*	0.3101
CABS	-4.41	-7.70	-7.50	<0.001	<0.001	0.783
PEC1	-1.11	-1.55	-1.46	0.013	0.054	0.523
PEC2	-1.09	-1.57	-1.54	0.013	0.024	0.820
PEC3	-0.98	-1.38	-1.38	0.010	0.013	0.954
PEC4	-1.01	-1.69	-1.58	<0.001	0.003	0.458
PEC5	-0.66	-1.13	-1.10	0.001	0.003	0.755
PEC responder	27 (42%)	79 (59%)	70 (57%)	0.0212	0.045	0.741

* When country was not included into the ANCOVA model, the p-value for this comparison was 0.041.

3.1.4.5 Reviewer's Findings and Comments

1. This reviewer confirmed the sponsor's analysis results for the primary efficacy endpoint, PEC total score and the 'Key' secondary endpoint, CGI-Improvement score for schizophrenia patients. It was noticed that the sponsor's analysis for the primary endpoint, PEC total score was the ANCOVA model with only treatment factor and a covariate, baseline score. The model to analyze the PEC total score for the whole study population in the protocol also included the country factor, so this reviewer also performed the analysis by including the country factor into the ANCOVA model. It was found that the results were consistent whether or not the factor of country was included in the ANCOVA model.
2. Based on the analysis results for the PEC total score and CGI-Improvement score, we can conclude that the data of this study from only schizophrenia patients support the efficacy of IM aripiprazole 10 mg as a treatment of acute agitation in patients with a diagnosis of schizophrenia.

3.1.5 Description of Study CN138050

This study was entitled "Randomized, Double-Blind, Dose-Ranging Study of Intramuscular aripiprazole in the Treatment of Acute Agitation in Patients with a Diagnosis of Schizophrenia, Schizoaffective, or Schizophreniform Disorder." There were 50 study centers (30 in USA, 3 in Canada, 2 in Estonia, 3 in Latvia, 2 in Lithuania, 2 in Czech Republic, 7 in France, and 1 in Spain) participating in the conduct of this study.

3.1.5.1 Study Objectives

Primary Objective:

- The primary objective was to compare the efficacy of IM aripiprazole with placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder, as assessed by the mean change from baseline to 2 hours postdose using the PEC scale.

Secondary Objectives:

- To assess the efficacy of IM aripiprazole compared with placebo in the treatment of acute agitation in patients with schizophrenia, schizoaffective, or schizophreniform disorder.
- To compare the effects of IM haloperidol, a known active therapy and standard of care in the treatment of acute agitation in patients with schizophrenia, schizoaffective, or schizophreniform disorder, with placebo.

- To describe the safety and tolerability of IM aripiprazole in the treatment of acute agitation in patients with schizophrenia, schizoaffective, or schizophreniform disorder.
- To explore the correlation between post-injection plasma concentrations of aripiprazole/active metabolite and response on the primary efficacy endpoint (change from baseline to 2 hours postdose on the PEC score), and to perform population pharmacokinetic (PK) analyses for aripiprazole IM.
- To provide data to be used in the selection of 1 of the 3 doses to be taken forward for evaluation in a confirmatory trial in this population.

3.1.5.2 Study Design

This was a randomized, double-blind, multicenter, dose-ranging study comparing 4 doses of IM aripiprazole (1 mg, 5 mg, 10 mg, and 15 mg) and 1 dose of IM haloperidol (7.5 mg) with placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder.

The study began with a screening evaluation, followed by baseline assessments that will be performed within 1 hour prior to administration of the first dose of study drug, followed by an inpatient evaluation period of 24 hours. Patients were randomized in a 1:1:1:1:1:1 ratio to receive an initial dose in one of the six dosage groups. A second dose was given, if needed, at least 2 hours after the initial dose followed by a third dose of study medication, if needed, which was given at least 4 hours after the initial dose and at least 2 hours after the second dose. A repeat dose of study medication might be given no later than 20 hours after the administration of the initial dose of study medication.

3.1.5.3 Efficacy Endpoints and Analyses

Efficacy Endpoints:

The primary efficacy endpoint was the mean change from baseline to 2 hours post first IM injection in the PEC Score for the LOCF data set. Key secondary efficacy endpoints were the mean change from baseline to 2 hours post first IM injection in the ACES Score, CABS Score and CGI Severity of Illness Score for the LOCF data set. In addition, the mean CGI Improvement Score was analyzed. Other secondary endpoints were the mean change from baseline to other time points in the ACES Score, CABS Score, and CGI Severity of Illness Score for the LOCF and OC data sets, the mean CGI Improvement Score, the mean change from baseline to 2 hours post first IM injection in the PEC Individual Item Score (LOCF and OC data sets) PEC Response Rate, defined as a reduction of $\geq 40\%$ in PEC Score compared with baseline, (LOCF and OC data sets), etc.

Reviewer's Note: Although the sponsor pre-specified four key secondary endpoints in this study, during the meeting with the sponsor on June 9, 2004, the FDA informed the sponsor that only one of CGI-I or CGI-S scores would be acceptable for being chosen as a key secondary endpoint. Since the sponsor only performed the CGI-I analysis for the schizophrenia subpopulation, this review only reported the sponsor's secondary endpoint analysis results for this CGI-I scores in Section 3.1.6.3.

Efficacy Analyses:

The primary efficacy endpoint, the mean change from baseline to 2 hours post first IM injection in the PEC Score was evaluated by the analysis of covariance (ANCOVA) model that included terms for treatment, country, and baseline score, using the LOCF data from the efficacy sample. In order to protect the overall type I error rate at 0.05 level when making 3 comparisons of IM aripiprazole doses (5, 10, 15 mg) with placebo, the statistical testing was carried out using the Hochberg procedure.

For the ACES, CABS, and CGI Severity scores, the analysis was ANCOVA, with baseline measure as covariate and country and treatment group as main effects. For CGI Improvement, the analysis was the Cochran-Mantel Haenszel (CMH) Row Means test, with adjustments for country and treatment group.

Based on the study report, the sponsor stated that for the key secondary analyses, Hochberg's procedure was applied, and a hierarchical testing procedure was used in order to minimize the overall experiment-wise type I error rate. Specifically, only treatment groups that showed statistically superior to placebo from the primary efficacy analysis were further tested for the key secondary endpoint.

Reviewer's Note:

- (1) Although there were four aripiprazole dose groups included in the study, based on the pre-specified Hochberg's procedure in the protocol, only three higher dose groups (5 mg, 10 mg and 15 mg) were interested in comparison with placebo.
- (2) The sponsor's multiple comparison procedure by the Hochberg's method as stated above in Section 3.1.5.3 for the primary endpoint and key secondary endpoints does not control the study-wise overall type I error rate. To control the study-wise type I error rate, the key secondary endpoint can only be tested when all interested treatment groups win on the comparisons with placebo by the pre-specified Hochberg's procedure.

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3.1.6 Efficacy Results for Study CN138050

3.1.6.1 Patient Disposition, Population and Baseline Demographic Characteristics

A total of 378 patients were enrolled in the study. Of these, 357 patients were randomized to double-blind treatments: 62 to the placebo group, 60 to the haloperidol group, 57 to 1-mg aripiprazole group, 63 to the 5-mg aripiprazole group, 57 to the 10-mg aripiprazole group, and 58 to the 15-mg aripiprazole group. A total of 338 (95%) of the 357 patients completed the double-blind study. Nineteen (5%) patients discontinued from double-blind treatments. The primary reason for discontinuation from double-blind treatment was patient withdrawal of consent (12 patients [3%]).

Table 3.1.6.1 shows the distribution of all randomized patients within each of the patient samples. Table 3.1.6.2 shows the demographic characteristics for the randomized sample. Table 3.1.6.3 shows the psychiatric evaluation of patients in the randomized sample.

Table 3.1.6.1 Number of Patients in Samples for Study CN138050

Sample	IM	IM	IM	IM	IM	IM	Total
	Placebo	Haloperidol 7.5 mg	Aripiprazole 1 mg	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg	
Randomized	62	60	57	63	57	58	357
Safety	61	57	56	62	56	58	350
Efficacy	61	57	56	62	56	58	350

Source: Table 8.2A of the sponsor's clinical study report.

Table 3.1.6.2 Demographic Characteristics in Randomized Sample for Study CN138050

	Variable	IM	IM	IM	IM	IM	IM
		Placebo	Haloperidol 7.5 mg	Aripiprazole 1 mg	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg
		N=62	N=60	N=57	N=63	N=57	N=58
Age (yrs)	Mean	40.29	40.85	41.46	39.46	41.18	44.24
	SD	10.74	10.16	10.12	10.19	10.88	9.96
Gender N(%)	Men	32 (52)	39 (65)	37 (65)	35 (56)	36 (63)	35 (60)
	Women	30 (48)	21 (35)	20 (35)	28 (44)	21 (37)	23 (40)
Race N(%)	White	38 (61)	43 (72)	39 (68)	47 (75)	41 (72)	40 (69)
	Black	17 (27)	13 (22)	12 (21)	12 (19)	9 (16)	13 (22)
	Asian/Pacific Islander	0	0	0	1 (2)	2 (4)	0
	Hispanic/Latino	7 (11)	3 (5)	5 (9)	2 (3)	5 (9)	4 (7)
	American/Alaskan Native	0	0	1 (2)	0	0	0
	Other	0	0	0	1 (2)	0	1 (2)

Source: Table 8.3 of the sponsor's clinical study report.

Table 3.1.6.3 Psychiatric Evaluation in Randomized Sample for Study CN138050

Number and Percentage	IM	IM	IM	IM	IM	Total	
	IM Placebo N=62	Haloperidol 7.5 mg N=60	Aripiprazole 1 mg N=57	Aripiprazole 5 mg N=63	Aripiprazole 10 mg N=57		Aripiprazole 15 mg N=58
Diagnosis							
Schizoaffective Disorder	21 (34)	13 (22)	26 (46)	21 (33)	18 (32)	14 (24)	113 (32)
Schizophrenia	39 (63)	46 (77)	30 (53)	41 (65)	37 (65)	44 (76)	237 (66)
Schizophreniform disorder	2 (3)	1 (2)	1 (2)	1 (2)	2 (4)	0	7 (2)

Source: Table 8.4A of the sponsor's clinical study report.

3.1.6.2 Sponsor's Efficacy Results for Primary Endpoint

Table 3.1.6.4 shows the sponsor's analysis results for the primary endpoint, change from baseline in PEC total score on schizophrenia subpopulation. Based on the sponsor's study report, statistically significant mean changes from baseline to 2 hours post first IM injection with placebo in LOCF data set, were demonstrated in the schizophrenia subpopulation for the haloperidol 7.5-mg group, and for the aripiprazole 5-mg, 10-mg and 15-mg groups. However, if we adjust alpha for multiple comparisons due to different doses, only the efficacy of 10 mg of aripiprazole was demonstrated (See Comment #2 of Section 3.1.6.4).

Table 3.1.6.4 Mean Change from Baseline in PEC Total Score for Schizophrenia Subpopulation LOCF Data Set for Study CN138050

Visit	Mean Change from Baseline						Nominal P-values*				
	Placebo	Halo 7.5 mg	Arip 1 mg	Arip 5 mg	Arip 10 mg	Arip 15 mg	Halo 7.5mg vs. P	Arip 1 mg vs. P	Arip 5 mg vs. P	Arip 10 mg vs. P	Arip 15 mg vs. P
	N=39	N=43	N=30	N=40	N=36	N=44					
Baseline	19.46	18.67	18.87	19.08	18.97	19.20	0.199	0.377	0.535	0.445	0.673
15 Min	-2.20	-0.82	-0.95	-1.35	-1.87	-1.92	0.032	0.076	0.191	0.622	0.661
30 Min	-3.08	-2.53	-1.81	-2.52	-4.31	-3.10	0.516	0.168	0.514	0.159	0.975
45 Min	-3.53	-4.50	-2.95	-4.17	-5.65	-4.08	0.290	0.568	0.488	0.028	0.546
60 Min	-4.26	-5.70	-3.35	-4.87	-6.54	-5.82	0.145	0.402	0.539	0.027	0.110
75 Min	-4.86	-6.08	-3.73	-5.52	-7.09	-5.89	0.226	0.300	0.517	0.033	0.303
90 Min	-5.27	-6.59	-4.43	-6.02	-7.79	-6.34	0.199	0.459	0.472	0.020	0.296
105 Min	-5.36	-7.30	-4.83	-6.87	-8.15	-6.70	0.071	0.656	0.166	0.013	0.209
120 Min	-4.78	-7.32	-4.87	-6.94	-7.82	-6.94	0.020	0.935	0.050	0.008	0.045
4 Hrs	-4.99	-8.22	-5.48	-7.99	-8.02	-8.30	0.003	0.674	0.006	0.007	0.002
6 Hrs	-6.36	-8.32	-6.18	-8.46	-8.64	-9.11	0.053	0.867	0.041	0.031	0.006
12 Hrs	-8.07	-9.24	-7.37	-10.31	-9.79	-10.36	0.224	0.510	0.023	0.087	0.017
24 Hrs	-5.92	-5.59	-4.65	-7.81	-7.15	-8.43	0.750	0.262	0.070	0.253	0.014

* ANOVA model, controlling for Treatment, is used for baseline comparisons. ANCOVA model, controlling for Treatment and Baseline value is used for mean change from baseline comparisons. The reported p-values are nominal p-values.

Source: Sponsor's Table 10.1B in the clinical study report.

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3.1.6.3 Sponsor's Efficacy Results for Key Secondary Endpoint

According to the sponsor, the mean change from baseline to 2 hours (LOCF) post first IM injection in ACES Score, the CABS Score, the mean CGI Improvement Score, and the mean change from baseline to 2 hours post first IM injection in the CGI Severity of Illness Score were pre-specified as key secondary outcome measures, although the FDA only accepted either CGI-I or CGI-S as a key secondary outcome measure. Since for the schizophrenia subpopulation patients, which is the main interested population of patients we focus on for this study, the sponsor only performed the analyses for the CGI Improvement score, in this section only sponsor's results for this key secondary outcome measure are reported. Table 3.1.6.5 shows the sponsor's analysis results for the mean CGI Improvement score in the schizophrenia subpopulation. As shown in the table at the 2 hour time point, the 7.5 mg haloperidol group, as well as the 5-mg, 10 mg and 15 mg aripiprazole groups were statistically significant from placebo.

Table 3.1.6.5 Mean CGI Improvement Score for Schizophrenia Subpopulation in LOCF Data Set for Study 138050

Visit	Least Square Mean Change from Baseline						Pair-wise Comparison P-values*				
	Placebo	Halo	Arip	Arip	Arip	Arip 15	Halo	Arip	Arip	Arip	Arip
	N=39	7.5 mg N=43	1 mg N=30	5 mg N=40	10 mg N=36	15 mg N=44	7.5mg vs. P	1 mg vs. P	5 mg vs. P	10 mg vs. P	15 mg vs. P
15 Min	3.82	3.88	3.93	3.80	3.56	3.66	0.547	0.364	0.858	0.062	0.269
30 Min	3.64	3.49	3.67	3.53	3.22	3.43	0.302	0.858	0.429	0.017	0.253
45 Min	3.46	3.05	3.43	3.20	3.00	3.23	0.023	0.864	0.152	0.024	0.215
60 Min	3.46	2.84	3.43	2.98	2.78	2.98	0.002	0.875	0.012	0.003	0.017
75 Min	3.38	2.86	3.37	2.88	2.67	2.86	0.010	0.923	0.006	0.002	0.014
90 Min	3.33	2.79	3.33	2.75	2.67	2.80	0.005	1.000	0.001	0.002	0.011
105 Min	3.36	2.70	3.17	2.68	2.64	2.70	0.001	0.324	<0.001	0.003	0.003
120 Min	3.38	2.65	3.30	2.65	2.67	2.68	<0.001	0.689	<0.001	0.004	0.002
4 Hrs	3.28	2.60	3.07	2.53	2.78	2.55	0.004	0.322	<0.001	0.044	0.002
6 Hrs	3.00	2.65	2.97	2.45	2.39	2.39	0.126	0.874	0.008	0.004	0.005
12 Hrs	2.72	2.63	2.67	2.25	2.22	2.25	0.696	0.807	0.014	0.020	0.017
24 Hrs	2.97	2.86	3.00	2.30	2.81	2.32	0.637	0.911	0.002	0.520	0.004

* CMH row means score test controlling for Treatment. The reported p-values are nominal p-values.

3.1.6.3 Reviewer's Efficacy Results for Other Secondary Endpoints

Except the CGI Improvement Score, for the schizophrenia subpopulation, the sponsor did not perform the analyses for other secondary endpoints. Table 3.1.6.6 showed this reviewer's analysis results for CGI-S, ACES, CABS and PEC individual item scores for the change from baseline to 2 hours by the ANCOVA model with treatment and country factors and the baseline scores as the covariate. It also included the unstratified CMH analysis for responder analysis on PEC scores ($\geq 40\%$ reduction).

For exploratory purpose, as we can see from the table, if we consider multiple comparisons for each variable due to three interested doses, the efficacy of aripiprazole was shown on 10 mg and 15 mg for CGI-S and CABS total scores, on all three doses for the first two PEC items, and only 10 mg for ACES score.

Table 3.1.6.6 Reviewer's Analysis Results for Some Secondary Endpoints for Study 138050

Variable	Least Square Mean Change from Baseline						Nominal P-values				
	Placebo	Halo	Arip	Arip	Arip	Arip	Halo	Arip	Arip	Arip	Arip
	N=39	7.5 mg N=43	1 mg N=30	5 mg N=40	10 mg N=36	15 mg N=44	7.5mg vs. P	1 mg vs. P	5 mg vs. P	10 mg vs. P	15 mg vs. P
CGI-S	-0.53	-0.99	-0.53	-0.88	-1.05	-1.04	0.035	0.998	0.123	0.023	0.019
ACES	0.80	1.66	0.71	1.11	1.71	1.13	0.005	0.796	0.323	0.005	0.278
CABS	-3.53	-8.26	-5.36	-6.46	-6.81	-6.64	<0.001	0.193	0.027	0.015	0.015
PEC1	-0.56	-1.32	-0.80	-1.38	-1.39	-1.27	0.001	0.365	0.001	0.001	0.003
PEC2	-0.90	-1.74	-1.08	-1.58	-1.96	-1.55	0.002	0.540	0.012	<0.001	0.013
PEC3	-0.58	-1.30	-0.80	-1.08	-1.13	-0.92	0.002	0.391	0.035	0.024	0.146
PEC4	-1.05	-1.62	-1.05	-1.43	-1.68	-1.46	0.036	~1	0.165	0.025	0.125
PEC5	-0.76	-1	-0.81	-1	-1.06	-0.95	0.249	0.820	0.257	0.166	0.344
PEC	14	25	9	19	20	23	0.045	0.609	0.299	0.09	0.137
Responder	(36%)	(58%)	(30%)	(48%)	(56%)	(52%)					

3.1.6.4 Reviewer's Findings and Comments

1. Similar to Study CN138012, the sponsor's analysis results on the primary endpoint PEC total score for the schizophrenia subpopulation was based on the ANCOVA model without the country factor. The ANCOVA model specified in the protocol included treatment and country factors and the covariate, baseline score. This reviewer found that the results were consistent whether or not the factor of country was included in the ANCOVA model.
2. Four key secondary endpoints were specified in the study report. During an IND meeting with the sponsor (held on 6/9/2004), the FDA informed them because of some redundancy between the primary endpoint and most proposed secondary endpoints, only either CGI-I or CGI-S scores could be accepted as a key secondary endpoint. Nevertheless, it is not clear which one of two scores (CGI-I and CGI-S) was chosen as a final key secondary endpoint before the data was unblinded for this study.
3. As mentioned in Section 3.1.5.3, only three higher dose groups (5 mg, 10 mg and 15 mg) were designed to be compared with placebo. As shown in Table 3.1.6.4, all three nominal p-values for the comparison between these individual aripiprazole dose group (5 mg, 10 mg and 15 mg) and placebo in the primary endpoint PEC total score were less than or equal to 0.05, so it is suitable to further perform the testing between these individual doses and placebo for the key secondary endpoint (either CGI-I or CGI-S scores). This reviewer found that for CGI-I scores, all three dose groups of aripiprazole were shown to be statistically superior to placebo. However, for CGI-S score, only 10 mg and 15 mg group of aripiprazole showed statistically significant differences in comparisons with placebo.

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3.2 EVALUATION OF SAFETY

The statistical reviewer did not perform the evaluation of safety for this application. Please see the clinical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

4.1.1 Study CN138013

In the bipolar I disorder study, based on the following Table 4.1, aripiprazole group appeared to perform better than placebo on all subset analyses.

Table 4.1 Sponsor's Subgroup Analysis for Gender, Race and Age on the Primary Endpoint: Mean Change from Baseline to 2 Hours Post First IM Injection on PEC Score

Subgroup	Value	PEC Score					
		N	Placebo	N	Lorazepam	N	Aripiprazole
Age	<= Upper Quartile	60	-5.96	52	-9.25	113	-8.55
	> Upper Quartile	13	-3.95	16	-10.23	37	-8.73
Gender	Male	42	-6.17	30	-9.42	79	-9.12
	Female	31	-4.80	38	-9.51	71	-8.04
Race	White	51	-5.52	51	-9.91	109	-8.43
	Black	17	-6.24	15	-8.09	37	-8.82
	Other	5	-3.98	2	-9.20	4	-11.17

Source: Sponsor's Table 3.3A-2 in clinical study report.

4.1.2 Study CN138012

The sponsor did not perform any further subgroup analysis for the schizophrenia sub-population. In this section, the subgroup analysis results reported are from the statistical reviewer. As is shown in Table 4.2, for all subgroups, aripiprazole treatment group showed larger changes from baseline to 2 hours post first IM injection than placebo.

Table 4.2 Reviewer's Subgroup Analysis for Gender, Race and Age on the Primary Endpoint: Mean Change from Baseline to 2 Hours Post First IM Injection on PEC Score

Subgroup	Value	PEC Score					
		N	Placebo	N	Haloperidol	N	Aripiprazole
Age	<= 48 (75 percentile)	51	-5.33	108	-8.23	88	-8.15
	> 48	14	-6.83	26	-8.40	35	-7.60
Gender	Male	42	-5.85	83	-8.22	82	-7.38
	Female	23	-5.42	51	-8.29	41	-9.22
Race	White	42	-4.95	79	-7.59	81	-7.12
	Black	22	-7.04	50	-8.75	37	-9.61
	Other	1	-8.29	5	-12.28	5	-11.26

4.1.3 Study CN138050

Similar to Study CN138012, The sponsor did not perform any further subgroup analysis for the schizophrenia sub-population. In this section, the subgroup analysis results reported are from the statistical reviewer. As shown in Table 4.3, for all subgroups, aripiprazole 10 mg treatment group showed numerically larger changes from baseline to 2 hours post first IM injection than placebo.

Table 4.3 Reviewer's Subgroup Analysis for Gender, Race and Age on the Primary Endpoint: Mean Change from Baseline to 2 Hours Post First IM Injection on PEC Score

Subgroup	Value	PEC Score					
		N	Placebo	N	Haloperidol	N	Aripiprazole 1 mg
Age	<= 48 (75 percentile)	33	-3.47	34	-6.09	22	-4.61
	> 48	6	-5.70	9	-7.92	8	-3.27
Gender	Male	27	-4.56	28	-6.20	19	-4.88
	Female	12	-0.68	15	-7.40	11	-3.62
Race	White	23	-3.55	32	-6.97	20	-4.63
	Black	11	-4.22	7	-9.04	6	-6.58
	Other	5	-5.08	3	-4.34	4	-1.26

Subgroup	Value	PEC Score					
		N	Aripiprazole 5 mg	N	Aripiprazole 10 mg	N	Aripiprazole 15 mg
Age	<= 48 (75 percentile)	34	-5.67	26	-6.81	33	-6.24
	> 48	6	-8.98	10	-6.39	11	-4.03
Gender	Male	23	-6.13	24	-7.31	29	-6.46
	Female	17	-5.47	12	-5.01	15	-4.26
Race	White	30	-5.99	27	-6.77	31	-6.20
	Black	7	-6.05	5	-9.84	9	-6.43
	Other	3	-10.78	4	-5.68	4	-6.32

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

4.2.1 Study CN138013

For this bipolar study, the sponsor also performed the subgroup analyses for underlying diagnosis (manic or mixed status) and for baseline PEC Score. Table 4.3 showed the sponsor's analysis results. As shown in the table, the mean decreases from baseline in all these subpopulations were numerically greater in the aripiprazole group than the placebo group.

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Table 4.3 Sponsor's Subgroup Analysis for Underlying Diagnosis and Baseline PEC Score on the Primary Endpoint: Mean Change from Baseline to 2 Hours Post First IM Injection on PEC Score

Subgroup	Value	PEC Score					
		N	Placebo	N	Lorazepam	N	Aripiprazole
Underlying Diagnosis	Bipolar I Disorder						
	Manic	47	-4.21	46	-9.47	95	-8.38
	Mixed	26	-8.03	22	-9.48	55	-9.01
Baseline PEC Score	<= median	52	-4.37	43	-8.43	88	-7.87
	> median	21	-7.90	25	-11.37	62	-9.85

Source: Sponsor's Table 3.3A-2 in clinical study report.

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

For all three studies, this reviewer confirmed the sponsor's analysis results on the primary endpoint and all secondary endpoints. However, for two studies that patients' agitation due to schizophrenia, schizoaffective or schizophreniform disorder, the sponsor did not provide analysis results on other secondary endpoints for patients with only schizophrenia. The model they used to analyze for the primary endpoint also excluded the country factor, although this reviewer found that the results were consistent whether or not the factor of country was included in the model.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted three efficacy studies to seek the approval for the efficacy and safety of the IM injection formulation as a treatment of agitation in patients with schizophrenia or bipolar I disorder. After evaluation, this reviewer agreed with the sponsor that 10-mg IM aripiprazole was confirmed as effective in all three studies, in terms of the primary endpoint (PEC total score) and the key secondary endpoint (CGI-Improvement score) if it was determined that the CGI-Improvement was the pre-specified key secondary endpoint for the multiple dosed schizophrenia study (Study CN138050).

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