

In order to evaluate the data from the 3 pooled studies in schizophrenia and bipolar disease relative to the 2 pooled studies in schizophrenia alone, Phase 2/3 data are categorized and presented throughout this document as follows:

- pooled for the 3 placebo-controlled studies (CN138012, CN138050, CN138013), 2 in patients with schizophrenia, schizoaffective, or schizophreniform disorder and 1 in patients with bipolar disease
- pooled for the 2 placebo-controlled studies in patients with schizophrenia, schizoaffective, or schizophreniform disorder (CN138012, CN138050)
- presented alone for Study CN138131, conducted in patients with dementia (Alzheimer's, vascular, or mixed)

The 2 pooled studies for schizophrenia are a subset of the data from the 3 pooled studies in schizophrenia and bipolar disease.

#### GERIATRIC EXPSOURE

Of the 749 patients treated with aripiprazole injection in clinical trials, 99(13%) were  $\geq 65$  years old and 78 (10%) were  $\geq 75$  years old. Placebocontrolled studies of aripiprazole injection in patients with agitation associated with schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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**Table 14: Numbers of Patients by Study and Treatment Group: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013, CN138131), Safety Sample**

Protocol	Number of Patients				Grand Total (CN138012, CN138050, CN138013, CN138131)
	CN138012 <sup>a</sup>	CN138050 <sup>b</sup>	Total (CN138012, CN138050)	CN138013 <sup>c</sup>	
<b>Aripiprazole</b>					
1 mg	--	56	56	--	56
5 mg	--	62	62	--	74
10 mg	175	56	231	75	382
15 mg	--	58	58	75	148
<b>Total Aripiprazole</b>	175	232	407	150	660
(10 mg) <sup>d</sup>	(31)	--	(31)	(31)	(62)
(15 mg) <sup>d</sup>	--	(27)	(27)	--	(27)
<b>Grand Total Aripiprazole<sup>e</sup></b>	206	259	465	181	749
<b>Haloperidol</b>					
6.5 mg	183	--	183	--	183
7.5 mg	--	57	57	--	57
<b>Lorazepam</b>					
2.0 mg	--	--	--	69	69
<b>Placebo</b>	87	61	148	72	245
<b>Total Safety Sample</b>	445	350	795	291	1214

- <sup>a</sup> CN138012 Randomized Sample: placebo = 88; 6.5-mg haloperidol = 185; 10-mg aripiprazole = 175.
- <sup>b</sup> CN138050 Randomized Sample: placebo = 62; 7.5-mg haloperidol = 60; 1-mg aripiprazole = 57; 5-mg aripiprazole = 63; 10-mg aripiprazole = 57; 15-mg aripiprazole = 58.
- <sup>c</sup> CN138013 Randomized Sample: placebo = 75; 2-mg lorazepam = 70; 10-mg aripiprazole = 78; 15-mg aripiprazole = 78.
- <sup>d</sup> Number in parentheses is number of patients in the placebo group who had a third injection, which was 10-mg aripiprazole in Studies CN138012 and CN138013 and 15-mg aripiprazole in Study CN138050.
- <sup>e</sup> Number of patients who received aripiprazole as their initial injection plus the number of patients randomized to placebo who received a third injection, which was 10-mg aripiprazole in Studies CN138012 and CN138013 and 15-mg aripiprazole in Study CN138050.
- Source: Tables 8.2A in Clinical Study Reports CN138012, CN138050, CN138013, CN138131.

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**Table 1.2.1.1: Numbers of Subjects by Study and Treatment Group in Clinical Pharmacology Studies (CN138016, CN138017, and CN138132)**

Protocol	Number of Subjects			Total
	CN138016	CN138017	CN138132	
<b>Aripiprazole</b>				
1 mg	X	4	X	4
3 mg	X	4	X	4
5 mg	15	X	X	15
7.5 mg	X	4	X	4
15 mg	X	4	17	21
22.5 (3x7.5) mg	X	4	X	4
30 mg	X	4	X	4
45 (3x15) mg	X	4	X	4
<b>Total Aripiprazole Alone</b>	15	28	17	60
<b>Aripiprazole+Lorazepam<sup>a</sup></b>				
15 mg + 2 mg	X	X	40	40
<b>Haloperidol</b>				
3x5 mg	X	4	X	4
<b>Lorazepam Alone</b>				
2 mg	X	X	19	19

Source: CN138016, CN138017, and CN138132 Clinical Study Reports

<sup>a</sup> Thirty of these subjects also received either Aripiprazole alone or Lorazepam alone in either Period 1 or Period 2 of the study.

7.2.2.2 Postmarketing experience

N/A

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

This was adequate.

### 7.2.5 Adequacy of Routine Clinical Testing

This was adequate.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This was adequate.

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This was adequate. I have no recommendations.

### 7.2.8 Assessment of Quality and Completeness of Data

This was adequate.

## **7.3 Summary of Selected Drug-Related Adverse Events**

See section 7.1.5.6. This was adequate.

## **7.4 General Methodology**

### 7.4.2 Explorations for Predictive Factors

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## Comparison of Efficacy in Subpopulations

### PEC Score: Population Subsets

In order to determine if there were differences in the mean change from baseline to 2 hours post first IM injection among subsets of the population the following comparisons were analyzed: age ( $\leq$  upper quartile,  $>$  upper quartile), gender (men, women), race (white, black, "other"), underlying diagnosis (schizophrenic, schizoaffective, or schizophreniform disorder for CN138012 and CN138050; manic or mixed status, bipolar I disorder for CN138013), and baseline PEC Score ( $\leq$  median [ $\leq 18$ ],  $>$  median [ $> 18$ ]). Because there were insufficient elderly patients ( $\geq 65$ ) in the 3 studies to make an analysis of this subpopulation meaningful (there were 5 elderly patients in CN138012, 2 in CN138013 [1  $>75$ ], and 1 in CN138050), age as defined by the upper quartile was examined. For the pooled analysis of the 2 schizophrenia studies (CN138012 and CN138050), the upper quartile for age was patients  $>$  age 49; for the 1 bipolar I disorder study (CN138013), the upper quartile was patients  $>$  age 48. It should be noted that these studies were not designed to show statistically significant treatment differences in these subpopulations.

In the 2 schizophrenia studies (CN138012 and CN138050), the efficacy of aripiprazole was demonstrated across all subsets, as evidenced by statistically significant treatment comparisons versus placebo, except for patients with age  $>$  upper quartile, race of "other," and patients with an underlying diagnosis of schizophreniform; however, there were greater mean decreases from baseline in the aripiprazole group than the placebo group in these subpopulations.

In the bipolar I disorder study (CN138013), aripiprazole was found to be statistically significantly different than placebo on all subset analyses except for patients with race of black or "other," for patients with an underlying diagnosis of mixed, and for patients with a baseline PEC Score  $>$  median; however, the mean decreases from baseline in these subpopulations were greater in the aripiprazole group than the placebo group.

Please see supporting tables in appendix section 10.3.

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Subpopulation treatment-emergent AEs were analyzed by study, age, gender and race. Statistical testing using the Breslow-Day tests was conducted for age, gender, and race.

When analyzed by study, the AE profile of aripiprazole compared with placebo was generally consistent for all 3 studies.

There were a limited number of older patients enrolled in the 3 studies; therefore, patients were categorized by age using the upper quartile (> 48 years) of the pooled Safety Sample. Results of the Breslow-Day tests showed that only fatigue ( $p \leq 0.05$ ) was statistically significantly different between the 2 age groups. The incidence was 2.7% in patients  $\leq 48$  and 0.8% in patients  $> 48$ . The increased incidence of fatigue in aripiprazole-treated patients compared with placebo-treated patients that was seen in patients  $\leq 48$  was not seen in patients  $> 48$ , although interpretation of these results is difficult because of the small number of patients in the age category  $> 48$ .

There were no statistically significant events for gender, according to the Breslow-Day tests.

When analyzed by race (whites versus blacks), results of the Breslow-Day tests showed a statistically significant result for blood pressure increased. The incidence of this AE for whites was 1.7% for aripiprazole-treated patients versus 0% for placebo-treated patients, while the trend was reversed for blacks: 0% for aripiprazole-treated patients versus 1.7% for placebo-treated patients

#### 7.4.2.1 Explorations for dose dependency for adverse findings

## Dose-Related Adverse Events

### Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia comparing various fixed doses (2, 10, 15, 20, and 30 mg/day) of oral aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

#### 7.4.2.2 Explorations for time dependency for adverse findings

Adverse events were compared after 2<sup>nd</sup> and 3<sup>rd</sup> doses to adverse events after 1<sup>st</sup> dose.

#### 7.4.2.3 Explorations for drug-demographic interactions

This was adequate. See 7.4.2./

#### 7.4.2.4 Explorations for drug-disease interactions

In the sub-population of patients with previous relevant cardiovascular disorders in Study CN138131, there were no safety issues identified. There was no increased incidence of cardiovascular-related AEs, and somnolence was the only AE that was reported at a higher incidence than placebo across all aripiprazole dose groups. There were no clinical concerns regarding vital sign results, and no safety issues regarding ECG measurements (including QT prolongation).

One patient experienced a cerebrovascular accident. A 77-year old female with Alzheimer's dementia received 2 doses of IM aripiprazole (total 10 mg) on Day 1 of the study. On Day 17 (16 days after completing study treatment), the patient was hospitalized with a probable stroke. The investigator considered the stroke severe in nature and not likely related to study medication. The stroke resolved on Day 23.

#### 7.4.2.5 Explorations for drug-drug interactions

One drug-interaction study was conducted using the IM formulation. Study CN138132 evaluated co-administration of IM aripiprazole (15 mg) and IM lorazepam (2 mg) in healthy subjects. Results showed that co-administration of IM aripiprazole and IM lorazepam had no effect on the pharmacokinetics of either compound. There was an interaction in the pharmacodynamics when aripiprazole and lorazepam were co-administered. The intensity of sedation was greater and the orthostatic hypotension observed was similar with the combination as compared to that observed with aripiprazole alone. In contrast, the intensity of sedation was similar and the orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

#### ***Recommended Dose and Onset of Efficacy***

The 10-mg aripiprazole dose showed the most consistent and effective results of the aripiprazole doses tested in the mean change scores for all efficacy measures (Table 7). In the first completed

pivotal study (CN138050), statistical separation from placebo in the 10-mg aripiprazole group was demonstrated as early as 45 minutes post first IM injection while the 1-mg group did not separate from placebo at any timepoint and the 5-mg group did not show significance until 60 minutes (Table 8). Therefore, the 10-mg dose was selected for evaluation in the second pivotal trial in schizophrenic patients (CN138012) and separation from placebo was achieved 60 minutes post first IM injection. Since it was not known whether the 10-mg dose would be effective in agitated patients with bipolar disorder, both the 10-mg and 15-mg dose groups were evaluated in Study CN138013. In this population, the 10-mg group showed separation from placebo at the 90 minute timepoint (Table 9). Response to treatment (defined as a  $\geq 40\%$  decrease from baseline in the PEC Score) for the 10-mg dose groups was shown as early as 90 minutes in Study CN138012, 30 minutes in Study CN138050, and 90 minutes in Study CN138013. Thus, the 10-mg dose is recommended in both patient populations.

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**Table 7: Efficacy Results at 2 Hours Post First IM Injection: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Samples**

Study/ Treatment	N	PEC		CGI-I		CGI-S		ACES		CABS	
		Score Mean Change									
<b>Schizophrenia, Schizoaffective</b>											
<b>CN138012</b>											
Placebo	88	-4.78	3.10	-0.71	0.83	-4.51					
Aripiprazole 10 mg	173	-7.27**	2.42**	-1.16**	1.41*	-8.03**					
Haloperidol 6.5 mg	184	-7.75**	2.37**	-1.17**	1.64**	-8.28**					
<b>Schizophrenia, Schizoaffective, Schizophreniform</b>											
<b>CN138050</b>											
Placebo	61	-3.28	3.46	-0.42	0.66	-2.95					
Aripiprazole 1 mg	56	-4.47	3.07*	-0.63	0.65	-5.16					
Aripiprazole 5 mg	62	-5.65**	2.82**	-0.82*	1.01	-5.97**					
Aripiprazole 10 mg	56	-6.69**	2.64**	-1.08**	1.50**	-7.08**					
Aripiprazole 15 mg	58	-5.72**	2.66**	-0.99**	0.99	-7.04**					
Haloperidol 7.5 mg	57	-6.38**	2.72**	-0.91*	1.50**	-8.13**					
<b>Bipolar I Disorder</b>											
<b>CN138013</b>											
Placebo	73	-5.76	3.05	-0.94	1.00	-6.37					
Aripiprazole 10 mg	75	-8.74**	2.17**	-1.48**	1.87**	-9.60**					
Aripiprazole 15 mg	75	-8.67**	2.33**	-1.34*	2.32**	-9.08**					

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**Table 7: Efficacy Results at 2 Hours Post First IM Injection: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Samples**

Lorazepam 2 mg	68	-9.57**	2.10**	-1.61**	2.34**	-10.35**
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Source: Table 3.2A-1, Module 2.7.3, Clinical Summary of Efficacy

\*\*p ≤ 0.01; \*p < 0.05

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**Table 8: Onset of Efficacy, PEC Score: Mean Change from Baseline to 2 Hours Post First IM Injection: IM Placebo-Controlled Studies (CN138012, CN138050), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	PEC Score											
		15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes	Mean Change	Mean Change	Mean Change	Mean Change
CN138012	88	--	-2.68	-3.57	-4.21	--	-4.45	--	-4.78	--	-4.78	--	-4.78
	173	--	-2.50	-3.93	-5.42*	--	-6.26**	--	-7.27**	--	-7.27**	--	-7.27**
	184	--	-2.90	-4.78*	-6.32**	--	-7.43**	--	-7.75**	--	-7.75**	--	-7.75**
CN138050	61	-0.95	-1.76	-2.22	-2.41	-2.78	-3.39	-3.45	-3.28	-3.45	-3.45	-3.45	-3.28
	56	-0.48	-1.80	-2.60	-2.86	-3.45	-3.95	-4.37	-4.47	-4.37	-4.37	-4.47	-4.47
	62	-1.54	-2.30	-3.68	-4.01*	-4.44*	-4.75	-5.48*	-5.65**	-5.48*	-5.48*	-5.48*	-5.65**
	56	-1.16	-3.19	-4.39**	-5.48**	-5.84**	-6.14**	-6.65**	-6.69**	-6.14**	-6.65**	-6.65**	-6.69**
	58	-1.15	-2.42	-3.33	-4.63**	-4.73*	-5.09*	-5.47*	-5.72**	-4.73*	-5.09*	-5.47*	-5.72**
57	-0.45	-1.85	-3.52	-3.94	-4.41	-4.88	-6.03**	-6.38**	-4.41	-4.88	-6.03**	-6.38**	

\*\* p <= 0.01, \* p <= 0.05

ANCOVA model, controlling for treatment, country and baseline value, is used for mean change from baseline comparisons.

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**Table 9: Onset of Efficacy, PEC Score: Mean Change from Baseline to 2 Hours Post First IM Injection: IM Placebo-Controlled Study (CN138013), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	PEC Score							
		30 Minutes	45 Minutes	60 Minutes	90 Minutes	120 Minutes	Mean Change	Mean Change	Mean Change
CN138013	73	-3.02	-4.14	-5.29	-6.08	-5.76	-5.76	-5.76	-5.76
Placebo	75	-2.82	-5.14	-6.36	-8.09**	-8.74**	-8.74**	-8.74**	-8.74**
Aripiprazole 10mg	75	-2.70	-5.18	-6.87*	-7.87*	-8.67**	-8.67**	-8.67**	-8.67**
Aripiprazole 15mg	68	-3.57	-5.58*	-7.07*	-8.80**	-9.57**	-9.57**	-9.57**	-9.57**
Lorazepam 2mg									

\*\* p <= 0.01, \* p <= 0.05

ANCOVA model, controlling for treatment, pooled study center and baseline value, is used for mean change from baseline comp

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## **8.2 Drug-Drug Interactions**

One drug-interaction study was conducted using the IM formulation. Study CN138132 evaluated co-administration of IM aripiprazole (15 mg) and IM lorazepam (2 mg) in healthy subjects. Results showed that co-administration of IM aripiprazole and IM lorazepam had no effect on the pharmacokinetics of either compound. There was an interaction in the pharmacodynamics when aripiprazole and lorazepam were co-administered. The intensity of sedation was greater and the orthostatic hypotension observed was similar with the combination as compared to that observed with aripiprazole alone. In contrast, the intensity of sedation was similar and the orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone.

## **8.3 Special Populations**

There were no adequate and well-controlled studies conducted in pregnant women using IM aripiprazole. In intravenous studies of embryo-fetal development in rats and rabbits using IM aripiprazole, there was no evidence of teratogenicity in either species at systemic exposures up to 15 (rat) and 29 times (rabbit) human exposures at the maximum recommended human dose (MRHD) of 30 mg. Fetal changes, including reduced fetal ossification, abortion, and fetal visceral and skeletal alterations, occurred only at doses that were maternally toxic. In the intravenous pre- and postnatal development assessment in rats, aripiprazole produced drug-related changes in the offspring, including stillbirths, increased neonatal mortality, transient decrease in pup body weights, and postweaning observations of increased incidence of dilated renal pelvis, at maternally toxic doses. Maternal systemic exposures to aripiprazole on postpartum Day 4 at the no-effect dose in offspring were equivalent to human exposures at the MRHD of 30 mg.

Given the limited IM clinical experience, it is not known whether IM aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. IM aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

No aripiprazole-treated patients became pregnant during the IM studies.

## 8.4 Pediatrics

## 8.5 Advisory Committee Meeting

I do not believe an advisory committee is needed.

## 8.6 Literature Review

### *World Literature Update*

An update to previously submitted literature searches for published articles pertaining to the safety and efficacy of aripiprazole was conducted. Articles published and posters presented pertaining to the rapid-acting intramuscular (IM) formulation of aripiprazole were the subject of this literature search. The literature search includes articles published through 25 March 2005, and excludes articles that do not reference the IM formulation.

### Response

Attached is a literature search pertaining to the safety and efficacy of aripiprazole IM formulation. This report includes the following:

- Criteria for the literature search

- CVs for Atsuko Nakano and Julia Jui-Mei Chuang who conducted the searches

- List of the twelve articles that have been reviewed

- Certification of no adverse findings by Shahid Ashfaque, MD, and William Carson, MD and Randall Owen, MD

- CVs for Dr. Ashfaque, Dr. Carson, and Dr. Owen

## **ARIPIPRAZOLE IM SEARCH SUMMARY**

The literature reference search for aripiprazole IM was conducted at the Office of Scientific Information of Otsuka Pharmaceutical Company, Japan. The search covers the time period for online bibliographic references as of 25 March 2005. The search was conducted by Atsuko Nakano, Office of Scientific Information and her curriculum vitae is attached. The search terms used were:

Search terms "Aripiprazole and (intramuscular or injection)"

ARIPIPRAZOLE

OPC-14597 (Including 14,597)

OPC 14597 (Including 14,597)

OPC14597 (Including 14,597)

OPC-31

OPC 31

OPC31

ABILITAT

ABILIFY

129722-12-9 (CAS Registry No.)

129722-13-0 (CAS Registry No.)

129722-14-1 (CAS Registry No.)

129722-15-2 (CAS Registry No.)

129722-16-3 (CAS Registry No.)

Intramuscular

Intra muscular

IM

I.M.

Injection

Inj

The databases searched for online bibliographic reference available as of 25 March 2005 were:

(Outside Japan)

Database

DERWENT DRUG FILE

EMBASE/EMBASE Alert

MEDLINE

BIOSIS

CHEMICAL ABSTRACTS

Adis Clinical Trials Insight

Scisearch

JICST E-PLUS

Pascal

(Japan)

Database

Igaku-Chuo Zasshi WEB

JMEDICINE

JAPICDOC

SOCIE

The literature reference search for aripiprazole IM was also conducted at Bristol-Myers Squibb and covers the time period for online bibliographic references as of 25 March 2005. The search was conducted by Julia Chuang. The search terms used were:

ARIPIPRAZOLE

ABILITAT

ABILIFY

OPC()14597 (which searches OPC-14597 and OPC 14597)

OPC14597

OPC()31 (which searches OPC-31 and OPC 31)

OPC31

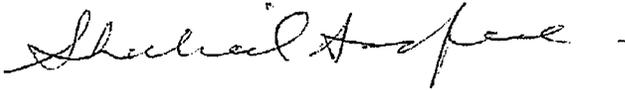
rn=129722-12-9 (searches the Chemical Abstract Registry number)  
rn=156680-99-8 (searches the Chemical Abstract Registry number)  
AND crossed with  
INTRAMUSCULAR  
INTRA()MUSCULAR (which searches intra-muscular and intra muscular)  
IM  
I.M.

The databases searched for online bibliographic references were:  
File CaPlus : The Chemical Abstracts Plus, FILE COVERS 1907-present  
File Toxcenter : Toxicology Center, FILE COVERS 1907 - present  
File MEDLINE(R): FILE COVERS 1966- present  
File Biosis Previews: FILE COVERS 1969- present  
File EMBASE: FILE COVERS 1974-present  
File DRUGU: Derwent Drug File, FILE COVERS 1983- present  
File Cancerlit: FILE COVERS 1975-2002/Oct  
File Scisearch : Science Citation Index, FILE COVERS 1974 – present  
File ADISCTI: Adis Clinical Trials Insight, FILE COVERS 1998 – present  
File JICST-EPLUS : Japanese Information Center, FILE COVERS 1985 - present  
File LIFESCI : Life Science Collection, FILE COVERS 1978 - present  
File IPA : International Pharmaceutical Abstracts, FILE COVERS 1970 – present

I have reviewed this search and agree with the sponsor's conclusion below.

October 31, 2005

This is to certify that I have thoroughly searched the literature for reports of studies evaluating the safety the aripiprazole injection formulation and, to the best of my knowledge, the attached bibliography is complete and accurate, and that I found no reports that would adversely affect the safety profile of IM Aripiprazole submission to — 60-158.



Shahid Ashfaque, MD  
Safety Scientist,  
Clinical Safety & Pharmacovigilance  
Otsuka Maryland Research Institute

## 8.7 Postmarketing Risk Management Plan

The usual postmarketing monitoring should be adequate.

## 8.8 Other Relevant Materials

### 8.9 Safety Summary

There are no safety issues which would prevent approval. I am in agreement with the sponsor's summary below in italics.

***OVERALL SAFETY PROFILE:** The safety profile of aripiprazole using the IM formulation was similar to that of the oral-tablet formulation. Based on data collected to date the IM formulation appears favorable. There was only a small number of SAEs, and very few AEs led to discontinuation. There were no important clinical concerns regarding laboratory, vital sign, or ECG findings. The safety profile of the subset of patients in the 2 pooled schizophrenia studies alone was the same as that in the 3 pooled studies in schizophrenia and bipolar disorder.*

*In the 3 pooled studies in schizophrenia and bipolar disorder patients (CN138012, CN138050, CN138013), IM aripiprazole was safe and well-tolerated at all doses tested. Nausea was the only event that met criteria for common AEs.*

*In the 2 pooled studies in schizophrenia patients alone (CN138012, CN138050), IM aripiprazole was safe and well-tolerated at all doses tested. Events of nausea, headache, dizziness, and somnolence met the criteria for common AEs.*

#### **DOSING AND EXPOSURE:**

*The safety profile of IM aripiprazole observed in the 3 pooled studies in schizophrenia and bipolar disorder patients (CN138012, CN138050, CN138013) supports the recommended dose of up to 30 mg over 24 hours. There was no statistically significant dose-response relationship between aripiprazole and any treatment-emergent AE. For patients who received more than 1 injection, the only AE that had an increased incidence compared with patients who received only 1 injection was insomnia, but the incidence was less than that observed for haloperidol.*

*In the 2 pooled studies in schizophrenia patients alone (CN138012, CN138050), there was no apparent dose-response relationship between aripiprazole and any treatment-emergent AE. The incidence of insomnia increased after a second injection in the 5-mg and 10-mg aripiprazole dose groups.*

#### **INJECTION SITE REACTION:**

*In the 3 pooled studies in schizophrenia and bipolar disorder patients (CN138012, CN138050, CN138013), the incidence of injection site reaction was low and not clinically meaningful.*

*In the 2 pooled studies in schizophrenia patients alone (CN138012, CN138050), the incidence of injection site reaction was low and not clinically meaningful.*

***SOMNOLENCE/SEDATION:***

*In the 3 pooled studies in schizophrenia and bipolar disorder patients (CN138012, CN138050, CN138013), IM aripiprazole did not cause excessive somnolence/sedation, as shown by the low incidence of sedation/somnolence related AEs.*

*In the 2 pooled studies in schizophrenia patients alone (CN138012, CN138050), IM aripiprazole did not cause excessive somnolence/sedation, as shown by the low incidence of sedation/somnolence related AEs.*

***EPS-RELATED SIDE EFFECTS:***

*In the 3 pooled studies in schizophrenia and bipolar disorder patients (CN138012, CN138050, CN138013), the incidence of EPS-related AEs was higher for aripiprazole-treated patients than placebo-treated patients, but lower than what was observed for haloperidol-treated patients. There was no noticeable increase in EPS-related AEs after a second injection.*

*In the 2 pooled studies in schizophrenia patients alone (CN138012, CN138050), the incidence of EPS-related AEs was slightly higher for aripiprazole-treated patients than placebo-treated patients, but lower than what was observed for haloperidol-treated patients, and there was no increased incidence after a second injection.*

***ORTHOSTATIC HYPOTENSION:***

*In the 3 pooled studies in schizophrenia and bipolar disorder patients (CN138012, CN138050, CN138013), there was no increased incidence of orthostatic hypotension in aripiprazole-treated patients.*

*In the 2 pooled studies in schizophrenia patients alone (CN138012, CN138050), there was no increased incidence of orthostatic hypotension in aripiprazole-treated patients.*

***ECG DATA:***

*In the 3 pooled studies in schizophrenia and bipolar disorder patients (CN138012, CN138050, CN138013), there was no evidence of a safety issue regarding ECGs (including QT prolongation) related to IM aripiprazole.*

*In the 2 pooled studies in schizophrenia patients alone (CN138012, CN138050), there was no evidence of a safety issue regarding ECGs (including QT prolongation) related to IM aripiprazole.*

***ORAL TRANSITION IN STUDY CN138012:*** *The transition from 1 day of aripiprazole IM dosing (10 mg) to 4 days of oral-tablet aripiprazole (15 mg) dosing was safe and well tolerated in patients with schizophrenia or schizoaffective disorder who were treated for agitation. This was demonstrated by a similar incidence of AEs and potentially clinically relevant laboratory results across treatment groups and the low incidence overall of potentially clinically relevant vital sign and ECG findings.*

***SAFETY IN ELDERLY PATIENTS WITH DEMENTIA (STUDY CN138131):***

*Somnolence was the most frequently reported event.*

*There was no apparent dose-response relationship between aripiprazole and any treatment-emergent AE.*

*There were no injection site reaction AEs reported.*

*There were no EPS-related AEs reported.*

*The incidence of orthostatic hypotension was low after IM aripiprazole.*

*There was no evidence of a safety issue regarding ECGs (including QT prolongation) related to IM aripiprazole.*

*In patients with previous significant cardiovascular disorders:*

⌚ *There was no increased incidence of cardiovascular-related AEs, and somnolence was the most frequently reported AE.*

⌚ *There were no clinical concerns regarding vital sign results.*

⌚ *There were no clinical concerns regarding ECG measurements of rate, rhythm, conduction, infarction, or increased ST/T morphology, and no significant findings regarding changes in the QT interval after treatment with IM aripiprazole.*

## **9 OVERALL ASSESSMENT**

### **9.1 Conclusions**

The study drug was effective in controlling acute agitation in all studies with Schizophrenia and Manic-Depressive patients for doses of 5mg, 10mg or 15mg. There were no safety issues to prevent approval.

### **9.2 Recommendation on Regulatory Action**

I recommend that we approve ABILIFY injection to be indicated for the treatment of acute agitation associated with schizophrenia or bipolar disorder, manic or mixed.

### **9.3 Recommendation on Postmarketing Actions**

The usual postmarketing monitoring should be adequate.

#### **9.3.1 Risk Management Activity**

The usual postmarketing monitoring should be adequate.

#### **9.3.2 Required Phase 4 Commitments**

I have no recommendations.

#### **9.3.3 Other Phase 4 Requests**

I have no recommendations.

6 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

**9.5 Comments to Applicant**

I have no recommendations.

**EARL D HEARST, M.D.**

HFD-130

**Appears This Way  
On Original**

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

#### SYNOPSIS

##### Clinical Study Report CN138012

**TITLE OF STUDY:** 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

**INVESTIGATORS AND STUDY CENTERS:** Investigators at 68 study centers (40 United States of America [USA], 6 Czech Republic, 6 France, 3 Estonia, 3 Latvia, 3 Poland, 3 Croatia, 1 Italy, 1 Puerto Rico, 1 South Africa, and 1 Spain) enrolled at least 1 patient from December 1, 2003 through June 10, 2004. The last patient visit occurred on June 15, 2004.

**PUBLICATIONS:** None

**STUDY PERIOD:** Date first subject enrolled: December 1, 2003

Date last subject completed: June 15, 2004

**CLINICAL PHASE:** 3

**HYPOTHESES:** 1) 10-mg intramuscular (IM) aripiprazole will have a greater mean change than placebo from baseline to 2 hours post first IM injection on the Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) score, in the treatment of acutely agitated patients with a diagnosis of schizophrenia or schizoaffective disorder; and 2) 10-mg IM aripiprazole will be non-inferior to 6.5 mg IM haloperidol in terms of mean change from baseline to 2 hours post first IM injection on the PEC score, in the treatment of acutely agitated patients with a diagnosis of schizophrenia or schizoaffective disorder.

**OBJECTIVES:** 1) To compare the efficacy of IM aripiprazole versus placebo 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; and 2) 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 were:

To compare the efficacy of IM aripiprazole versus placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia or schizoaffective disorder as assessed by the Agitation-Calmness Evaluation Scale (ACES), Clinical Global Impressions-Severity of Illness (CGI-S), Clinical Global Impressions-Improvement (CGI-I), 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) versus 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.

**METHODOLOGY:** This was a randomized, double-blind, multicenter study comparing 1 dose of IM

aripiprazole (10 mg) and 1 dose of IM haloperidol (6.5 mg) with placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia or schizoaffective disorder. The study began with a minimum 2-hour screening period prior to initiation of baseline assessments. Baseline assessments were performed within 1 hour prior to the first injection of study drug and included administration of the PEC, ACES, CGI-S, CABS, SAS, and Barnes Akathisia Rating Scale. The PEC consists of 5 items of the PANSS (hostility, uncooperativeness, excitement, poor impulse control, and tension). Following the first IM injection of study medication, patients were evaluated as inpatients for 24 hours. Efficacy evaluations were performed at timepoints 0.5, 0.75, 1, 1.5, 2, 4, 6, 12, and 24 hours after the initial injection and just before each repeat injection of study medication. Efficacy evaluations for a repeat injection of medication (if administered) were also performed at 1 and 2 hours after the injection.

Patients were randomly assigned in a 2:2:1 ratio to receive an initial IM injection of 1 of the 3 treatment groups (10-mg aripiprazole, 6.5-mg haloperidol, and placebo). A second IM injection was given, if needed, at least 2 hours after the initial IM injection, followed by a third IM injection of study medication, if needed, at least 4 hours after the initial IM injection and at least 2 hours after the second IM injection. A second and/or third IM injection of study medication was given no later than 20 hours after the administration of the initial IM injection of study medication. The maximum IM aripiprazole dose was 30 mg. The maximum IM haloperidol dose was 19.5 mg. For patients randomized to placebo, the first and second IM injections contained placebo and the third IM injection contained 10 mg aripiprazole.

After completing the 24-Hour IM Phase, patients received blinded oral tablet study medication corresponding to their initial treatment arm for 4 days. Patients randomized to aripiprazole or placebo during the 24-Hour IM Phase received 15-mg aripiprazole oral tablets (with the option of decreasing to 10-mg aripiprazole based on clinical judgement). Patients initially assigned to haloperidol received 10-mg haloperidol oral capsules (with the option of decreasing to 7-mg haloperidol based on clinical judgement). Baseline values for the 4-Day Oral Phase were the last value obtained during the 24-Hour IM Phase.

Assessments were made at Day 2 and Day 5 during the 4-Day Oral Phase.

**NUMBER OF SUBJECTS/PATIENTS:** A total of 469 patients were enrolled in the study. Of these, 448 patients were randomized to double-blind treatment: 88 to the 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. 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 the 10-mg aripiprazole group.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** Patients must have had a diagnosis of schizophrenia or schizoaffective disorder as defined by Diagnostic and Statistics Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and were experiencing acute agitation. Additionally, 2 components of the PEC score must have been  $\geq 4$  (moderate) and the sum of all 5 components must have been  $\geq 15$  and  $\geq 32$ .

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:**

IM Injection

Aripiprazole injection, 10 mg (7.5 mg/mL, 2 mL vial), administered intramuscularly, batch numbers 3C74147 and C01340

Oral Tablet

Aripiprazole tablets, 10 and 15 mg administered orally, batch numbers 00F85A010 and 00F90A015A, respectively

**DURATION OF TREATMENT:**

24-Hour IM Phase: 24 hours (treatment and observation period) from first IM injection

4-Day Oral Phase: Day 2 (first day of 4-day treatment and observation period) through Day 5

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:**

IM Injection

Haloperidol injection, 6.5 mg (5 mg/mL, 1 mL ampoule), administered intramuscularly, batch numbers 3H64336, 3H66558, 4A72144, 4A80020, and 4E80941

Placebo for aripiprazole injection, (2 mL vial), administered intramuscularly, batch numbers C01044 and 3C70446

#### Oral Tablet/Capsule

Haloperidol capsules, 2 mg and 5 mg, administered orally, batch numbers 3G73505 and 3G73507, respectively

Placebo for aripiprazole tablet, administered orally, batch number 00F82P000

Placebo for haloperidol capsule, administered orally, batch number 3G73510

#### **CRITERIA FOR EVALUATION:**

**Efficacy:** The primary efficacy outcome measure was the mean change from baseline to 2 hours post first IM injection in the PEC. Efficacy scales were completed during the study in the following order: PEC, ACES, CGI-S, CGI-I, CABS, and PANSS.

**Safety:** Safety assessments included review of adverse event (AE) reports, vital sign measurements, 12-lead standard and ambulatory electrocardiograms (ECG), concomitant medications, clinical laboratory tests, and physical examination. Extrapyramidal symptom (EPS) scales completed during the study included the SAS and the Barnes Akathisia Rating Scale.

**STATISTICAL METHODS:** It was expected that 420 patients would need to be randomized to obtain 400 (160 in each of the IM aripiprazole and IM haloperidol treatment groups, and 80 in the IM placebo group) evaluable patients, ie, having a baseline PEC assessment and at least 1 PEC assessment post first IM injection. This sample size would yield 90% power to show non-inferiority of IM aripiprazole 10 mg to IM haloperidol 6.5 mg, when the non-inferiority bound for the difference in the mean changes from baseline in PEC scores was 2.5. This assumed an expected difference in mean changes from baseline of 0.5 (in favor of haloperidol), a standard deviation of 5.5 and a 2-sided test at the 0.05 level of significance. The planned sample size of 400 evaluable patients would also provide 99% power to differentiate between placebo and the aripiprazole treatment group when the true difference in the mean changes from baseline in PEC score was 3.4, assuming a standard deviation of 5.5 and a 2-sided test at the 0.05 level of significance. The Randomized Sample comprised all patients who were randomized to treatment. The Safety Sample included those patients who were randomized to treatment and who received at least 1 dose of study medication, as indicated on the dosing record. The Efficacy Sample included those patients in the Safety Sample who had at least 1 postrandomization efficacy evaluation and a corresponding baseline value (not applicable to CGI-I).

The primary efficacy measure (mean change from baseline to 2 hours post first IM injection in the PEC) was assessed using an analysis of covariance (ANCOVA) model with baseline score as the covariate and also included terms for treatment and country. In order to preserve the experiment-wise type I error rate at 0.05, the 2 research hypotheses involving the primary efficacy measure were tested sequentially. First, a 2-sided test to compare the 10-mg aripiprazole IM group versus 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 versus 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.

The CGI-I was prospectively identified as a key secondary endpoint and thus a hierarchical testing procedure was planned so that the overall experiment-wise type I error rate was 0.05. The CGI-I was tested only if, first, the aripiprazole treatment group was shown to be significantly different versus 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.

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.

Other efficacy endpoints were the repeated measures on PEC Score, CGI Response Rate (response defined as a patient with a score of 1 or 2 in CGI-I), time to first PEC response within the 2-hour period post first

IM injection, time to discontinuation due to lack of efficacy or AE, time to second IM injection, time third IM injection, time to third injection or concomitant benzodiazepine use, number of IM injections per patient, proportion of patients requiring concomitant benzodiazepine use, and the mean change from baseline to 2 hours and 24 hours post first IM injection in the PANSS-derived BPRS Total Score and the BPRS Positive Score.

Additionally, subgroup analyses included the mean change from baseline on the PEC Score and the mean CGI-I Score for the subgroup of patients with a diagnosis of schizophrenia, the PEC Score contrasted to the effects of sedation (based on the ACES Score and based on sedation-related AEs), the PEC, CGI-I, CGI-S, ACES, and CABS Scores relative to the second IM injection for all patients and for patients who were nonresponders to the first injection, and the PEC, CGI-I, CGI-S, ACES, and CABS Scores relative to the third IM injection for all patients.

**EFFICACY RESULTS:** The primary efficacy measure was the mean change from baseline to 2 hours post first IM injection in the PEC Score. In order to preserve the experiment-wise type I error rate at 0.05, the 2 research hypotheses involving the primary efficacy measure were tested sequentially. The 10-mg aripiprazole dose group was significantly superior to placebo in the change from baseline to 2-hours post first IM injection in the PEC ( $p < 0.001$ ). The non-inferiority hypothesis of IM aripiprazole to IM haloperidol was then tested, and it was concluded that aripiprazole was non-inferior to haloperidol in this study.

For the schizophrenia subpopulation, the mean change from baseline to 2 hours post first IM injection in PEC Total Score showed statistically significant differences versus placebo for the 10-mg aripiprazole and 6.5-mg haloperidol treatment groups. For nonsedated patients, the mean change from baseline in PEC Total Score (based on the ACES Score and based on AES related to sedation) showed statistically significant differences versus placebo at 2 hours for the 10-mg aripiprazole and 6.5-mg haloperidol treatment groups. The CGI-I was prospectively identified as a key secondary endpoint, and thus a hierarchical testing procedure was planned so that the overall experiment-wise type I error rate was 0.05. Testing of the CGI-I was permitted, and a statistically significant difference at 2 hours post first IM injection for the CGI-I was demonstrated in favor of the 10-mg aripiprazole group ( $p < 0.001$ ) versus the placebo group.

There were statistically significant differences at 2 hours post first IM injection for the 10-mg aripiprazole group in all other secondary outcome measures including CGI-S ( $p = 0.004$ ), ACES ( $p = 0.012$ ), CABS ( $p < 0.001$ ), PEC Responder Analysis ( $p = 0.004$ ), and PEC Individual Item Scores (poor impulse control, tension, hostility, excitement, lack of cooperation). Haloperidol (6.5-mg) was statistically significantly different versus placebo for all secondary outcome measures.

The aripiprazole treatment group showed statistically significant differences versus placebo during the IM Phase for the following other efficacy measures: Repeated measures in the mean PEC Score through 120 minutes, and CGI responders from 4 hours to 24 hours post first IM injection. Furthermore, patients in the 10-mg aripiprazole group required statistically significant fewer injections than patients in the placebo group, and did not require second and third injections as early as the placebo group.

The mean change from predose (prior to second injection) to post second IM injection in the PEC Score for all patients showed statistically significant differences versus placebo at 60 minutes and 2 hours for the 10-mg aripiprazole and 6.5-mg haloperidol groups. For patients who were nonresponders after the first IM injection, statistically significant differences versus placebo were observed at 60 minutes and 2 hours for the 10-mg aripiprazole and 6.5-mg haloperidol groups. Following the third injection, the 10-mg aripiprazole dose was comparable to haloperidol for all patients in the mean change from baseline to 2 hours in PEC Score.

The mean CGI-I Score for all patients showed statistically significant differences versus placebo at 2 hours post second IM injection for the 10-mg aripiprazole and 6.5-mg haloperidol treatment groups. For patients who were nonresponders after the first injection, statistically significant differences versus placebo were observed at 2 hours post second IM injection for both the aripiprazole and haloperidol treatment groups. In the 4-Day Oral-Tablet Phase, the 15-mg aripiprazole and 10-mg haloperidol treatment groups showed additional small decreases in the mean change from the last evaluation in the IM Phase in PEC Score indicating that switching to oral medication was effective in maintaining the response achieved during the IM phase. Additionally, on the other outcome measures of CGI-I, CGI-S, ACES, and CABS, both the

15-mg aripiprazole and 10-mg haloperidol treatment groups maintained the response achieved during the IM phase.

## **SYNOPSIS**

### **Clinical Study Report CN138013**

**TITLE OF STUDY:** 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 I Disorder, Manic or Mixed

**INVESTIGATORS AND STUDY CENTERS:** Investigators at 37 study centers (35 United States of America [USA], 1 Latvia, and 1 Poland) enrolled at least 1 patient from November 12, 2003 through June 16, 2004. The last patient visit occurred on June 17, 2004.

**PUBLICATIONS:** None

**STUDY PERIOD:** Date first subject enrolled: 12-Nov-2003

Date last subject completed: 17-Jun-2004

**CLINICAL PHASE:** 3

**HYPOTHESIS:** At least 1 of the 2 aripiprazole doses (10 mg or 15 mg) will have a greater mean change than placebo from baseline to 2 hours post first intramuscular (IM) injection on the Positive and Negative Syndrome Scale (PANSS) Excitement Component (PEC) score in the treatment of acutely agitated patients with a diagnosis of Bipolar I Disorder, manic or mixed.

**OBJECTIVES:** The primary objective was to compare the efficacy of IM aripiprazole versus placebo in the treatment of acutely agitated patients with a diagnosis of Bipolar I Disorder, manic or mixed. This was assessed by the mean change from baseline to 2 hours post first IM injection using the PEC scale.

Secondary objectives were:

To compare the efficacy of IM aripiprazole versus 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).

To compare the effects in this study 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, versus placebo.

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 (Barnes). Safety and tolerance was evaluated by reports of adverse events (AEs) and clinically significant changes in electrocardiograms (ECGs), vital signs, and laboratory tests.

**METHODOLOGY:** 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. The study began with a minimum 2-hour screening period prior to initiation of baseline assessments. Baseline assessments were performed within 1 hour prior to the first dose of study drug and included administration of the PEC, ACES, CGI-S, CABS, SAS, and Barnes Akathisia Rating Scale. The PANSS and the Young Mania Rating Scale (Y-MRS) were performed just prior to the baseline assessments. The PEC consists of 5 items of the PANSS (hostility, uncooperativeness, excitement, poor impulse control, and tension). Following the first IM injection of study medication, patients were evaluated as inpatients for 24 hours. Efficacy evaluations were performed at timepoints 0.5, 0.75, 1, 1.5, 2, 4, 6, 12, and 24 hours after the initial injection and just before each repeat injection of study medication. Efficacy evaluations for a repeat dose of medication (if administered) were also performed at 1 and 2 hours after the dose.

Patients were randomly assigned to receive an initial injection of 1 of 4 treatment groups (placebo, 2-mg

lorazepam, 10-mg aripiprazole, and 15-mg aripiprazole). A second injection was given, if needed, at least 2 hours after the initial injection, followed by a third injection of study medication, 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 later than 20 hours after the administration of the initial injection of study medication. The maximum aripiprazole doses were 30 mg and 45 mg, respectively, in the 2 dosage groups. The maximum lorazepam dose was 6 mg. For patients randomized to placebo, the first and second injections contained placebo and the third injection contained 10 mg aripiprazole.

**NUMBER OF PATIENTS:** Three hundred twenty-nine patients were enrolled in the study and 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. Of the 301 patients randomized to treatment, 291 were included in the Safety and Efficacy Samples. Two hundred eighty-two (94%) of the 301 randomized patients completed the study.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** Patients must have had a diagnosis of Bipolar I Disorder, manic or mixed, as defined by Diagnostic and Statistics Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and were experiencing acute agitation. Additionally, 2 components of the PEC score must have been  $\leq 4$  (moderate) and the sum of all 5 components must have been  $\leq 15$  and  $\leq 32$ .

**TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBERS:**

Aripiprazole injection, 10 and 15 mg (7.5 mg/mL, 2 mL vial), administered intramuscularly, batch numbers 3C74147 and C01340

**DURATION OF TREATMENT:** The IM treatment and observation period lasted for up to 24 hours after administration of the first dose.

**REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBERS:**

Lorazepam injection, 2.0 mg (2 mg/mL, 1 mL vial), administered intramuscularly, batch numbers 3K73479 and 043050

Placebo (2 mL vial) for aripiprazole injection, all dose levels, administered intramuscularly, batch numbers C01044 and 3C70446

**CRITERIA FOR EVALUATION:**

**Efficacy:** The primary efficacy outcome measure was the mean change from baseline to 2 hours post first IM injection in the PEC. Efficacy rating scales completed during this study included PEC, ACES, CGI-I, CGI-S, CABS, PANSS, and Y-MRS.

**Safety:** Safety assessments included review of adverse event (AE) reports, vital sign measurements, standard and ambulatory 12-lead electrocardiograms (ECG), concomitant medications, clinical laboratory tests, and physical examination. Extrapyramidal (EP) symptom scales completed during the study included the SAS and the Barnes Akathisia Rating Scale.

**STATISTICAL METHODS:** The planned sample size of 260 evaluable patients (65 per treatment group) would yield 90% power to differentiate between placebo and at least 1 of the 2 aripiprazole treatment groups (10 mg or 15 mg), when the true difference in the mean changes from baseline in PEC score was 3.4. This assumed a standard deviation of 5.4 and a 2-sided test at the 0.025 level of significance (adjusted for 2 comparisons versus placebo to ensure an overall probability of Type 1 error  $\leq 0.05$ ).

The Randomized Sample comprised all patients who were randomized to treatment. The Safety Sample included those patients who were randomized to treatment and who received at least 1 dose of study medication, as indicated on the dosing record. The Efficacy Sample included those patients in the Safety Sample who had at least 1 postrandomization efficacy evaluation and a corresponding baseline value (not applicable to CGI-I). The analysis of the Last Observation Carried Forward (LOCF) data set were considered primary.

The primary efficacy measure was the mean change from baseline to 2 hours (LOCF) post first IM injection in the PEC Score, and was evaluated by analysis of covariance (ANCOVA) with baseline score as covariate, and treatment and center as main effects. For the primary efficacy analysis, in order to protect the alpha level at 0.05 when making comparisons of the IM aripiprazole doses of 10 and 15 mg versus placebo, statistical testing was carried out using the Hochberg sequentially rejective procedure.

Secondary outcome measures analyzed using ANCOVA included the mean change from baseline to 2 hours post first IM injection in the CGI-S, ACES, CABS, and PEC Individual Item Score. The mean CGI-I

Score was analyzed using the Cochran-Mantel-Haenszel (CMH) Row Means test. PEC response rate (defined as a  $\geq$  40% decrease in PEC) was analyzed using CMH General Association Test.

Other outcome measures included CGI response rate (defined as patients with a 1 or 2 in the CGI-I Score [CMH General Association Test]), mean change from baseline to 2 hours post first IM injection in the YMRS Total Score (ANCOVA), time to first PEC response, time to second and third injection (Log-rank test), and number of injections (CMH Raw Means test).

Additional analyses included the mean change from baseline in PEC Score for the subgroup of nonsedated patients based on ACES Score (defined as patients who did not have ACES scores of 8 [deep sleep] or 9 [unarousable] during the first 2 hours after the first IM injection) and the subgroup of nonsedated patients based on the absence of AEs related to sedation (defined as patients who did not experience AEs of sedation or somnolence during the first 2 hours after the first IM injection), and efficacy scales (PEC, CGII, CGI-S, ACES, CABS) relative to the second and third injections.

**EFFICACY RESULTS:** Aripiprazole 10-mg and 15-mg (both  $p < 0.001$ ) were statistically superior to placebo in the primary efficacy measure. Statistical separation from placebo (ie,  $p \leq 0.05$ ) was demonstrated as early as 60 minutes ( $p = 0.028$ ) for the 15-mg aripiprazole group and as early as 90 minutes ( $p = 0.008$ ) for the 10-mg aripiprazole group. Lorazepam was statistically superior to placebo in the primary efficacy measure ( $p < 0.001$ ) and demonstrated statistical separation from placebo as early as 45 minutes ( $p = 0.040$ ).

For the subgroup of nonsedated patients (defined on the basis of the ACES Score), statistically significant differences versus placebo in the primary efficacy measure were observed in favor of the 10-mg and 15-mg aripiprazole groups, as well as for the lorazepam group. Similar results were observed for the subgroup of nonsedated patients defined on the basis of the absence of AEs related to sedation.

Aripiprazole 10-mg and 15-mg were statistically superior to placebo on all secondary efficacy measures at 2 hours post first IM injection (LOCF data set). The mean CGI-I Score, and the mean change from baseline in the CGI-S, ACES, and CABS Score showed statistically significant comparisons versus placebo in favor of the 10-mg and 15-mg aripiprazole groups. Furthermore, statistically significantly higher rates of PEC response were observed for 10-mg and 15-mg aripiprazole than for placebo. Lorazepam was statistically superior to placebo on these secondary outcome measures. Furthermore, all active treatment groups were statistically superior to placebo on the mean change from baseline in all PEC Individual Item Scores at 2 hours (LOCF).

The repeated measures analysis on the PEC Score through 2 hours post first IM injection showed improvement over time for all treatment groups. The improvement was statistically significantly greater for the 10-mg and 15-mg aripiprazole and lorazepam groups than placebo. Statistically significantly higher rates in terms of CGI response were observed for all active treatment groups at all timepoints. Patients in the 10-mg and 15-mg aripiprazole groups were more likely to respond and/or to respond sooner in terms of PEC response than patients in the placebo group during the 2-hour period post first IM injection. Similar conclusions can be drawn for the lorazepam group. Furthermore, patients in the placebo group were more likely to require and/or require sooner a second or third injection than patients in the 10-mg and 15-mg aripiprazole groups, as well as in the lorazepam group.

Aripiprazole 10-mg and 15-mg, as well as lorazepam, were statistically superior to placebo for the mean change in the PEC Score from predose (ie, immediately prior to second IM injection) to 2 hours post second IM injection. In addition, aripiprazole 10-mg and lorazepam also showed superiority over placebo at the 60 minute time point. For the subgroup of patients who were nonresponders to the first IM injection (defined as a patient who received a second injection within 4 hours of the first and who was not a PEC responder in the evaluation just prior to the second injection), statistically significant differences versus placebo were observed in the mean change from predose in favor of the 10-mg and 15-mg aripiprazole and lorazepam groups. In addition, aripiprazole 10-mg and lorazepam also showed superiority over placebo at the 60 minute time point. Following the third IM injection, 10-mg aripiprazole appeared to be similar in effect as lorazepam for the mean change in the PEC Score from baseline (ie, immediately prior to first IM injection).

The mean CGI-I Score for all patients at 1 and 2 hours post second IM injection showed statistically significant differences versus placebo in favor of 10-mg and 15-mg aripiprazole, as well as lorazepam. For

the subgroup of patients who were nonresponders after the first injection, the mean CGI-I Score at 1 and 2 hours post second IM injection showed statistically significant differences versus placebo in favor of 10-mg aripiprazole and lorazepam. The treatment difference versus placebo showed a trend ( $p = 0.061$ ) in favor of 15-mg aripiprazole.

A summary of primary and secondary efficacy results at 2 hours (LOCF) is presented in following table.  
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## SYNOPSIS

### Clinical Study Report CN138050

**TITLE OF STUDY:** 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

**INVESTIGATORS AND STUDY CENTERS:** Investigators at 50 study centers (30 United States of America [USA], 3 Canada, 2 Estonia, 3 Latvia, 2 Lithuania, 2 Czech Republic, 7 France, and 1 Spain) participated in the conduct of this study

**PUBLICATIONS:** 1) Modell S, Wilber R, Marcus R, McQuade RD, Abou-Gharbia N, Carson WH. Efficacy and safety of intramuscular aripiprazole [abstract]. *Eur Psychiatry* 2004;19(supp.1):177s-178s. Abstracts of the 12th Association of the European Psychiatrists Congress, Geneva, Switzerland, April 14 - 18, 2004.

2) Daniel D, Stock E, Wilber R, et al. Intramuscular aripiprazole in acutely agitated psychotic patients. American Psychiatric Association 157th Annual Meeting, New York, New York, May 1 - 6, 2004.

3) Oren D, Stock E, Wilber R, et al. Intramuscular aripiprazole in acutely agitated psychotic patients. New Clinical Drug Evaluation Unit 44th Annual Meeting, Phoenix, Arizona, June 1 - 4, 2004.

4) Modell S, Daniel D, Stock E, et al. Intramuscular aripiprazole treatment for acute agitation in patients with psychosis. *Int J Neuropsychopharmacol.* 2004;7(supp.2):s417. The 24th Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Paris, France, June 20 - 24, 2004.

**STUDY PERIOD:** Date first patient enrolled: 02-Apr-2002

Date last patient completed: 26-Jan-2003

**CLINICAL PHASE:** 3

**HYPOTHESIS:** At least 1 of the following aripiprazole fixed doses (5 mg, 10 mg, 15 mg) will have a greater mean change from baseline to 2-hours postdose on the Positive and Negative Syndrome Scale (PANSS) Excitement Component (PEC) score than placebo, in the treatment of acute agitation in patients with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder.

**OBJECTIVES:** The primary objective was to compare the efficacy of intramuscular (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 were:

To assess the efficacy of IM aripiprazole with placebo in the treatment of acute agitation in patients with schizophrenia, schizoaffective, or schizophreniform disorder, utilizing the secondary efficacy endpoints

To measure 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, versus 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) analysis 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

The tertiary objective was:

To conduct an exploratory cost-effectiveness analysis (CEA) using information on clinical efficacy measures and health care utilization between aripiprazole and haloperidol. However, outcomes research analysis is considered a sub-study analysis of this current clinical trial; therefore, results of this exploratory CEA are included in a separate report

**METHODOLOGY:** 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 haloperidol (7.5 mg) with placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder. The 1-mg aripiprazole dose was included to establish the no-effects dose. The study began with a 2-hour screening period prior to initiation of baseline assessments. Baseline assessments were performed within 1 hour prior to the first dose of study drug and included administration of the PEC, PANSS Total, Agitation-Calmness Evaluation Scale (ACES), Corrigan Agitated Behavior Scale (CABS), and Clinical Global Impressions (CGI) Severity of Illness scale. The PEC consists of 5 items of the PANSS Total and includes hostility, lack of cooperation, excitement, poor impulse control, and tension. Following the first IM dose of study medication, patients were evaluated as inpatients for 24 hours. Efficacy evaluations were performed every 15 minutes for 2 hours, and at 4, 6, 12, and 24 hours after the initial dose and just before each repeat dose of study medication or rescue medication (lorazepam or lorazepam equivalent, if needed). Efficacy evaluations for a repeat dose of medication (if administered) were also performed at 1 and 2 hours after the dose.

Patients were randomly assigned to receive an initial dose in 1 of the 6 treatment groups. A second dose may have been given, if needed, at least 2 hours after the initial dose, followed by a third dose of study medication, if needed, at least 4 hours after the initial dose and at least 2 hours after the second dose. A repeat dose of study medication may have been given no later than 20 hours after the administration of the initial dose of study medication. A patient was considered a non-responder after 2 hours if he/she did not have a 40% decrease in the primary efficacy variable (mean change from baseline to 2 hours post first IM injection in the PEC). The maximum aripiprazole doses given were 3 mg, 15 mg, 30 mg, and 45 mg, respectively, in the 4 dosage groups. The maximum haloperidol dose was 22.5 mg. For patients randomized to placebo, the first and second doses contained placebo and the third dose contained 15-mg aripiprazole. If needed, rescue medication (lorazepam, up to 4 mg/day, or lorazepam equivalent) was administered at least 60 minutes after the second dose of study medication and whenever needed thereafter during the remainder of the 24 hour period. Rescue medication (lorazepam or lorazepam equivalent) was given if the PEC score was unchanged or worsened from the baseline value or if the investigator deemed it absolutely necessary. Plasma samples for PK analysis were collected on at least 20 patients in each treatment group at baseline and at 2 hours and 15 minutes after each dose of study medication (after efficacy rating scales had been completed) and at approximately 24 hours and 120 hours after the first dose of study medication. Patients were not reminded of the blood draw until the rating scales were completed.

**NUMBER OF PATIENTS:** Three hundred seventy-eight patients were enrolled in the study and 357 patients were randomized to double-blind treatment: 62 to the placebo group, 60 to the haloperidol 7.5-mg group, 57 to the aripiprazole 1-mg group, 63 to the aripiprazole 5-mg group, 57 to the aripiprazole 10-mg group, and 58 to the aripiprazole 15-mg group. Of the 357 patients randomized to treatment, 350 were included in the Safety and Efficacy Samples. Three hundred thirty-eight (95%) of the 357 randomized patients completed the study.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** Patients must have had a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder as defined by Diagnostic and Statistics Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, and have been experiencing acute agitation. Additionally, 2 components of the PEC must have been  $\geq 4$  (moderate) and the sum of all 5 components must have been  $\geq 15$  but  $< 33$ .

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:**

aripiprazole injection, 1 mg (4 mg/vial, 2 mg/mL) administered intramuscularly, batch number C01339  
aripiprazole injection, 5, 10, and 15 mg (15 mg/vial, 7.5 mg/mL) administered intramuscularly, batch number C01340

haloperidol injection, 7.5 mg (5mg/mL vial, clear; 5 mg/mL vial, amber [French sites]) administered intramuscularly, batch numbers C563, C01313, and 01CB434, respectively

**DURATION OF TREATMENT:** The IM treatment and observation period lasted for up to 24 hours after administration of the first dose.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:**

Placebo for aripiprazole injection, all dose levels administered intramuscularly, batch number C01044.

**CRITERIA FOR EVALUATION:**

**Efficacy:** The primary efficacy outcome measure was the mean change from baseline to 2 hours post first IM injection in the PEC. Efficacy rating scales completed during this study included the PEC, ACES, CABS, CGI Severity of Illness and Improvement Scales, PANSS, and the PANSS-derived Brief Psychiatric Rating Scale (BPRS).

**Safety:** Safety assessments included review of adverse event (AE) reports, vital sign measurements, 12-lead standard and ambulatory electrocardiograms (ECG), concomitant medications, clinical laboratory tests, and physical examination. Extrapyramidal syndrome (EPS) scales completed during the study included the Simpson-Angus Scale (SAS) and the Barnes Akathisia Rating Scale.

**STATISTICAL METHODS:** The planned sample size of 306 evaluable patients (51 per treatment group) was estimated to yield 90% power to differentiate between placebo and at least 1 of the 3 higher-dose aripiprazole treatment groups (5 mg, 10 mg, or 15 mg), when the true difference in the mean changes from baseline in PEC scores was 4.0. This assumed a standard deviation of 5.4 and a 2-sided test at the 0.0167 level of significance (adjusted for 3 comparisons versus placebo to ensure an overall significance level  $\delta$  0.05).

The Randomized Sample comprised all patients who were randomized to double-blind treatment. The Safety Sample included those patients who received at least 1 dose of study medication as indicated on the dosing record. The Efficacy Sample included those patients in the Safety Sample who had at least 1 postrandomization efficacy evaluation and a corresponding baseline value (not applicable to CGI Improvement).

The primary outcome measure (mean change from baseline to 2 hours post first IM injection in the PEC score) was assessed using a 2-way analysis of covariance (ANCOVA) model with baseline score as the covariate and also included terms for country and treatment.

Secondary outcome measures were analyzed using a hierarchical testing procedure in order to minimize the overall experiment-wise alpha level when making comparisons. Only treatment groups that were significant versus placebo from the primary efficacy analysis were used. Testing of the key confirmatory endpoints proceeded sequentially. First, the ACES was tested for those treatment groups significantly different versus placebo from the primary analysis. Then, only those treatment groups for which the ACES was significantly different versus placebo were tested for the CABS, and, in sequence, only treatment groups for which the CABS was significantly different versus placebo were then tested for CGI Improvement. Finally, only those treatment groups for which the CGI Improvement was significantly different versus placebo were tested for CGI Severity. The outcome of the tests for the key confirmatory endpoints did not affect the statistical significance achieved for the primary endpoint. Hochberg's sequentially rejective procedure was applied.

Key secondary outcome measures analyzed using ANCOVA were the mean change from baseline to 2 hours post first IM injection in the ACES, CABS, and CGI Severity Scores. The mean CGI Improvement Score was analyzed using the Cochran-Mantel-Haenszel (CMH) Row Means test.

Other secondary outcome measures included the mean change from baseline to 2 hours post first IM injection in the PEC Individual Item Score (ANCOVA); response rate (defined as a  $\geq$  40% decrease in PEC Score [CMH Row Means test]); repeated measures on the PEC score (mixed effects model); mean change from baseline to 2 and 24 hours post first IM injection in the BPRS Total and BPRS Positive Scores (ANCOVA); CGI response rate (defined as a score of 1 or 2 in the CGI Improvement scale [CMH General Association Test]); and time to response within the 2-hour post first IM injection, time to discontinuation due to lack of efficacy or AE, and time to second and third IM injections or lorazepam rescue (all analyzed by survival analysis); number of IM injections per patient (CMH Row Means test score); and number of patients requiring rescue medication (CMH General Association test).

Based on discussions with the FDA indicating that efficacy must be demonstrated in the subpopulation of schizophrenic patients and that the effect of sedation on efficacy should be described, the following post-hoc efficacy analyses were added to the planned analyses for this study: the mean change from baseline in PEC Total Score and mean CGI Improvement Score for the subpopulation of patients with an underlying diagnosis of schizophrenia; the mean change from baseline in PEC Total Score for nonsedated (defined as patients who did not have ACES scores of 8 [deep sleep] or 9 [unarousable]) patients based on ACES Score and based on AEs related to sedation; and analyses of PEC Total Score and CGI Improvement Score relative to the second and third injections. Additionally, the following post-hoc safety analyses were added to the planned analyses: analysis of AEs with first onset or increased severity after a repeat dose, and analyses of ECG parameters by time relative to each dose.

The PK data set included all available concentration-time data from subjects who had blood samples collected for PK evaluation. PK data was combined with necessary information from the clinical database to perform population PK analysis, and results will be presented in a separate report.

**EFFICACY RESULTS:** The primary efficacy measure was the mean change from baseline to 2 hours post first IM injection in the PEC Score. Results showed statistically significant mean changes from baseline to 2 hours post first IM injection versus placebo for the IM haloperidol 7.5-mg group ( $p = 0.001$ ), and for the IM aripiprazole 5-mg ( $p = 0.008$ ), 10-mg ( $p < 0.001$ ), and 15-mg ( $p = 0.007$ ) groups. Statistical separation from placebo was demonstrated as early as 45 minutes ( $p = 0.007$ ) for the 10-mg aripiprazole group, and there was a trend at 30 minutes ( $p = 0.051$ ). In order to minimize the overall experiment-wise alpha level when making comparisons of the IM aripiprazole doses of 5, 10, and 15 mg versus placebo, hierarchical testing using Hochberg sequentially rejective procedure was applied to key secondary efficacy measures. This resulted in statistically significant comparisons at 2 hours post first IM injection for the 10-mg aripiprazole dose versus placebo in the ACES ( $p = 0.003$ ), CABS ( $p < 0.001$ ), CGI Improvement Score ( $p < 0.001$ ), and CGI Severity of Illness Score ( $p = 0.001$ ). While the treatment comparisons for the 5- and 15-mg aripiprazole doses did not meet the sequential testing criteria because of failure on the ACES Score, both doses showed efficacy compared with placebo on the CABS Score (5 mg,  $p = 0.007$ ; 15 mg,  $p < 0.001$ ), the CGI Improvement Score (5 mg and 15 mg,  $p < 0.001$ ), and the CGI Severity of Illness Score (5 mg,  $p = 0.034$ ; 15 mg,  $p = 0.003$ ). The 1-mg aripiprazole dose did not achieve statistical significance on the PEC ( $p = 0.191$ ), ACES ( $p = 0.980$ ), or CABS ( $p = 0.054$ ) Scores, although it did show efficacy on the CGI Improvement Score ( $p = 0.011$ ).

The use of the Hochberg sequentially rejective procedure at each step in the hierarchy testing minimized the overall experiment-wise error rate, but it did not necessarily control it at the 0.05 level. An alternate testing procedure used the Bonferroni correction in addition to the Hochberg procedure and tested the 3 aripiprazole doses versus placebo at the 0.0167 level at each step in the testing hierarchy. As with the Hochberg procedure, testing proceeded to the next outcome measure in the hierarchy only for those doses that were statistically significant in the previous step of the hierarchy. Using this alternative testing procedure controlled the overall experiment-wise error rate at 0.05. Application of this post-hoc procedure resulted in the same conclusions as did the protocol-specified procedure: the 5-mg, 10-mg, and 15-mg doses of aripiprazole were statistically superior to placebo on the primary outcome measure (PEC at 2 hours), and the 10-mg aripiprazole dose was statistically superior to placebo on the key secondary efficacy measures (ACES, CABS, CGI Improvement, CGI Severity of Illness at 2 hours).

Other secondary efficacy measures were the repeated measures on the PEC Score, PEC individual item scores, PANSS-derived BPRS Total and Positive Scores, PEC (defined as a reduction of  $\geq 40\%$  in the PEC Score) and CGI (defined as patients with a 1 or 2 in the CGI Improvement Score) responder analyses, time to response, time to second and third injections, and either third injection or rescue medication, number of injections, and number of patients requiring rescue medication.

A statistically significant greater number of patients in the 7.5-mg haloperidol group and 10-mg aripiprazole group than the placebo group were PEC responders at 120 minutes. Furthermore, the mean change from baseline to 2 hours post first IM injection in the BPRS Total Score showed a statistically significant treatment difference between placebo and the 7.5-mg haloperidol group, and 5-mg, 10-mg, and 15-mg aripiprazole groups, but no statistically significant differences were demonstrated on the BPRS Positive Score for these treatment groups.

Statistically significant mean changes from baseline to 2 hours post first IM injection in PEC Score 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. Similar results were observed in the schizophrenia subpopulation for the mean CGI Improvement Score at the 2-hour timepoint for these same treatment groups. For nonsedated patients, the mean change from baseline in PEC Total Score (based on the ACES Score and based on AEs related to sedation) showed statistically significant differences versus placebo at 2 hours for the 7.5-mg haloperidol group, and for the 5-mg, 10-mg, and 15-mg aripiprazole groups. The mean change from predose (prior to second injection) to post second IM injection in the PEC Total Score for patients who were nonresponders was statistically significant different versus placebo for the 7.5-mg haloperidol group, and the 10-mg and 15-mg aripiprazole groups. The mean CGI Improvement Score relative to a second injection for nonresponders was statistically significantly different versus placebo at 60 minutes and 2 hours post second IM injection for the 7.5-mg haloperidol group and for the 5-mg and 15-mg aripiprazole groups. The 1-mg aripiprazole group was statistically significantly different at 2 hours ( $p = 0.037$ ). The 10-mg aripiprazole group showed a trend ( $p = 0.057$ ) at 2 hours post second IM injection.

## 10.2 Efficacy tables

### **CGI Improvement Score**

In the 2 studies in schizophrenia (CN138050) and the study in bipolar I disorder (CN138013), all aripiprazole dose groups were statistically significantly different from placebo on the mean CGI-I Score (1-mg dose  $p = 0.011$ ; all other doses  $p < 0.001$ ) (Table 3.2C-1). The active comparators in each of these studies was also effective (6.5-mg haloperidol:  $p < 0.001$ ; 7.5-mg haloperidol:  $p < 0.001$ ; 2-mg lorazepam:  $p < 0.001$ ).

For the schizophrenia-only population (CN138012, CN138050), the treatment comparisons for the 10-mg aripiprazole dose ( $p = 0.001$ ) and 6.5-mg haloperidol dose ( $p < 0.001$ ) in CN138012, and the 5-mg ( $p < 0.001$ ), 10-mg ( $p = 0.004$ ), and 15-mg ( $p = 0.002$ ) aripiprazole doses and 7.5-mg haloperidol dose ( $p = 0.001$ ) in CN138050 were statistically significant versus placebo. The treatment comparison for the 1-mg aripiprazole dose was not statistically significant ( $p = 0.689$ ) (Table 3.2C-2).

The CGI-I was specified and was fully protected statistically as a key secondary measure in Study CN138012 (schizophrenia and schizoaffective disorder). In Study CN138050 (schizophrenia, schizoaffective, and schizophreniform disorder), the CGI-I was also specified as a key secondary measure and met the prespecified Hochberg sequentially rejective procedure. However, while the use of the Hochberg sequentially rejective procedure at each step in the hierarchy testing minimized the overall experiment-wise error rate, it did not necessarily control it at the 0.05 level. Therefore, an alternate testing procedure, the Bonferroni correction, was used and tested the 3 aripiprazole doses versus placebo at the 0.0167 level at each step in the testing hierarchy. As with the Hochberg procedure, testing proceeded to the next outcome measure in the hierarchy only for those doses that were statistically significant in the previous step of the

hierarchy. Using this alternative testing procedure controlled the overall experiment-wise error rate at 0.05. Application of this post-hoc procedure resulted in the same conclusions regarding the CGI-I as did the protocol-specified procedure: the 5-mg, 10-mg, and 15-mg doses of aripiprazole were statistically superior to placebo on the primary outcome measure (PEC at 2 hours), and the 10-mg aripiprazole dose was statistically superior to placebo on the key secondary efficacy measure (CGI-I at 2 hours).

In Study CN138013 (bipolar I disorder), the CGI-I was not specified as a key secondary measure, but it was listed as the first secondary efficacy measure. Similar to Study CN138050, 2 doses of aripiprazole (10 mg and 15 mg) were used. If a similar post-hoc hierarchical procedure was applied (ie, use of the Bonferroni correction), the conclusions for the primary efficacy measure (PEC at 2 hours) would not change since both doses of aripiprazole were statistically superior to placebo at the 0.025 level. Additionally, both doses of aripiprazole were statistically superior to placebo at the 0.025 level for the CGI-I and thus, the overall experiment-wise error rate was controlled at the 0.05 level for the analyses of the PEC and CGI-I at 2 hours.

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**Table 3.2C-1: Mean CGI Improvement Score at 2 Hours Post First IM Injection: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	Mean Score	P-Value
Schizophrenia, Schizoaffective	88	3.10	--
	173	2.42	<0.001
	184	2.37	<0.001
CN138012			
	Placebo		
	Aripiprazole 10mg		
	Haloperidol 6.5mg		
Schizophrenia, Schizoaffective, Schizophreniform	61	3.46	--
	56	3.07	0.011
	62	2.82	<0.001
	56	2.64	<0.001
	58	2.66	<0.001
CN138050			
	Placebo		
	Aripiprazole 1mg		
	Aripiprazole 5mg		
	Aripiprazole 10mg		
	Aripiprazole 15mg		
	Haloperidol 7.5mg		
Bipolar I Disorder			
CN138013			
	Placebo	3.05	--
	Aripiprazole 10mg	2.17	<0.001
	Aripiprazole 15mg	2.33	<0.001
	Lorazepam 2mg	2.10	<0.001

CGI row means score test controlling for treatment, country (CN138-012, CN138-050) or pooled study center (CN138-013), is used for CGI-I score means.

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**Table 3.2C-2: Mean CGI Improvement Score at 2 Hours Post First IM Injection: IM Placebo-Controlled Studies, Schizophrenia Population Only (CN138012, CN138050), LOCF Data Set, Efficacy Sample**

Study/ Treatment		N	Mean Score	P-Value
CN138012	Placebo	65	3.03	--
	Aripiprazole 10mg	123	2.41	0.001
	Haloperidol 6.5mg	134	2.39	<0.001
CN138050	Placebo	39	3.38	--
	Aripiprazole 1mg	30	3.30	0.689
	Aripiprazole 5mg	40	2.65	<0.001
	Aripiprazole 10mg	36	2.67	0.004
	Aripiprazole 15mg	44	2.68	0.002
	Haloperidol 7.5mg	43	2.65	0.001

OMH row means score test controlling for treatment is used for CGI-I score means.

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### **CGI Severity of Illness Score**

Statistically significant treatment comparisons versus placebo were demonstrated in the mean change from baseline to 2 hours post first IM injection in CGI-S for the 10-mg aripiprazole dose in the 2 schizophrenia studies (CN138012:  $p = 0.004$ ; CN138050:  $p = 0.001$ ) and in the 1 study in bipolar I disorder CN138013:  $p = 0.001$ ). Additionally, the treatment comparisons for the 6.5-mg haloperidol dose ( $p = 0.003$ ) in Study CN138012, the 5-mg ( $p = 0.034$ ) and 15-mg ( $p = 0.003$ ) aripiprazole doses and 7.5-mg haloperidol dose ( $p = 0.011$ ) in Study CN138050, and the 15-mg aripiprazole dose ( $p = 0.015$ ) and 2-mg lorazepam dose ( $<0.001$ ) in Study CN138013, were better than placebo. The 1-mg aripiprazole dose ( $p = 0.280$ ) in Study CN138050 was not statistically different from placebo (Table 3.2D-1).

For the schizophrenia-only population (CN138012, CN138050), statistically significant differences versus placebo were demonstrated for the 10-mg aripiprazole doses in each study (CN138012:  $p = 0.017$ ; CN138050:  $p = 0.022$ ), as well as the 15-mg aripiprazole dose in Study CN138050 ( $p = 0.011$ ) and the 6.5-mg haloperidol dose ( $p = 0.014$ ) in Study CN138012 (Table 3.2D-2).

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**Table 3.2D-1: Mean Change from Baseline to 2 Hours Post First IM Injection in CGI Severity Score: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
Schizophrenia, Schizoaffective					
CN138012	88	4.58	-0.71	--	--
Placebo	173	4.56	-1.16	-0.46 (-0.76, -0.15)	0.004
Aripiprazole 10mg	184	4.57	-1.17	-0.46 (-0.77, -0.16)	0.003
Haloperidol 6.5mg					
Schizophrenia, Schizoaffective, Schizophreniform					
CN138050	61	4.91	-0.42	--	--
Placebo	56	4.85	-0.63	-0.21 (-0.58, 0.17)	0.280
Aripiprazole 1mg	62	4.81	-0.82	-0.40 (-0.76, -0.03)	0.034
Aripiprazole 5mg	56	5.10	-1.08	-0.65 (-1.03, -0.28)	0.001
Aripiprazole 10mg	58	4.89	-0.99	-0.57 (-0.94, -0.20)	0.003
Aripiprazole 15mg	57	4.97	-0.91	-0.48 (-0.86, -0.11)	0.011
Haloperidol 7.5mg					
Bipolar 1 Disorder					
CN138013	73	4.12	-0.94	--	--
Placebo	75	4.24	-1.48	-0.55 (-0.87, -0.22)	0.001
Aripiprazole 10mg	75	4.09	-1.34	-0.40 (-0.72, -0.08)	0.015
Aripiprazole 15mg	68	4.16	-1.61	-0.67 (-1.00, -0.34)	<0.001
Lorazepam 2mg					

ANCOVA model, controlling for treatment, country (CN138-012, CN138-050) or pooled study center (CN138-013), and baseline value, is used for mean change from baseline comparisons.

**Table 3.2D-2: Mean Change from Baseline to 2 Hours Post First IM Injection in CGI Severity Score: IM Placebo-Controlled Studies, Schizophrenia Population Only (CN138012, CN138050), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
CN138012	65	4.38	-0.85	--	--
	123	4.38	-1.29	-0.45 (-0.81, -0.08)	0.017
	134	4.38	-1.30	-0.45 (-0.81, -0.09)	0.014
CN138050	39	4.90	-0.56	--	--
	30	4.83	-0.53	0.03 (-0.46, 0.52)	0.908
	40	4.75	-0.95	-0.39 (-0.84, 0.06)	0.090
	36	5.06	-1.10	-0.54 (-1.01, -0.08)	0.022
	44	4.80	-1.14	-0.58 (-1.02, -0.13)	0.011
	43	4.81	-0.98	-0.42 (-0.86, 0.03)	0.066

ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline comparisons.

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### **ACES Score**

The treatment comparison for the 10-mg aripiprazole dose was statistically significant versus placebo in the mean change from baseline to 2 hours post first IM injection in the ACES Score in the 2 schizophrenia studies (CN138012:  $p = 0.012$ ; CN138050:  $p = 0.003$ ) and in the 1 bipolar I disorder study (CN138013:  $p = 0.003$ ). The treatment comparison for the 15-mg aripiprazole dose in Study CN138013 was also statistically significant ( $p < 0.001$ ). The active comparators in all 3 studies were also better than placebo (6.5-mg haloperidol  $p < 0.001$ ; 7.5-mg haloperidol  $p = 0.003$ ; 2-mg lorazepam  $p < 0.001$ ) (Table 3.2E-1).

In the schizophrenia-only population (CN138012, CN138050), the 10-mg dose was the only aripiprazole dose that was statistically significant versus placebo in either study (CN138012:  $p = 0.041$ ; CN138050:  $p = 0.010$ ). Both haloperidol doses were also better than placebo (6.5 mg:  $p = 0.004$ ; 7.5 mg:  $p = 0.016$ ) (Table 3.2E-2).

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**Table 3.2E-1: Mean Change from Baseline to 2 Hours Post First IM Injection in ACES Score: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample**

Study/ Treatment		N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
Schizophrenia, Schizoaffective	CN138012					
	Placebo	88	2.02	0.83	--	--
	Aripiprazole 10mg	173	2.00	1.41	0.58 (0.13, 1.03)	0.012
	Haloperidol 6.5mg	184	2.01	1.64	0.81 (0.36, 1.25)	<0.001
Schizophrenia, Schizoaffective, Schizophreniform	CN138050					
	Placebo	61	2.07	0.66	--	--
	Aripiprazole 1mg	56	2.09	0.65	-0.01 (-0.56, 0.54)	0.980
	Aripiprazole 5mg	62	2.14	1.01	0.35 (-0.18, 0.89)	0.197
	Aripiprazole 10mg	56	2.11	1.50	0.84 (0.30, 1.39)	0.003
	Aripiprazole 15mg	58	2.08	0.99	0.34 (-0.21, 0.88)	0.223
	Haloperidol 7.5mg	57	2.07	1.50	0.84 (0.30, 1.39)	0.003
Bipolar 1 Disorder	CN138013					
	Placebo	73	2.38	1.00	--	--
	Aripiprazole 10mg	75	2.28	1.87	0.87 (0.30, 1.44)	0.003
	Aripiprazole 15mg	75	2.41	2.32	1.32 (0.75, 1.89)	<0.001
	Lorazepam 2mg	68	2.38	2.34	1.34 (0.75, 1.92)	<0.001

ANCOVA model, controlling for treatment, country (CN138-012, CN138-050) or pooled study center (CN138-013), and baseline value, is used for mean change from baseline comparisons.

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**Table 3.2E-2: Mean Change from Baseline to 2 Hours Post First IM Injection in ACES Score: IM Placebo-Controlled Studies, Schizophrenia Population Only (CN138012, CN138050), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
CN138012	65	2.28	1.20	--	--
	123	2.18	1.76	0.56 (0.02, 1.10)	0.041
	134	2.16	1.99	0.79 (0.26, 1.32)	0.004
CN138050	39	2.08	0.99	--	--
	30	2.10	0.79	-0.20 (-0.87, 0.48)	0.567
	40	2.18	1.21	0.22 (-0.41, 0.84)	0.496
	36	2.19	1.84	0.85 (0.21, 1.50)	0.010
	44	2.14	1.30	0.31 (-0.31, 0.92)	0.326
	43	2.14	1.74	0.75 (0.14, 1.37)	0.016

ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline comparisons.

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### CABS Score

The treatment comparisons for the 10-mg aripiprazole dose versus placebo in the mean change from baseline to 2 hours post first IM injection in CABS Score were statistically significant for in the 2 schizophrenia studies (CN138012 and CN138050;  $p < 0.001$ ) and in the 1 bipolar I disorder study (CN138013;  $p < 0.001$ ). Furthermore, the treatment comparisons for the 6.5-mg haloperidol dose ( $p < 0.001$ ) in Study CN138012, the 5-mg ( $p = 0.007$ ) and 15-mg ( $p < 0.001$ ) aripiprazole dose groups and 7.5-mg haloperidol dose ( $p < 0.001$ ) in Study CN138050, and the 15-mg aripiprazole dose ( $p = 0.002$ ) and 2-mg lorazepam dose ( $p < 0.001$ ) in Study CN138013 were statistically significant. The 1-mg aripiprazole dose was not statistically different from placebo ( $p = 0.054$ ) in Study CN138050 (Table 3.2F-1).

For the schizophrenia-only population (CN138012, CN138050), the treatment comparisons for the 10-mg aripiprazole dose groups were statistically significant versus placebo (CN138012:  $p < 0.001$ ; CN138050:  $p = 0.023$ ). The 5-mg ( $p = 0.041$ ) and 15-mg ( $p = 0.018$ ) aripiprazole dose groups also showed significant treatment comparisons in this population, as did both haloperidol doses (6.5 mg:  $p < 0.001$ ; 7.5 mg:  $p = 0.002$ ) (Table 3.2F-2).

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**Table 3.2F-1: Mean Change from Baseline to 2 Hours Post First IM Injection in CABS Score: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
Schizophrenia, Schizoaffective					
CN138012					
Placebo	88	31.06	-4.51		
Aripiprazole 10mg	173	32.01	-8.03	-3.53 (-5.04, -2.02)	<0.001
Haloperidol 6.5mg	184	31.78	-8.28	-3.77 (-5.26, -2.28)	<0.001
Schizophrenia, Schizoaffective, Schizophreniform					
CN138050					
Placebo	61	31.18	-2.95		
Aripiprazole 1mg	56	31.45	-5.16	-2.21 (-4.46, 0.04)	0.054
Aripiprazole 5mg	62	30.05	-5.97	-3.02 (-5.21, -0.82)	0.007
Aripiprazole 10mg	56	31.51	-7.08	-4.13 (-6.38, -1.88)	<0.001
Aripiprazole 15mg	58	31.22	-7.04	-4.09 (-6.33, -1.86)	<0.001
Haloperidol 7.5mg	57	32.10	-8.13	-5.18 (-7.42, -2.94)	<0.001
Bipolar I Disorder					
CN138013					
Placebo	73	28.38	-6.37		
Aripiprazole 10mg	75	29.36	-9.60	-3.23 (-4.95, -1.52)	<0.001
Aripiprazole 15mg	75	28.00	-9.08	-2.71 (-4.42, -1.01)	0.002
Lorazepam 2mg	68	28.96	-10.3	-3.98 (-5.73, -2.24)	<0.001

ANCOVA model, controlling for treatment, country (CN138-012, CN138-050) or pooled study center (CN138-013), and baseline value, is used for mean change from baseline comparisons.

**Table 3.2F-2: Mean Change from Baseline to 2 Hours Post First IM Injection in CABS Score: IM Placebo-Controlled Studies, Schizophrenia Population Only (CN138012, CN138050), LOCF Data Set, Efficacy Sample**

Study/ Treatment		N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
CN138012	Placebo	65	28.37	-5.52	--	--
	Aripiprazole 10mg	123	29.37	-8.83	-3.30 (-5.07, -1.54)	<0.001
	Haloperidol 6.5mg	134	29.25	-9.01	-3.49 (-5.23, -1.75)	<0.001
CN138050	Placebo	39	30.83	-4.35	--	--
	Aripiprazole 1mg	30	30.71	-5.74	-1.38 (-4.24, 1.47)	0.341
	Aripiprazole 5mg	40	28.40	-7.13	-2.77 (-5.44, -0.11)	0.041
	Aripiprazole 10mg	36	29.51	-7.51	-3.16 (-5.88, -0.44)	0.023
	Aripiprazole 15mg	44	29.96	-7.47	-3.12 (-5.70, -0.53)	0.018
	Haloperidol 7.5mg	43	30.47	-8.58	-4.22 (-6.82, -1.62)	0.002

ANOVA model, controlling for treatment and baseline value, is used for mean change from baseline comparisons.

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**Table 4A-1: Onset of Efficacy, PEC Score: Mean Change from Baseline to 2 Hours Post First IM Injection: IM Placebo-Controlled Studies (CN138012, CN138050), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	PEC Score											
		15 Minutes Mean Change	30 Minutes Mean Change	45 Minutes Mean Change	60 Minutes Mean Change	75 Minutes Mean Change	90 Minutes Mean Change	105 Minutes Mean Change	120 Minutes Mean Change				
CN138012	88	--	-2.68	-3.57	-4.21	--	-4.45	--	-4.78				
Placebo	173	--	-2.50	-3.93	-5.42*	--	-6.26**	--	-7.27**				
Aripiprazole 10mg	184	--	-2.90	-4.78*	-6.32**	--	-7.43**	--	-7.75**				
Haloperidol 6.5mg													
CN138050	61	-0.95	-1.76	-2.22	-2.41	-2.78	-3.39	-3.45	-3.28				
Placebo	56	-0.48	-1.80	-2.60	-2.86	-3.45	-3.95	-4.37	-4.47				
Aripiprazole 1mg	62	-1.54	-2.30	-3.68	-4.01*	-4.44*	-4.75	-5.48*	-5.65**				
Aripiprazole 5mg	56	-1.16	-3.19	-4.39**	-5.48**	-5.84**	-6.14**	-6.65**	-6.69**				
Aripiprazole 10mg	58	-1.15	-2.42	-3.33	-4.63**	-4.73*	-5.09*	-5.47*	-5.72**				
Aripiprazole 15mg	57	-0.45	-1.85	-3.52	-3.94	-4.41	-4.88	-6.03**	-6.38**				
Haloperidol 7.5mg													

\*\* p <= 0.01, \* p <= 0.05

ANCOVA model, controlling for treatment, country and baseline value, is used for mean change from baseline comparisons.

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**PEC and CGI-I: Patients Who Received a Second Injection**

Although the 3 studies were not designed to prove treatment differences in patients who received a second injection, results showed that the 10-mg dose was an effective dose when given as multiple injections. Patients could have received a second IM injection  $\geq 2$  hours (but less than 20 hours) following the first IM injection, if necessary. The tables in this section (4B-1, 4B-2, 4B-3) refer to all patients who received 2 or more injections.

For patients who received a second IM injection in Study CN138012 (schizophrenia and schizoaffective disorder), a statistically significant difference versus placebo was shown for the 10-mg aripiprazole group and for the 6.5-mg haloperidol group for the mean change from PEC Score prior to first injection to 2 hours post second IM injection, and for the PEC Score prior to the second injection to 2 hours post second IM injection. A statistically significant difference versus placebo was also demonstrated in the mean CGI-I score at 2 hours post second IM injection for both treatment groups (Table 4B-1).

In Study CN138050, statistically significant comparisons versus placebo were demonstrated for the 5-mg and 15-mg aripiprazole groups and the 7.5-mg haloperidol group in the mean change from PEC Score prior to the first injection to 2 hours post second IM injection, the mean change from PEC Score prior to the second injection to 2 hours post second injection, and the mean CGI-I Score at 2 hours post second IM injection (Table 4B-2). Although the 10-mg aripiprazole group did not show statistical significance on these measures, there was greater improvement in the 10-mg aripiprazole group than in the placebo group.

In Study CN138013, the 10-mg aripiprazole dose and the 2-mg lorazepam dose were statistically significantly superior to placebo in the mean change from PEC Score prior to the first injection and prior to the second injection to 2 hours post second injection, and in the mean CGI-I Score at 2 hours post second IM injection (Table 4B-3).

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**Table 4B-1: PEC and CGI-I: Patients Who Received Second Injection: IM Placebo-Controlled Study (CN138012), LOCF Data Set, Efficacy Sample**

	Placebo		Haloperidol 6.5mg		Aripiprazole 10mg	
	N	Mean	N	Mean	N	Mean
PEC Score	50	19.34	62	19.08	71	19.20
Baseline PEC Score Prior to First Injection						
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Second Injection	50	-3.20	62	-8.66**	71	-7.75**
PEC Score Prior to Second Injection	50	18.88	62	16.87*	70	17.20*
Mean Change from PEC Score Prior to Second Injection to 2 Hours Post Second Injection	50	-2.16	62	-6.73**	70	-5.92**
CGI-I Score	50	4.20	61	3.74**	70	3.73**
CGI-I Score Prior to Second Injection						
Mean Score 2 Hours Post Second Injection	50	3.68	61	2.52**	71	2.55**

\*\* p<=0.01, \* p<=0.05  
 ANCOVA model, controlling for treatment and baseline value, is used for mean change comparisons.  
 CMH row means score test controlling for treatment is used for CGI-I score means

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	Placebo	Lorazepam 2.0mg	10mg	15mg
PEC Score	N=46	N=24	N=30	N=23
Baseline PEC Score Prior to First Injection	17.61	18.50	18.93*	18.61
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Second Injection	-4.93	-9.83**	-9.55**	-8.26*
PEC Score Prior to Second Injection	16.41	15.00	16.93	16.04
Mean Change from PEC Score Prior to Second Injection to 2 Hours Post Second Injection	-3.06	-7.12**	-7.68**	-6.04*
CGI-I Score	3.89	3.71	3.73	4.13
Mean Score 2 Hours Post Second Injection	3.26	2.13**	1.87**	2.52*

\*\* p<=0.01, \* p<=0.05  
 ANCOVA model, controlling for treatment and baseline value, is used for mean change comparisons.  
 OWH row means score test controlling for treatment is used for CGI-I score means

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**PEC and CGI-I Scores: Second Injection in Patients Who Were Nonresponders**

To focus on patients who might clinically be in need of a second injection, the PEC Score and CGI-I Score were analyzed for patients who received a second injection within 4 hours of the first injection and who were nonresponders prior to the second injection. It should be noted that these studies were not designed to show statistically significant differences in patients who received a second injection; however, both the 10-mg and 15-mg aripiprazole doses in the 2 schizophrenia studies (CN138012, CN138050) and the bipolar I disorder study (CN138013) effectively reduced agitation when given as a second injection to patients who were nonresponders to the first injection. The haloperidol doses (6.5 and 7.5 mg) and the lorazepam dose also effectively reduced agitation. The tables in this section (4C-1, 4C-2, 4C-3) refer to all patients who received 2 or more injections.

In Study CN138012, the mean change from PEC Score prior to the first injection to 2 hours post second injection was statistically significant versus placebo for the 10-mg aripiprazole dose and the 6.5-mg haloperidol dose, as was the mean change from PEC Score prior to the second injection to 2 hours post second injection, and the mean CGI-I Score at 2 hours post second injection (Table 4C-1).

In Study CN138050, the mean change from PEC Score prior to the first injection to 2 hours post second injection for the 10-mg aripiprazole dose and the 7.5-mg haloperidol dose was statistically significant versus placebo, as was the mean change from PEC Score prior to the second injection at 2 hours post second injection. There were no statistically significant differences for the 10-mg aripiprazole group versus placebo in the mean CGI-I Score at 2 hours post second injection, but the 7.5 mg haloperidol dose was significant on this measure (Table 4C-2).

In Study CN138013, the mean change from PEC Score prior to first injection to 2 hours post second injection was statistically significant versus placebo for the 10- and 15-mg aripiprazole dose groups, while these groups and the 2-mg lorazepam group were statistically significant versus placebo on the mean change from PEC Score prior to second injection to 2 hours post second injection and the mean CGI-I Score at 2 hours post second injection (Table 4C-3).

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**Table 4C-1: PEC and CGI-I: Patients Who Received Second Injection Within 4 Hours of First Injection and Who Were PEC Nonresponders Prior to Second Injection: IM Placebo-Controlled Study (CN138012), LOCF Data Set, Efficacy Sample**

	Placebo	Haloperidol 6.5mg	Aripiprazole 10mg
PEC Score			
Baseline PEC Score Prior to First Injection	N=39 19.51	N=34 19.29	N=38 19.68
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Second Injection	-2.00	-7.89**	-6.08**
PEC Score Prior to Second Injection	18.95	17.76	17.92
Mean Change from PEC Score Prior to Second Injection to 2 Hours Post Second Injection	-1.16	-6.48**	-4.49**
CGI-I Score			
CGI-I Score Prior to Second Injection	4.21	3.82*	3.66**
Mean Score 2 Hours Post Second Injection	3.95	2.82**	2.95**

\*\* p<=0.01, \* p<=0.05  
 ANCOVA model, controlling for treatment and baseline value, is used for mean change comparisons.  
 CH row means score test controlling for treatment is used for the CGI-I score means.

PROGRAM SOURCE: /w/bdm/clin/proj/cn/138/incse/val/stats/table4\_c\_1.sas

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**Table 4C-2: PEC and CGI-I: Patients Who Received Second Injection Within 4 Hours of First Injection and Who Were PEC Nonresponders Prior to Second Injection: IM Placebo-Controlled Study (CN138050), LOCF Data Set, Efficacy Sample**

	Placebo	Haloperidol			Aripiprazole		
		7.5mg	1mg	5mg	10mg	15mg	
PEC Score	N=27	N=10	N=18	N=19	N=12	N=15	
Baseline PEC Score Prior to First Injection	19.89	19.50	19.11	19.79	20.50	19.87	
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Second Injection	-2.11	-6.88**	-4.80	-6.15**	-6.12*	-7.30**	
PEC Score Prior to Second Injection	19.59	18.80	18.17	17.58	19.33	18.20	
Mean Change from PEC Score Prior to Second Injection to 2 Hours Post Second Injection	-1.67	-6.07**	-3.76	-4.16	-5.03*	-5.75**	
CGI-I Score	4.11	3.80	3.89	3.63*	4.17	3.87	
CGI-I Score Prior to Second Injection	3.74	2.30**	3.06*	2.95*	3.00	2.87*	

\*\* p<=0.01, \* p<=0.05  
 ANCOVA model, controlling for treatment and baseline value, is used for mean change comparisons.  
 O/H row means score test controlling for treatment is used for CGI-I score means

PROGRAM SOURCE: /wbdm/clin/proj/cn/138/incse/val/stats/table4\_C\_2.sas

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**Table 4C-3: PEC and CGI-I: Patients Who Received Second Injection Within 4 Hours of First Injection and Who Were PEC Nonresponders Prior to Second Injection: IM Placebo-Controlled Study (CN138013), LOCF Data Set, Efficacy Sample**

	Placebo N=34	Lorazepam 2.0mg N=12	Aripiprazole	
			10mg N=16	15mg N=12
PEC Score Baseline PEC Score Prior to First Injection	17.32	18.17	19.13**	18.92*
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Second Injection	-2.68	-8.81**	-7.08*	-6.75*
PEC Score Prior to Second Injection	16.47	14.92	17.13	17.67
Mean Change from PEC Score Prior to Second Injection to 2 Hours Post Second Injection	-1.51	-5.70**	-5.46**	-5.76**
CGI-I Score CGI-I Score Prior to Second Injection	3.85	3.42*	3.94	4.25
Mean Score 2 Hours Post Second Injection	3.65	2.17**	2.50**	2.83

\*\* p <=0.01, \* p<=0.05  
ANCOVA model, controlling for treatment and baseline value, is used for mean change comparisons.  
OVI row means score test controlling for treatment is used for CGI-I score means.

PROGRAM SOURCE: /wbdbm/clin/proj/cn/138/incse/val/stats/table4\_c\_3.sas

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**PEC Score: Patients Who Received a Third Injection**

Third injections of aripiprazole also resulted in improvements in PEC Scores. Patients could have received a third IM injection at least 2 hours following the second IM injection (but less than 20 hours after the first injection), if necessary. For patients in the placebo group, a third injection was either 10-mg aripiprazole (CN138012, CN138013) or 15-mg aripiprazole (CN138050). For each treatment group, a 1-sample t-test was used to test the hypothesis that the change from baseline was zero.

In each the 2 schizophrenia studies (CN138012, Table 4D-1; CN138050, Table 4D-2) and the bipolar I disorder study (CN138013, Table 4D-3), the 10-mg aripiprazole group was statistically significantly different than zero for each assessment, and the changes were clinically relevant. The 6.5-mg haloperidol dose in Study CN138012 and the 2-mg lorazepam dose in Study CN138013 were also statistically significantly different from zero. The changes observed in the placebo group are reflective of a first dose of aripiprazole.

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**Table 4D-1: PEC: Patients Who Received Third Injection: IM Placebo-Controlled Study (CN138012), LOCF Data Set, Efficacy Sample**

	Placebo	Haloperidol 6.5mg	Aripiprazole 10mg
All Patients	N=31	N=18	N=23
Baseline PEC Score Prior to First Injection	18.87	18.33	19.13
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Third Injection	-8.71**	-8.83**	-9.73**
PEC Score Prior to Third Injection	18.32	16.11	16.86
Mean Change from PEC Score Prior to Third Injection to 2 Hours Post Third Injection	-8.16**	-6.61**	-7.67**
PEC Nonresponders Prior to Third Injection	N=31	N=17	N=20
Baseline PEC Score Prior to First Injection	18.87	18.29	19.15
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Third Injection	-8.71**	-8.53**	-9.58**
PEC Score Prior to Third Injection	18.32	16.41	17.45
Mean Change from PEC Score Prior to Third Injection to 2 Hours Post Third Injection	-8.16**	-6.65**	-8.05**

\*\* p <= 0.01 , \* p <= 0.05 (one sample t-test for change score significantly different than zero change)

PROGRAM SOURCE: /wbdm/clin/proj/cn/138/incse/val/stats/table4\_D\_1.sas RUN DATE: 30SEP04 15:30

**Table 4D-2: PEC: Patients Who Received Third Injection: IM Placebo-Controlled Study (CN138050), LOCF Data Set, Efficacy Sample**

	Haloperidol	Aripiprazole
	129	

	Placebo	7.5mg	1 mg	5 mg	10 mg	15 mg
All Patients	N=27	N=4	N=14	N=15	N=10	N=5
Baseline PEC Score Prior to First Injection	19.81	20.75	18.64	20.00	20.20	19.40
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Third Injection	-7.74**	-6.00	-5.50**	-8.07**	-8.80**	-7.60*
PEC Score Prior to Third Injection	19.04	20.50	16.79	17.47	17.50	16.20
Mean Change from PEC Score Prior to Third Injection to 2 Hours Post Third Injection	-6.96**	-5.75	-3.64**	-5.53**	-6.10**	-4.40
PEC Nonresponders Prior to Third Injection	N=26	N=4	N=14	N=15	N=9	N=4
Baseline PEC Score Prior to First Injection	19.92	20.75	18.64	20.00	20.00	19.75
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Third Injection	-7.62**	-6.00	-5.50**	-8.07**	-7.89**	-6.25
PEC Score Prior to Third Injection	19.38	20.50	16.79	17.47	18.00	18.00
Mean Change from PEC Score Prior to Third Injection to 2 Hours Post Third Injection	-7.08**	-5.75	-3.64**	-5.53**	-5.89**	-4.50

\*\* p <= 0.01 , \* p <= 0.05 (one sample t-test for change score significantly different than zero change)

PROGRAM SOURCE: /w/bdm/clin/proj/cn/138/imcse/val/stats/table4\_d\_2.sas

RUN DATE: 30SEP04 15:30

**Table 4D-3: PEC: Patients Who Received Third Injection: IM Placebo-Controlled Study (CN138013), LOCF Data Set, Efficacy Sample**

	Placebo	Aripiprazole		
		Lorazepam 2mg	10mg	15mg
All Patients	N=31	N=6	N=6	N=7
Baseline PEC Score Prior to First Injection	17.90	17.83	18.67	18.57

Mean Change from PEC Score Prior to First Injection to 2 Hours Post Third Injection	-9.58**	-11.50**	-10.00*	-8.57*
PEC Score Prior to Third Injection	16.74	16.50	16.83	18.43
Mean Change from PEC Score Prior to Third Injection to 2 Hours Post Third Injection	-8.42**	-10.17**	-8.17*	-8.43**
PEC Nonresponders Prior to Third Injection	N=30	N=6	N=6	N=7
Baseline PEC Score Prior to First Injection	17.93	17.83	18.67	18.57
Mean Change from PEC Score Prior to First Injection to 2 Hours Post Third Injection	-9.53**	-11.50**	-10.00*	-8.57*
PEC Score Prior to Third Injection	17.00	16.50	16.83	18.43
Mean Change from PEC Score Prior to Third Injection to 2 Hours Post Third Injection	-8.60**	-10.17**	-8.17*	-8.43**

\*\* p <= 0.01 , \* p <= 0.05 (one sample t-test for change score significantly different than zero change)

PROGRAM SOURCE: /wwbdm/clin/proj/cn/138/imcse/val/stats/table4\_D\_3.sas

## 10.2 subpopulation analysis

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**Table 3.3A-1: PEC Score, Mean Change from Baseline to 2 Hours Post First IM Injection by Population Subset: IM Placebo-Controlled Studies (CN138012, CN138050), LOCF Data Set, Efficacy Sample**

Subgroup	Value	Placebo		Haloperidol		Aripiprazole(a)	
		N	Mean	N	Mean	N	Mean
Age	<= Upper Quartile	119	-4.94	193	-7.85**	263	-7.82**
	> Upper Quartile	30	-4.78	48	-8.41**	86	-6.87
Gender	Men	87	-5.47	148	-8.17**	214	-7.80**
	Women	62	-4.24	93	-7.66**	135	-7.26**
Race	White	98	-4.48	154	-7.40**	248	-7.13**
	Black	43	-6.17	76	-9.44**	80	-8.91**
	Other	8	-6.61	10	-8.39	21	-9.06
Underlying Diagnosis	Schizophrenia	104	-5.23	177	-7.80**	243	-7.59**
	Schizoaffective Disorder	43	-4.54	63	-8.44**	103	-7.60**
	Schizophreniform	2	0.36	1	-8.86	3	-3.62
Baseline PEC Score	<= median	84	-5.55	130	-6.98*	162	-7.10**
	> median	65	-3.99	111	-9.07**	187	-8.08**

\*\* p <= 0.01 , \* p <= 0.05  
(a) The 1-mg aripiprazole dose is not included in the overall aripiprazole summary because it was shown to be an ineffective dose. ANCOVA model, controlling for treatment, protocol, and baseline value, is used for mean change from baseline comparisons.

PROGRAM SOURCE: /wbdm/clin/proj/cn/138/imcse/val/stats/table3\_3A\_1.sas RIN DATE: 27SEP04 12:02

**Table 3.3A-2: PEC Score, Mean Change from Baseline to 2 Hours Post First IM Injection by Population Subset: IM Placebo-Controlled Study (CN138013), LOCF Data Set, Efficacy Sample**

PEC Score

Subgroup	Value	N	Placebo	N	Lorazepam	N	Aripiprazole (a)
Age	<= Upper Quartile	60	-5.96	52	-9.25**	113	-8.55**
	> Upper Quartile	13	-3.95	16	-10.23**	37	-8.73**
Gender	Men	42	-6.17	30	-9.42**	79	-9.12**
	Women	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
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

\*\* p <= 0.01 , \* p <= 0.05  
(a) The 1-mg aripiprazole dose is not included in the overall aripiprazole summary because it was shown to be an ineffective dose.  
ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline comparisons

PROGRAM SOURCE: /w/bdm/clin/proj/cn/138/incse/val/stats/table3\_3A\_2.sas

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**PEC Score: Nonsedated Patients Based on the ACES Score**

Efficacy was demonstrated to be independent of oversedation, as measured by the ACES Score. The mean change from baseline to 2 hours post first IM injection in PEC Score was analyzed by excluding patients with scores of 8 or 9 on the ACES scale during the first 2 hours. The ACES was scored as follows: 1 = marked agitation, 2 = moderate agitation, 3 = mild agitation, 4 = normal, 5 = mild calmness, 6 = moderate calmness, 7 = marked calmness, 8 (deep sleep) and 9 (unarousable).

Results of this analysis showed that the treatment difference for the 10-mg aripiprazole group versus placebo was statistically significant in the 2 schizophrenia studies (CN138012:  $p = 0.001$ ; CN138050:  $p < 0.001$ ) as well as in the bipolar I disorder study (CN138013:  $p < 0.001$ ). In addition, all other treatment groups, except for the 1-mg aripiprazole group in Study CN138050, were significant versus placebo (Table 3.3B-1).

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**Table 3.3B-1: Mean Change from Baseline to 2 Hours Post First IM Injection in PEC Score Excluding Patients with Scores of 8 (Deep Sleep) or 9 (Unarousable) on ACES During the First 2 Hours: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
Schizophrenia, Schizoaffective					
CN138012	83	18.76	-4.89	--	--
Placebo	159	18.75	-7.20	-2.31 (-3.62, -1.00)	0.001
Aripiprazole 10mg	157	18.75	-7.53	-2.64 (-3.95, -1.33)	<0.001
Haloperidol 6.5mg					
Schizophrenia, Schizoaffective, Schizophreniform					
CN138050	59	19.05	-4.33	--	--
Placebo	55	19.15	-5.65	-1.32 (-3.17, 0.53)	0.161
Aripiprazole 1mg	62	19.45	-7.06	-2.73 (-4.53, -0.93)	0.003
Aripiprazole 5mg	54	19.37	-7.73	-3.40 (-5.26, -1.54)	<0.001
Aripiprazole 10mg	57	19.37	-7.23	-2.90 (-4.74, -1.07)	0.002
Aripiprazole 15mg	52	18.75	-7.22	-2.89 (-4.77, -1.01)	0.003
Haloperidol 7.5mg					
Bipolar I Disorder					
CN138013	68	17.91	-5.10	--	--
Placebo	70	18.76	-8.44	-3.34 (-4.96, -1.71)	<0.001
Aripiprazole 10mg	62	18.19	-7.72	-2.62 (-4.29, -0.95)	0.002
Aripiprazole 15mg	55	18.31	-8.70	-3.60 (-5.33, -1.88)	<0.001
Lorazepam 2mg					

ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline comparisons.

PROGRAM SOURCE: /wbdm/clin/proj/cn/138/incse/val/stats/table3\_3B\_1.sas

RUN DATE: 08SEP04 14:22

**PEC Score: Nonsedated Patients Based on Adverse Events**

Efficacy on the PEC Score was demonstrated to be independent of oversedation, as measured by adverse events (AEs) of sedation or somnolence. The mean change from baseline to 2 hours post first IM injection in PEC Score was analyzed for patients who did not have AEs of sedation or somnolence during the first 2 hours. Patients with AEs of sedation or somnolence during the first 2 hours were excluded from the analysis.

Results of this analysis showed that the treatment differences for the 10-mg aripiprazole group versus placebo were statistically significant in the 2 schizophrenia studies (CN138012:  $p < 0.001$ ; CN138050:  $p = 0.001$ ) and the bipolar I disorder study (CN138013:  $p < 0.001$ ), as were all other treatment groups in all studies, except for the 1-mg aripiprazole group in Study CN138050 (Table 3.3B-2).

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**Table 3.3B-2: Mean Change from Baseline to 2 Hours Post First IM Injection in PEC Score Excluding Patients with Sedation/Somnolence Related AEs During the First 2 Hours: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
Schizophrenia, Schizoaffective					
CN138012	86	18.78	-5.05		
Placebo	169	18.76	-7.68	-2.64 (-3.95, -1.33)	--
Aripiprazole 10mg	177	18.80	-8.02	-2.97 (-4.27, -1.67)	<0.001
Haloperidol 6.5mg					<0.001
Schizophrenia, Schizoaffective, Schizophreniform					
CN138050	58	19.19	-4.56		
Placebo	53	19.17	-5.54	-0.98 (-2.94, 0.98)	--
Aripiprazole 1mg	57	19.39	-7.05	-2.48 (-4.41, -0.56)	0.325
Aripiprazole 5mg	52	19.46	-7.84	-3.27 (-5.24, -1.30)	0.012
Aripiprazole 10mg	53	19.40	-7.14	-2.58 (-4.54, -0.62)	0.001
Aripiprazole 15mg	50	19.00	-7.80	-3.23 (-5.22, -1.24)	0.010
Haloperidol 7.5mg					0.002
Bipolar 1 Disorder					
CN138013	69	18.00	-5.47		
Placebo	70	18.69	-8.59	-3.12 (-4.77, -1.48)	--
Aripiprazole 10mg	66	18.24	-8.20	-2.73 (-4.39, -1.07)	<0.001
Aripiprazole 15mg	59	18.44	-9.09	-3.62 (-5.34, -1.91)	0.001
Lorazepam 2mg					<0.001

ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline comparisons.

PROGRAM SOURCE: /w/bdm/clin/proj/cn/138/ancse/val/stats/table3\_3B\_2.sas

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**PEC Score: Stratified by ACES Scores**

Efficacy on the PEC Score, independent of oversedation, was also demonstrated by stratifying patients into the following groups based on ACES Scores: scores of 1 to 7 during the first 2 hours after first injection versus scores of 8 or 9 at any timepoint during that interval.

The results of these analyses showed that over time through the first 240 minutes post first IM injection, the number of aripiprazole-treated patients that were considered sedated (ie, ACES Scores of 8 or 9) was small. In those patients who were not considered sedated (ie, ACES Scores of 1 to 7), the efficacy of aripiprazole versus placebo was observed over time and was consistent with that seen in the total sample.

For patients who had ACES Scores of 1 to 7 in Study CN138012, there were similar mean change results in all treatment groups at 30 minutes, with patients in the haloperidol and aripiprazole groups showing greater mean changes than patients in the placebo group beginning at 45 minutes. No aripiprazole-treated patients had ACES Scores of 8 or 9 at 30, 45, or 60 minutes post first IM injection. At 90, 120, and 240 minutes post first IM injection, the treatment groups had similar mean change from baseline values in PEC Score (Table 3.3B-3).

For patients who had ACES Scores of 1 to 7 in Study CN138050, the 5-mg, 10-mg, and 15-mg aripiprazole groups and 7.5-mg haloperidol group had greater mean changes than placebo beginning at 15 minutes. There were few aripiprazole-treated patients with ACES Scores of 8 or 9 through 120 minutes. At 240 minutes, mean change results were similar across all treatment groups (Table 3.3B-4).

For patients who had ACES Scores of 1 to 7 in Study CN138013, the 10-mg and 15-mg aripiprazole groups and 2-mg lorazepam group had greater mean changes from baseline than the placebo group beginning at 30 minutes and 45 minutes, respectively. No placebo-treated or 10-mg aripiprazole-treated patients had ACES Scores of 8 or 9 at 30 or 45 minutes. At 60, 90, 120, and 240 minutes, the mean changes were similar for all treatment groups (Table 3.3B-5).

**Table 3.3B-3: Mean Change from Baseline in PEC Score, Stratified by ACES  
IM Placebo-Controlled Study CN138012, LOCF Data Set, Efficacy Sample**

ACES/ Timepoint	Placebo		Haloperidol 6.5mg		Aripiprazole 10mg	
	N	Mean	N	Mean	N	Mean
<b>ACES = 1 - 7</b>						
30 Minutes	85	-2.80	182	-3.23	173	-3.03
45 Minutes	84	-3.83	177	-5.07	173	-4.66
60 Minutes	84	-4.48	176	-6.64	173	-6.12
90 Minutes	85	-4.82	170	-7.75	171	-6.92
120 Minutes	86	-4.99	169	-7.69	159	-7.20
240 Minutes	82	-5.40	159	-8.70	161	-8.43
<b>ACES = 8, 9</b>						
30 Minutes	3	-14.00	2	-17.00		
45 Minutes	4	-13.25	7	-15.71		
60 Minutes	4	-13.25	8	-15.00		
90 Minutes	3	-14.00	14	-12.86	2	-12.00
120 Minutes	2	-13.00	15	-13.47	14	-13.36
240 Minutes	6	-13.33	25	-13.40	12	-13.33

PROGRAM SOURCE: /w/bdm/clin/proj/cn/138/incse/val/stats/table3\_3B\_3\_17.sas

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**Table 3.3B-4: Mean Change from Baseline in PEC Score, Stratified by ACES IM Placebo-Controlled Study CN138050, LOCF Data Set, Efficacy Sample**

ACES/ Timepoint	Placebo		Haloperidol 7.5m		7.5m		5mg		10mg		15mg	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
ACES = 1 - 7												
15 Minutes	61	-1.85	57	-1.28	56	-1.32	62	-2.47	56	-2.05	58	-2.21
30 Minutes	60	-2.55	57	-2.79	56	-2.73	62	-3.34	55	-3.95	58	-3.59
45 Minutes	60	-3.10	56	-4.38	56	-3.61	62	-4.79	55	-5.25	58	-4.59
60 Minutes	61	-3.95	54	-4.94	56	-4.29	62	-5.55	55	-6.85	57	-6.26
75 Minutes	61	-4.41	54	-5.50	55	-4.78	62	-6.08	55	-7.31	57	-6.47
90 Minutes	60	-4.88	53	-5.96	55	-5.35	62	-6.44	55	-7.65	57	-6.89
105 Minutes	60	-4.92	53	-7.04	55	-5.75	62	-7.16	55	-8.15	57	-7.26
120 Minutes	60	-4.52	53	-7.13	55	-5.64	62	-7.13	54	-7.78	57	-7.28
240 Minutes	60	-4.82	47	-7.64	54	-6.39	57	-8.09	54	-8.19	53	-7.77
ACES = 8, 9												
30 Minutes	1	-16.00										
45 Minutes	1	-16.00	1	-14.00					1	-15.00		
60 Minutes			3	-14.00					1	-15.00	1	-13.00
75 Minutes			3	-14.00					1	-15.00	1	-13.00
90 Minutes	1	-16.00	4	-13.25	1	-15.00			1	-15.00	1	-13.00
105 Minutes	1	-16.00	4	-14.75	1	-15.00			1	-15.00	1	-13.00
120 Minutes	1	-16.00	4	-15.00	1	-15.00			2	-16.00	1	-13.00
240 Minutes	1	-13.00	10	-14.80	2	-11.50	5	-13.60	2	-15.00	5	-13.80

PROGRAM SOURCE: /wbdm/clin/proj/cn/138/imcse/val/stats/table3\_3b\_4\_17.sas

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**Table 3.3B-5: Mean Change from Baseline in PEC Score, Stratified by ACES  
IM Placebo-Controlled Study CN138013, LOCF Data Set, Efficacy Sample**

ACES/ Timepoint	Placebo			Lorazepam 2mg			Aripiprazole					
							10mg			15mg		
	N	Mean		N	Mean		N	Mean	N	Mean	N	Mean
ACES = 1 - 7												
30 Minutes	73	-3.08		66	-3.36		75	-3.21	73	-2.58		
45 Minutes	73	-3.97		67	-5.40		75	-5.33	73	-4.92		
60 Minutes	72	-4.90		65	-6.66		73	-6.40	73	-6.56		
90 Minutes	68	-5.13		61	-8.16		72	-7.94	69	-7.13		
120 Minutes	70	-4.93		58	-8.84		72	-8.76	66	-7.82		
240 Minutes	69	-5.48		47	-8.89		62	-8.74	59	-9.03		
ACES = 8, 9												
30 Minutes				2	-16.00				2	-12.50		
45 Minutes				1	-12.00				2	-12.50		
60 Minutes	1	-15.00		3	-14.00		2	-13.00	2	-14.00		
90 Minutes	5	-13.00		7	-13.43		3	-13.33	6	-13.00		
120 Minutes	3	-14.67		10	-13.60		3	-13.67	9	-13.00		
240 Minutes	4	-12.25		21	-13.71		13	-14.54	16	-13.88		

PROGRAM SOURCE: /w/bdm/clin/proj/cn/138/incse/val/stats/table3\_3B\_5\_17.sas

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**CGI-I Score: Nonsedated Patients Based on the ACES Score**

Efficacy on the CGI-I was demonstrated to be independent of oversedation, as measured by the ACES Score. The mean change from baseline to 2 hours post first IM injection in CGI-I Score was analyzed by excluding patients with scores of 8 or 9 on the ACES scale during the first 2 hours.

Results of this analysis showed that the treatment difference for the 10-mg aripiprazole group versus placebo was statistically significant in the 2 schizophrenia studies (CN138012:  $p < 0.001$ ; CN138050:  $p < 0.001$ ) and the bipolar I disorder study (CN138013:  $p < 0.001$ ), as were all other treatment group comparisons (Table 3.3C-1).

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**Table 3.3C-1: Mean CGI Improvement Score at 2 Hours Post First IM Injection Excluding Patients with Scores of 8 (Deep Sleep) or 9 (Unarousable) on ACES During the First 2 Hours: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	Mean Score	P-Value
Schizophrenia, Schizoaffective			
CN138012			
Placebo	83	3.17	--
Aripiprazole 10mg	159	2.53	<0.001
Haloperidol 6.5mg	157	2.51	<0.001
Schizophrenia, Schizoaffective, Schizophreniform			
CN138050			
Placebo	59	3.46	--
Aripiprazole 1mg	55	3.07	0.028
Aripiprazole 5mg	62	2.82	0.001
Aripiprazole 10mg	54	2.67	<0.001
Aripiprazole 15mg	57	2.67	<0.001
Haloperidol 7.5mg	52	2.79	0.001
Bipolar 1 Disorder			
CN138013			
Placebo	68	3.13	--
Aripiprazole 10mg	70	2.24	<0.001
Aripiprazole 15mg	62	2.55	0.006
Lorazepam 2mg	55	2.27	<0.001

OMH row means score test controlling for treatment is used for CGI-I score means.

PROGRAM SOURCE: /wbdm/clin/proj/cn/138/incse/val/stats/table3\_3c\_1.sas

RUN DATE: 08SEP04 14:22

**CGI-I Score: Nonsedated Patients Based on Adverse Events**

Efficacy on the CGI-I was demonstrated to be independent of oversedation, as measured by AEs of sedation or somnolence. The mean CGI-I Score at 2 hours post first IM injection was analyzed for patients who did not have AEs of sedation or somnolence during the first 2 hours. Patients with AEs of sedation or somnolence were excluded from the analysis.

Results of this analysis showed that the treatment difference for the 10-mg aripiprazole group versus placebo was statistically significant in the 2 schizophrenia studies (CN138012 and CN138050:  $p < 0.001$ ) and the bipolar I disorder study (CN138013:  $p < 0.001$ ), as were all other treatment group comparisons (Table 3.3C-2).

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**Table 3.3C-2: Mean CGI Improvement Score at 2 Hours Post First IM Injection: Excluding Patients with Sedation/Somnolence Related AEs During the First 2 Hours: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample**

Study/ Treatment	N	Mean Score	P-Value
Schizophrenia, Schizoaffective	86	3.13	--
	Aripiprazole 10mg	2.44	<0.001
	Haloperidol 6.5mg	2.39	<0.001
Schizophrenia, Schizoaffective, Schizophreniform	58	3.47	--
	Aripiprazole 1mg	3.08	0.028
	Aripiprazole 5mg	2.79	<0.001
	Aripiprazole 10mg	2.63	<0.001
	Aripiprazole 15mg	2.66	<0.001
Bipolar 1 Disorder	50	2.68	<0.001
	Haloperidol 7.5mg		
	Placebo		
	Aripiprazole 1mg		
CN138013	69	3.09	--
	Aripiprazole 10mg	2.21	<0.001
	Aripiprazole 15mg	2.41	0.002
	Lorazepam 2mg	2.22	<0.001

CMH row means score test controlling for treatment is used for CGI-I score means.

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There were 1086 patients in the Efficacy Sample (Table 3.1A) for the 3 studies in schizophrenia or bipolar I disorder (CN138012, CN138050, CN138013): 795 patients in the 2 schizophrenia studies (CN138012, CN138050) and 291 patients in the bipolar I disorder study (CN138013). Of the 1086 patients, 555 received doses of IM aripiprazole, 241 patients received IM haloperidol, 68 patients received IM lorazepam, and 222 patients received placebo. In addition, there were 380 patients in the 4-Day Oral Phase Efficacy Sample of Study CN138012: 229 patients received oral-tablet aripiprazole (153 of these patients received IM aripiprazole during the IM Phase) and 151 patients received oral-capsule haloperidol.

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**Table 3.1A: Number of Patients by Study and Treatment Group: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), Efficacy Sample**

Protocol	Number of Patients			Total All Studies
	CN138012 <sup>a</sup>	CN138050 <sup>b</sup>	CN138013 <sup>c</sup>	
<b>Aripiprazole</b>				
1 mg	--	56	--	56
5 mg	--	62	--	62
10 mg	173	56	75	304
15 mg	--	58	75	133
<b>Total Aripiprazole</b>	173	232	150	555
<b>Haloperidol</b>				
6.5 mg	184			184
7.5 mg		57		57
<b>Lorazepam</b>				
2.0 mg	88	61	68	217
<b>Placebo</b>				
	88	61	73	222
<b>Total All Treatments</b>	<b>445</b>	<b>350</b>	<b>291</b>	<b>1086</b>

Source: Tables 8.2A in Clinical Study Reports CN138012, CN138050, CN138013

<sup>a</sup> CN138012 Randomized Sample: placebo = 88; 6.5-mg haloperidol = 185; 10-mg aripiprazole = 175.

<sup>b</sup> CN138050 Randomized Sample: placebo = 62; 7.5-mg haloperidol = 60; 1-mg aripiprazole = 57; 5-mg aripiprazole = 63; 10-mg aripiprazole = 57; 15-mg aripiprazole = 60.

<sup>c</sup> CN138013 Randomized Sample: placebo = 75; 2-mg lorazepam = 70; 10-mg aripiprazole = 78; 15-mg aripiprazole = 78.

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### **Demographics**

Treatment groups were similar with respect to age, gender, race, and ethnicity in the schizophrenia studies population (Table 3.1B-1). In the bipolar I disorder population (Table 3.1B-2), treatment groups were similar with respect to age, race, and ethnicity, but not gender. There were fewer men in the lorazepam group than in the placebo and aripiprazole groups.

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**Table 3.1B-1: Demographic Characteristics: IM Placebo-Controlled Studies (CN138012, CN138050), Efficacy Sample**

	Placebo N=149	Haloperidol N=241	Aripiprazole N=405
Age (years)			
Mean	40.23	41.43	41.76
Median	40	42	43
Min-Max	19-68	18-69	18-66
SD	10.13	9.70	10.53
Gender			
N(%)	87(58)	148(61)	251(62)
Men			
Women	62(42)	93(39)	154(38)
Race			
N(%)	98(66)	154(64)	287(71)
White			
Black	43(29)	76(32)	91(22)
Hispanic (CN138050)	7(2)	3(1)	15(4)
Asian	1(1)	1(0)	5(1)
Other Race		6(2)	7(2)
Not Available		1(0)	
Ethnicity (CN138012)			
N(%)	59(67)	116(63)	116(67)
Not Hispanic			
Hispanic	5(6)	17(9)	12(7)
Not Available	24(27)	51(28)	45(26)

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**Table 3.1B-2: Demographic Characteristics: IM Placebo-Controlled Study (CN138013), Efficacy Sample**

	Placebo	Lorazepam	Aripiprazole
	N=73	N=68	N=150
Age (years)			
Mean	40.37	41.59	40.54
Median	41	43	40
Min-Max	20-63	18-65	20-79
SD	9.49	10.53	10.88
Gender N(%)			
Male	42 (58)	30 (44)	79 (53)
Female	31 (42)	38 (56)	71 (47)
Race N(%)			
White	51 (70)	51 (75)	109 (73)
Black	17 (23)	15 (22)	37 (25)
Asian	1 (1)		
Other	4 (5)	2 (3)	4 (3)
Ethnicity N(%)			
Not Hispanic	65 (89)	61 (90)	138 (92)
Hispanic	4 (5)	5 (7)	8 (5)
Not Available	4 (5)	2 (3)	4 (3)

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**Underlying Diagnosis and Key Baseline Scores**

In the schizophrenia studies population (CN138012, CN138050), the treatment groups were similar with respect to the percentage of patients with each underlying diagnosis. There was a greater percentage of patients in each group with a diagnosis of schizophrenia compared with schizoaffective or schizophreniform disorder (Table 3.1C-1). Treatment groups were similar with respect to key baseline scores (Table 3.1C-2) for this population.

In the bipolar I disorder population (CN138013), the treatment groups were similar with respect to underlying diagnosis. There was a greater percentage of patients with a diagnosis of manic compared with mixed bipolar disorder (Table 3.1C-3). Baseline scores on key efficacy scales were similar across treatment groups (Table 3.1C-4).

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**Table 3.1C-1: Key Baseline Psychiatric Characteristics: IM Placebo-Controlled Studies (CN138012, CN138050), Efficacy Sample**

Underlying Diagnosis N (%)	Placebo N=149	Haloperidol N=241	Aripiprazole N=405
Schizophrenia	104 (70)	177 (73)	273 (67)
Schizoaffective Disorder	43 (29)	63 (26)	128 (32)
Schizophreniform Disorder	2 (1)	1 (0)	4 (1)

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**Table 3.1C-2: Key Baseline Scores: IM Placebo-Controlled Studies (CN138012,CN138050), Efficacy Sample**

	Placebo N=149	Haloperidol N=241	Aripiprazole N=405
<b>PBC Score</b>			
Mean	18.92	18.80	19.08
Median	18	18	19
Min-Max	15-29	15-31	15-34
SD	2.81	2.60	2.78
<b>CGI-S Score</b>			
Mean	4.53	4.49	4.59
Median	4	4	4
Min-Max	3-7	3-6	3-7
SD	0.79	0.75	0.76
<b>ACES Score</b>			
Mean	2.17	2.18	2.16
Median	2	2	2
Min-Max	1-3	1-3	1-4
SD	0.50	0.52	0.50
<b>CABS Score</b>			
Mean	29.21	29.73	29.91
Median	28	29	30
Min-Max	20-53	19-47	15-47
SD	5.54	5.34	5.86

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**Table 3.1C-3: Key Baseline Psychiatric Characteristics: IM Placebo-Controlled Study (CN138013), Efficacy Sample**

Underlying Diagnosis N (%)	Placebo N=73	Lorazepam N=68	Aripiprazole N=150
Bipolar I Disorder	47 (64)	46 (68)	95 (63)
Manic	26 (36)	22 (32)	55 (37)
Mixed			

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**Table 3.1C-4: Key Baseline Scores: IM Placebo-Controlled Study (CN138013), Efficacy Sample**

	Placebo N=73	Lorazepam N=68	Aripiprazole N=150
PEC Score	Mean	17.92	18.41
	Median	17	18
	Min-Max	15-29	15-25
	SD	2.63	2.33
CGI-S Score	Mean	4.10	4.14
	Median	4	4
	Min-Max	3-5	2-5
	SD	0.56	0.62
ACES Score	Mean	2.38	2.34
	Median	2	2
	Min-Max	1-3	1-3
	SD	0.52	0.52
CABS Score	Mean	28.03	28.36
	Median	28	28
	Min-Max	19-38	19-42
	SD	4.80	4.52

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### **Disposition of Patients**

The disposition of patients, including reasons for discontinuation, is based on data recorded on the end-of-study form for the Randomized Sample. A majority of patients in each treatment group completed the studies.

In the schizophrenia studies population (CN138012 and CN138050), more patients in the haloperidol treatment groups discontinued from the studies, with the most common reason for discontinuation in each study being patient withdrawal of consent (Table 3.1D-1).

In the bipolar I disorder population (CN138013), the rate of patient discontinuation was similar across treatment groups, and the most common reason for discontinuation from the study was patient withdrawal of consent (Table 3.1D-2).

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**Table 3.1D-1: Disposition of Patients: IM Placebo-Controlled Studies (CN138012,CN138050), Randomized Samples**

	Placebo	Haloperidol	Aripiprazole
<b>CN138012</b>			
Randomized Sample	88(100)	185(100)	175(100)
Total Discontinuation	1(1)	7(4)	5(3)
AE		2(1)	1(1)
Lack of Efficacy	1(1)	1(1)	1(1)
Lost to Follow-up			2(1)
Subject Withdrew Consent		3(2)	1(1)
Poor/Non-Compliance			1(1)
Other		1(1)	
Completed Study	87(99)	178(96)	170(97)
<b>CN138050</b>			
Randomized Sample	62(100)	60(100)	235(100)
Total Discontinuation	3(5)	8(13)	8(3)
AE			2(1)
Lack of Efficacy	1(2)		
Lost to Follow-up			
Subject Withdrew Consent	1(2)	6(10)	5(2)
Poor/Non-Compliance			
Other	1(2)	2(3)	1(0)
Completed Study	59(95)	52(87)	227(97)

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**Table 3.1D-2: Disposition of Patients: IM Placebo-Controlled Study (CN138013), Randomized Sample**

	Placebo	Lorazepam	Aripiprazole
CN138013			
Randomized Sample	75 (100)	70 (100)	156 (100)
Total Discontinuation	4 (5)	4 (6)	11 (7)
AE	1 (1)	1 (1)	1 (1)
Lack of Efficacy			
Lost to Follow-Up		1 (1)	5 (3)
Subject Withdrew Consent	2 (3)	1 (1)	3 (2)
Subject No Longer Meets Study Criteria		1 (1)	1 (1)
Poor/Non-Compliance	1 (1)	1 (1)	1 (1)
Other	71 (95)	66 (94)	145 (93)
Completed Study			

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### **Extent of Exposure**

The first dose of IM study medication was administered within 1 hour of when the baseline evaluations had been completed. Thereafter, a second dose was given, if needed, at least 2 hours after the initial dose, followed by a third injection of study medication, if needed, at least 4 hours after the initial dose and at least 2 hours after the second dose. These repeat doses of study medication were given no later than 20 hours after the administration of the initial dose of study medication. For schizophrenia Studies CN138012 and CN138050, a concomitant dose of lorazepam (up to 4 mg/day), or an equivalent dose of another benzodiazepine, may have been given at least 60 minutes after the second dose of study medication and whenever needed thereafter during the remainder of the 24-hour period. Concomitant benzodiazepine was given if the PEC Score was unchanged or worsened from the baseline value or if the investigator deemed it absolutely necessary. After concomitant medication was given, no further study medications were administered.

Patients in the placebo group required more injections than patients in other treatment groups, as shown in Study CN138012 (Table 3.1E-1), Study CN138050 (Table 3.1E-2), and Study CN138013 (Table 3.1E-3).

In Study CN138012, a greater percentage of patients required concomitant medication in the placebo (19%) and 6.5-mg haloperidol (12%) groups than in the 10-mg aripiprazole group (8%). In Study CN138050, the percentage of patients requiring concomitant medication was similar for the placebo group (21%) and 1-mg (20%) and 15-mg (21%) aripiprazole groups, and less for the 7.5-mg haloperidol group (11%) and the 5-mg (8%) and 10-mg (13%) aripiprazole groups (Table 3.1E-4).

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**Table 3.1E-1: Number and Percentage of Patients Who Received Study Medication by Number of Injections:  
IM Placebo-Controlled Study CN138012, Efficacy Sample**

Injections	Placebo N=88	Haloperidol 6.5mg N=184	Aripiprazole 10mg N=173
Only One Injection	38 (43)	122 (66)	102 (59)
Only Two Injections	19 (22)	44 (24)	48 (28)
Three Injections (a)	31 (35)	18 (10)	23 (13)

(a) Third Injection for placebo was 10-mg aripiprazole

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**Table 3.1E-2: Number and Percentage of Patients Who Received Study Medication by Number of Injections:  
IM Placebo-Controlled Study CN138050, Efficacy Sample**

Injections	Placebo N=61	Haloperidol 7.5mg		Aripiprazole		
		7.5mg N=57	42 (74)	1mg N=56	5mg N=62	10mg N=56
Only One Injection	23 (38)	42 (74)	26 (46)	35 (56)	33 (59)	35 (60)
Only Two Injections	11 (18)	11 (19)	16 (29)	12 (19)	13 (23)	18 (31)
Three Injections (a)	27 (44)	4 (7)	14 (25)	15 (24)	10 (18)	5 (9)

(a) Third Injection for placebo was 15-mg aripiprazole

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**Table 3.1E-3: Number and Percentage of Patients Who Received Study Medication by Number of Injections:  
 IM Placebo-Controlled Study CN138013, Efficacy Sample**

Injections	Placebo N=73	Lorazepam 2mg N=68	Aripiprazole	
			10mg N=75	15mg N=75
Only One Injection	27 (37)	44 (65)	45 (60)	52 (69)
Only Two Injections	15 (21)	18 (26)	24 (32)	16 (21)
Three Injections (a)	31 (42)	6 (9)	6 (8)	7 (9)

(a) Third Injection for placebo was 10-mg aripiprazole

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/s/  
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Earl Hearst  
8/28/2006 10:35:28 PM  
MEDICAL OFFICER

Ni Aye Khin  
8/29/2006 10:55:38 AM  
MEDICAL OFFICER

I agree with Dr. Hearst's recommendation that this NDA  
be considered for approval; see memo to file  
for additional comments.

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