

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-436/S-018**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology and Biopharmaceutics Review

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NDA: 21-436 S018, 21-713 S013, 21-729 S005, 21-866 S005  
Generic Name: Aripiprazole  
Trade Name: Abilify™  
Dosage Forms: Tablets, Oral Solution, ODT, IM  
Indication: Adjunctive treatment of Major Depressive Disorder  
Sponsor: Otsuka/Bristol Myer Squibb

Submission Type: Efficacy Supplement  
Submission Date: 5/16/07

OCP Division: DCP1 (HFD-860)  
OND Division: DPP (HFD-130)

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## 1. Executive Summary

### 1.1. Recommendations

Based on the review of the drug-drug interaction studies included in this efficacy supplement, the following are recommended to be incorporated in the approved label (Refer to draft label attached).

#### Escitalopram

Coadministration of 10 mg daily oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of 10 mg once daily escitalopram, a substrate of CYP2C19 and CYP3A4. No dosage adjustment of escitalopram is required when aripiprazole is added to escitalopram.

#### Venlafaxine

Coadministration of 10 (b) (4) oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg once daily venlafaxine XR, a CYP2D6 substrate. No dosage adjustment of venlafaxine is required when aripiprazole is added to venlafaxine.

#### Fluoxetine, Paroxetine and Sertraline

(b) (4)  
steady state plasma concentration of fluoxetine and norfluoxetine increased by about 18% and 36%, respectively and concentrations of paroxetine decreased by about 27%. The steady state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these ADTs were co-administered with aripiprazole. (b) (4)

### 1.2. Phase IV Commitments

There are no Phase 4 commitments from OCP

### 1.3. Comments to Medical Division

There is a suggestion that there is possible interaction when aripiprazole is co-administered with fluoxetine and paroxetine as adjunctive therapy in MDD patients. The concentrations of fluoxetine and norfluoxetine increased about 18% and 36%, respectively. Paroxetine concentration decreased by 27%, respectively. These changes were significant based on our usual criteria of 90% CI. These results were unexpected based on studies submitted in the original application. It must be noted that similar changes in ADT concentrations were observed in patients randomized to placebo treatment but the magnitude of change was smaller in magnitude (No effect on fluoxetine, about 14% increase in norfluoxetine and 10% decrease in paroxetine. These changes were not significant). Whether these changes in the plasma concentrations of these

ADTs contributed significantly to the safety and efficacy of Aripiprazole when used in adjunctive therapy was not clear from a pharmacokinetic perspective

OCP Labeling recommendations are incorporated into the proposed label in the Appendix.

#### **1.4. Comments to Sponsor**

It is recommended that the sponsor performs a traditional population pharmacokinetic analysis to confirm the pharmacokinetic results. This is strongly recommended because even though the statistical method used to compare the concentrations of ADT in Phases B and C seems reasonable, it is selective and may not provide an accurate and true reflection of the changes in plasma concentrations of the ADTs and their active metabolites.

The data collected is sufficient to perform the traditional population pharmacokinetic analysis. The rationale you provided for not conducting the traditional population pharmacokinetic analysis is not valid.

Please forward the above two comments in this section (1.4.) to the sponsor

#### **1.5. Summary of Clinical Pharmacology Findings**

##### **1.5.1. Background**

The clinical pharmacology program in support of the use of adjunctive aripiprazole in the treatment of Major Depressive Disorder (MDD) focused on the assessments of potential pharmacokinetic drug-drug interactions between aripiprazole and the Anti-Depressant Therapy (ADTs) employed in the double-blind placebo controlled studies, namely escitalopram, fluoxetine, paroxetine CR, sertraline, and venlafaxine XR. Two clinical pharmacology studies in healthy subjects were conducted to assess for any effect of aripiprazole added to steady-state venlafaxine XR (CN138462) and escitalopram (CN138463). In addition, sparse plasma samples for the measurement of citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine plasma concentrations were collected in the Phase 3 efficacy studies (CN138139 and CN138163).

In the OCP review of the original application (Refer to OCP review of NDA 21-436) and in the current approved label, it is stated that.

1) Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g. carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g. ketoconazole) or CYP2D6 (e.g. quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

2) Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates.

Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*.

### **1.5.2. Drug interaction studies summary**

#### *1.5.2.1. Co-administration of Venlafaxine with Aripiprazole (Study CN138462)*

The primary objective of the study was to assess the effects of daily 10 to 20 mg oral doses of aripiprazole on the steady-state pharmacokinetics of venlafaxine in healthy subjects.

Aripiprazole co-administered with venlafaxine did not significantly affect the overall systemic exposure to venlafaxine or O-desmethylvenlafaxine. There was about 15% increase in C<sub>max</sub> and 18% in AUC<sub>τ</sub> of venlafaxine in the presence of aripiprazole. The median T<sub>max</sub> for venlafaxine and O-desmethylvenlafaxine were similar with or without aripiprazole co-administration. There were no significant increases in the active metabolite, O-desmethylvenlafaxine, C<sub>max</sub> and AUC<sub>τ</sub> when aripiprazole were co-administered with venlafaxine.

A pharmacokinetic drug-drug interaction is not expected to occur for venlafaxine and O-desmethylvenlafaxine when aripiprazole is co-administered with venlafaxine.

Results of Statistical Analyses for Venlafaxine Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Treatment	Geometric Mean	Point Estimate	90% Confidence Limits
C <sub>max</sub> (ng/mL)	venlafaxine	48.82	1.148	(1.083, 1.217)
	venlafaxine + aripiprazole	56.06		
AUC(TAU) (ng•h/mL)	venlafaxine	657.05	1.183	(1.130, 1.238)
	venlafaxine + aripiprazole	777.27		

Results of Statistical Analyses for O-desmethylvenlafaxine Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Treatment	Geometric Mean	Point Estimate	90% Confidence Limits
C <sub>max</sub> (ng/mL)	venlafaxine	135.90	1.017	(0.964, 1.073)
	venlafaxine + aripiprazole	138.20		
AUC(TAU) (ng•h/mL)	venlafaxine	2520.11	1.024	(0.973, 1.077)
	venlafaxine + aripiprazole	2580.18		

1.5.2.2. Co-administration of Escitalopram with Aripiprazole (Study 138463)

The primary objective of this study was to assess the effects of daily 10 mg oral doses of aripiprazole on the steady-state pharmacokinetics of escitalopram in healthy subjects.

There was a 4% increase in escitalopram C<sub>max</sub> and 7% in AUC(τ) in the presence of aripiprazole. These increases were not significant. A pharmacokinetic drug-drug interaction between escitalopram and aripiprazole is unlikely.

Results of Statistical Analyses for Escitalopram Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Treatment	Geometric Mean	Point Estimate	90% Confidence Limits
C <sub>max</sub> (ng/mL)	escitalopram	19.2	1.04	(0.99,1.09)
	escitalopram + aripiprazole	20.0		
AUC(TAU) (ng•h/mL)	escitalopram	308	1.07	(1.04,1.11)
	escitalopram + aripiprazole	331		

1.5.2.3. Co-administration of Aripiprazole and Anti-Depressive Therapy (ADT)

In the Phase 3 efficacy studies (CN138139 and CN138163), plasma concentration data from population pharmacokinetic samples from patients who had an incomplete/partial response at the end of 8 weeks of ADT alone (Phase B) who were randomized to receive either aripiprazole or placebo for 6 weeks (Phase C) were analyzed to examine the effect of adding aripiprazole to the ADT on the concentrations of ADT the patient were stabilized on.

The plasma concentrations in Phase C compared to Phase B were about 18% and 36% higher, respectively, for fluoxetine and norfluoxetine when aripiprazole is added to the ADT. The plasma concentrations of paroxetine were 27% lower when aripiprazole is added to the ADT. These differences were significant.

The results of analyses on pooled antidepressant plasma concentrations in Phase C Compared to Phase B for the two studies are provided in the following table.

Results of Analyses on Pooled Antidepressant Plasma Concentrations in Phase C Compared to Phase B (CN138139, CN138163)

Antidepressant Therapy Analyte	Treatment in Phase C	Number of Subjects with Evaluable Data	Phase C to Phase B Geometric Mean Plasma Concentration Ratio	
			Point Estimate	90% Confidence Interval
Citalopram	Aripiprazole	86	0.970	(0.911, 1.033)
	Placebo	77	0.917	(0.863, 0.975)
Fluoxetine	Aripiprazole	28	1.177	(1.049, 1.321)
	Placebo	27	1.008	(0.895, 1.136)
Norfluoxetine	Aripiprazole	28	1.361	(1.205, 1.538)
	Placebo	27	1.136	(1.060, 1.217)
Paroxetine	Aripiprazole	20	0.730	(0.598, 0.892)
	Placebo	18	0.909	(0.838, 0.987)
Sertraline	Aripiprazole	45	0.958	(0.887, 1.035)
	Placebo	45	0.987	(0.890, 1.095)
Desmethylsertraline	Aripiprazole	45	1.012	(0.951, 1.076)
	Placebo	45	1.025	(0.966, 1.088)
Venlafaxine	Aripiprazole	72	0.966	(0.887, 1.051)
	Placebo	80	0.884	(0.805, 0.972)
O-Desmethylvenlafaxine	Aripiprazole	72	0.963	(0.909, 1.021)
	Placebo	80	0.997	(0.938, 1.059)

**2. Detailed Labeling Recommendations**

Detailed OCP Labeling Recommendations are included in the proposed label attached under

# 55 Page(s) Withheld

           Trade Secret / Confidential  
(b4)

  X   Draft Labeling (b4)

           Draft Labeling (b5)

           Deliberative Process (b5)

## 3.2. Individual Study Reports

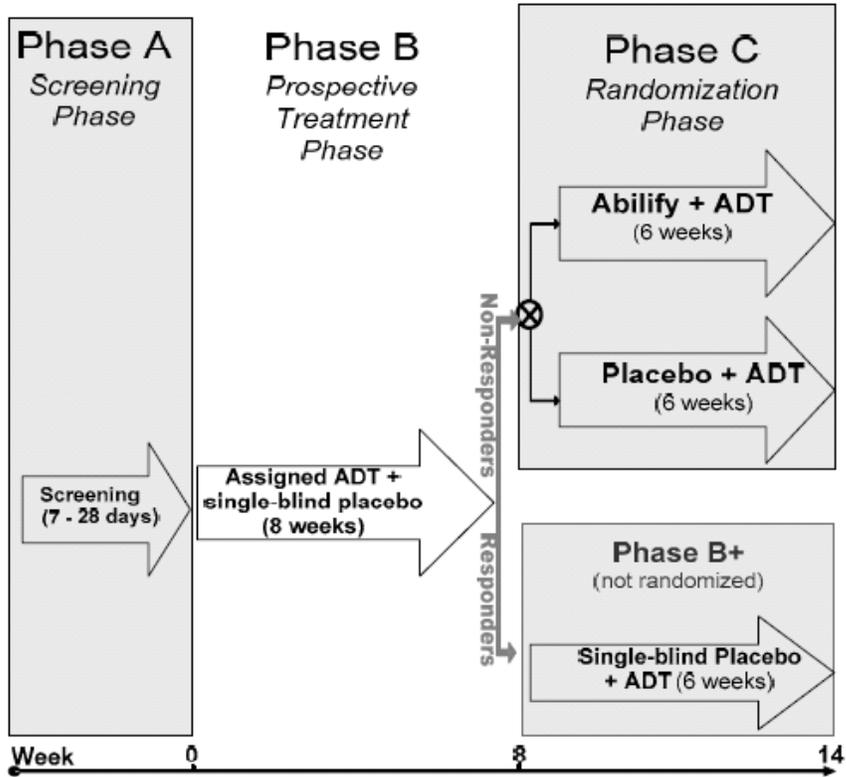
**3.2.1. Title (Study CN138139):** Assessment of the potential for drug-drug interactions between aripiprazole and five antidepressants in a multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of aripiprazole as adjunctive therapy in the treatment of patients with major depressive disorder

**Objectives:** To assess the potential for drug-drug interactions between the antidepressant therapies (ADTs) and aripiprazole by comparing plasma concentrations of the ADTs administered alone (Phase B) with plasma concentrations of the ADTs co-administered with aripiprazole (Phase C) in Study CN138139.

**Study Design:** This was a multicenter, randomized, double-blind, placebo-controlled study of efficacy and safety in patients with major depressive disorder. The study was divided into 3 main phases: Screening Phase (Phase A); Prospective Treatment Phase (Phase B); a Randomization Phase (Phase C), for patients who had an incomplete/partial response at the end of Week 8; and Phase B+, for patients who had a response at the end of Week 8 and were therefore not randomized. A total of 1044 patients were enrolled into Phase A; 781 entered Phase B, 362 were randomized to Phase C (178 to placebo and 184 to aripiprazole). 257 patients continued in Phase B+ (non randomized).

Patients who met entrance criteria at the end of screening (Phase A) were enrolled into the 8-week Prospective Treatment Phase (Phase B) and were dispensed single-blind placebo plus an assigned open label marketed ADT (placebo-plus-ADT). The specific ADT (escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine) for each patient was chosen by the Investigator by considering each patient's antidepressant treatment history. Patients who met criteria for an incomplete response at the end Phase B (Week 8 visit) were randomized into the 6 week double-blind Randomization Phase (Phase C) in a 1:1 ratio to receive either placebo-plus-ADT (ie, double-blind placebo plus the same open-label ADT taken during Phase B) or aripiprazole-plus-ADT (ie, double blind aripiprazole plus the same open-label ADT taken during Phase B). Patients who met criteria for a response at the end of Phase B (Week 8 visit) continued treatment with single-blind placebo-plus-ADT for 6 additional weeks (defined as Phase B+). The test product, dose and mode of administration, duration of treatment, batch numbers are: Aripiprazole, 2 mg and 5 mg tablets, flexibly dosed (2 mg, 5 mg, 10 mg, 15 mg, and 20 mg once daily) for 6 weeks in Phase C, administered orally; batch numbers: 2 mg tablets: 4C86465, 4C83826; 5 mg tablets: 4C90548, 4C83828, 5A03459, 5A09327. The reference therapy, dose and mode of administration, duration of treatment, batch numbers: Placebo, matching tablets administered orally (between 1-4 tablets once daily) for 8 weeks in Phase B, 6 weeks in Phase C and 6 weeks in Phase B+, administered orally; batch numbers: 4C86466, 4C83829, 4C83830, 4G83537, 4M63881. During Phase B, single-blind placebo-plus-ADT was taken orally once daily at approximately the same time each day without regard to meals except for venlafaxine XR, which was to be taken with food. During Phase C, double-blind placebo- or aripiprazole-plus-ADT was taken orally, once daily, at approximately the same time each day without regard to meals except for venlafaxine XR, which was taken with food. No dose increases in ADT are allowed after week 3 visit and no dose decreases are allowed after week 4 visit in Phase B. The patients remained on the same dose of ADT in Phase C. Pharmacokinetic samples were obtained at office visits at study Weeks 4, 6, and 8 (during Phase B) for all patients and study Weeks 12, 13 and 14 (during Phase C) for randomized patients only. The following is a flow chart of the study

Schematic for Study CN138139



**Analytical Method:** Plasma samples were analyzed by validated liquid chromatography-tandem mass spectroscopy (LC-MS/MS) or high performance liquid chromatography (HPLC) with fluorescence detection methods for concentrations of venlafaxine and O-desmethylvenlafaxine or as appropriate for the ADT. The assay for citalopram was not enantiospecific and concentrations of escitalopram were not directly measured. However, escitalopram does not convert to its antipode (R-citalopram) in humans and the nonenantiospecific method was considered appropriate to examine for changes in escitalopram pharmacokinetics in this study.

The between-run variability and within-run variability for the analytical QCs of citalopram were  $\leq 6.02\%$  CV and  $10.01\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 4.25\%$ . The between-run variability and within-run variability for the analytical QCs of fluoxetine were  $\leq 7.75\%$  CV and  $16.30\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 3.28\%$ . The between-run variability and within-run variability for the analytical QCs of norfluoxetine were  $\leq 8.65\%$  CV and  $16.58\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 4.18\%$ . The between-run variability and within-run variability for the analytical QCs of paroxetine were  $\leq 14.39\%$  CV and  $30.22\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were no more than  $\pm 6.08\%$ . The between-run variability and within-run variability for the analytical QCs of sertraline were  $\leq 10.2\%$  CV and  $20.1\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 3.78\%$ . The between-run variability and within-run variability for the analytical QCs of desmethylsertraline were  $\leq 16.5\%$  CV and  $36.1\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 4.89\%$ . The linear concentration range was 0.100 to 50.0 ng/mL. The between-run variability and within-run variability for the analytical QCs of venlafaxine were  $\leq 6.38\%$  CV and  $12.4\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 3.31\%$ . The between-run variability and within-run variability for the analytical QCs of O-desmethylvenlafaxine were  $\leq 6.19\%$  CV and  $15.66\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations within  $\pm 4.07\%$ . The linear concentration range for venlafaxine and its metabolite was 2.00 to 200 ng/mL.

**Data Analysis:** Citalopram, fluoxetine and norfluoxetine, paroxetine, sertraline and desmethylsertraline and venlafaxine and O-desmethylvenlafaxine plasma concentration-time data from plasma samples collected in Phases B and C. In the study, the timing of the collection of the single blood sample for the pharmacokinetics assessment at each visit was not controlled with respect to the time of dosing of the ADT. Thus, it was possible that blood samples were collected at different times post-dose at each visit. In the study report, it is stated that since plasma concentrations of the ADT (and metabolites) will vary with time post-dose, a direct comparison of all concentrations from each visit would not be a valid comparison in many cases due to the variation in post-dose collection times at each visit. According to the sponsor, a traditional population pharmacokinetic modeling approach to assess for the potential for a drug-drug interaction between aripiprazole and the ADTs was not possible, since only a single sample was collected at each visit.

Accordingly, a pre-specified selection algorithm was employed to compare ADT concentrations from samples collected from randomized subjects (non-responders) at similar times in Phases B and C. Because, the steady-state apparent half-lives of the ADTs and their active metabolites range from 5 h (venlafaxine) to 16 days (norfluoxetine), thus the intra-day steady-state peak-to-trough ratios will vary substantially between the ADTs employed. In addition, since the timing of the blood sample for pharmacokinetics assessment was not collected at a specific nominal time in this study the sample may have been collected in the absorptive phase or the elimination phase. Therefore, intervals were evaluated in the 0-24 hour post-dose period from Phase B and C for compatibility of sampling times. A time window was algorithmically chosen for each individual subject to maximize the number of samples collected within a 4 h ( $\pm 2$  hr) time period with at least one sample in Phases B and C. A 4 h ( $\pm 2$  hr) interval was chosen a priori as the most pragmatic compromise between the known changing plasma concentrations of all 5 ADTs and their active metabolites and maximizing the number of samples included in the analysis. The optimal window for each patient was selected by choosing a time for which the number of time points for Phase B and for Phase C were maximized; i.e., the algorithm (attached) was used to score a particular 4-hour time interval,  $t_i$ .

Point estimates and 90 % confidence intervals were calculated to assess the effect of aripiprazole exposure on the average concentration ( $C_p$ ) of each ADT or its metabolite in Phase C compared to Phase B. A priori, the point estimates for the Phase C to Phase B geometric mean plasma concentration ratio was to be summarized with a 95% CI. However, a 90% CI is traditionally used to describe the variability in point estimates for pharmacokinetic data and the 90% CI was used to describe the current dataset. For each patient,  $C_p$  was defined as the within-subject geometric mean concentration for a selected common optimal window (across Phase B and Phase C) for that subject. Since the comparison window times were only comparable within subject, within-subject mean ratios were estimated for this optimum window. That is, for each subject log-concentrations were calculated. The selected concentrations were then analyzed using a linear mixed effects model with a random subject effect and a fixed phase effect. Point estimates and confidence intervals based on this analysis were calculated. The results were then summarized by treatment and the point estimates and confidence intervals were back transformed. The resulting estimated relative concentration ratios were summarized by treatment and aripiprazole status (placebo or aripiprazole).

**Results:** The results of the statistical analysis on antidepressant plasma concentrations in Phase C (Aripiprazole or Placebo) compared to Phase B are provided in the following table.

Results of Statistical Analyses on Andidepressant Plasma Concentrations in Phase C Compared to Phase B

Antidepressant Therapy Analyte	Treatment in Phase C	Number of Patients with Evaluable Data	Phase C to Phase B Geometric Mean Plasma Concentration Ratio	
			Point Estimate	90% Confidence Interval
Citalopram	Aripiprazole	44	1.009	(0.942, 1.081)
	Placebo	45	0.926	(0.853, 1.006)
Fluoxetine	Aripiprazole	24	1.171	(1.045, 1.312)
	Placebo	22	1.047	(0.912, 1.202)
Norfluoxetine	Aripiprazole	24	1.390	(1.215, 1.590)
	Placebo	22	1.148	(1.062, 1.240)
Paroxetine	Aripiprazole	13	0.899	(0.790, 1.023)
	Placebo	11	0.911	(0.812, 1.021)
Sertraline	Aripiprazole	30	0.940	(0.866, 1.019)
	Placebo	29	0.966	(0.883, 1.057)
Desmethylsertraline	Aripiprazole	30	0.985	(0.915, 1.062)
	Placebo	29	1.054	(0.992, 1.119)
Venlafaxine	Aripiprazole	37	0.965	(0.864, 1.078)
	Placebo	47	0.865	(0.767, 0.976)
O-Desmethylvenlafaxine	Aripiprazole	37	0.940	0.868, 1.019)
	Placebo	47	1.007	(0.942, 1.076)

There was no evidence of a significant drug-drug interaction between aripiprazole and any of the ADTs studied. Except for norfluoxetine, fluoxetine and paroxetine; the 90% CI was outside the 80 to 125% limit. No significant effect was seen on placebo treated patients.

**Summary of Pharmacokinetics:** According to the sponsor, although the study was not designed or powered *a priori* to statistically test for pharmacokinetic differences in ADT concentrations between Phase C and Phase B, the 90% confidence intervals for the parent ADT ratios for citalopram, sertraline and venlafaxine in the aripiprazole-treated patients met the usual criteria to conclude equivalence (contained within the interval of 80% to 125%). Although the 90% confidence intervals for the paroxetine and fluoxetine and norfluoxetine ratios for the aripiprazole treatment groups extended outside of these bounds, the number of patients in the paroxetine CR ADT group was the smallest (tending to decrease the precision); and the point estimates and 90% confidence intervals were very similar to those of the placebo-treated group. For fluoxetine, the geometric mean plasma concentrations were approximately 17% higher in Phase C compared to Phase B and the corresponding norfluoxetine concentrations were approximately 39% higher. The Phase C to Phase B geometric mean ratios and their 90% confidence intervals for the plasma

concentrations of the active metabolites desmethylsertraline and O-desmethylvenlafaxine were generally similar between aripiprazole and the placebo treated patients.

**Reviewer comment:** *There is a suggestion based on average concentrations (not AUC) evaluated within the sampling window that there are no significant changes in the anti-depressant therapy (ADT) concentration studied when aripiprazole is added to them. Except for the concentrations of paroxetine, fluoxetine and norfluoxetine. The 90% confidence intervals around the ratio of the means for paroxetine, fluoxetine and norfluoxetine were outside the limit of 80 to 125%. It must be noted that similar changes in ADT concentrations were observed for patients administered placebo and ADT, but the changes were of smaller magnitude. The study did not evaluate the effect of the anti-depressant drugs on aripiprazole.*

*The statistical method used by the sponsor to compare concentrations is reasonable and acceptable. However, it is recommended the sponsor performs a traditional population pharmacokinetic analysis to confirm the computed results. The data collected should be sufficient to perform the traditional population pharmacokinetic analysis.*

*The sponsor stated that traditional population pharmacokinetic analysis was not performed because only one sample per patient per visit was collected, and the timing of the collection of the single blood sample for the pharmacokinetic assessment at each visit was not controlled with respect to the time of dosing of the ADT. After consultation with the pharmacometrics it is believed that the sponsor's rationale is invalid. Therefore, it is recommended the sponsor conduct a traditional pharmacokinetic analysis*

Attachments

**Table 4.1.4A: Daily Dosing Schedule for ADTs and Placebo in Phase B**

Study Week <sup>a</sup>	1	2	3	4	5	6	7	8
Escitalopram (mg)	10	10 or 20	10 or 20	10 or 20	10 or 20	10 or 20	10 or 20	10 or 20
Fluoxetine (mg)	20	20	20 or 40	20 or 40	20 or 40	20 or 40	20 or 40	20 or 40
Paroxetine CR (mg)	25	25 or 37.5	25, 37.5 or 50	37.5 or 50				
Serrtraline (mg)	50	50 or 100	100 or 150	100 or 150	100 or 150	100 or 150	100 or 150	100 or 150
VenlafaxineXR (mg)	37.5 - 75 <sup>b</sup>	75 or 150	150 or 225	150 or 225	150 or 225	150 or 225	150 or 225	150 or 225
Placebo (tablets)	1	1	1	1	1	1	1	1

<sup>a</sup> The prescribed dose for a study week was made at the previous Study Visit (i.e. the prescribed dose for Week 1 is made at the Baseline Visit, the prescribed dose for Week 2 is made at the Week 1 Visit, etc.).

<sup>b</sup> For the first week, patients were prescribed 37.5 mg of venlafaxine XR for 3 days followed by 75 mg/day.

**Table 4.1.4B: Dosing Schedule for Aripiprazole and Placebo in Phase C**

Study Week <sup>a,b</sup>	9	10	11	12	13	14
Aripiprazole Dose (mg/day)	5	2, <sup>c</sup> 5 or 10	2, 5, 10 or 15	2, 5, 10, 15 or 20 <sup>d</sup>	2, 5, 10, 15 or 20 <sup>d</sup>	2, 5, 10, 15 or 20 <sup>d</sup>
Placebo (tablets / day)	1	1 - 2	1 - 3	1 - 4 <sup>e</sup>	1 - 4 <sup>e</sup>	1 - 4 <sup>e</sup>

Source: Table 3.4.4B of the CN138139 Clinical Study Report<sup>1</sup>

<sup>a</sup> The prescribed dose for a study week is made at the previous Study Visit (ie, the prescribed dose for study week 9 is made at the Week 8 Visit, the prescribed dose for study week 10 is made at the Week 9 Visit, etc.).

<sup>b</sup> ADT doses remained unchanged in Phase C from Phase B (ie, patients remained on the same dose as at the end of Phase B).

<sup>c</sup> Dose decreases from 5 mg/day to 2 mg/day entailed continued dosing with one tablet per day; however, the tablet strength was decreased (ie, 2 mg instead of 5 mg of aripiprazole).

<sup>d</sup> This dose was not an option for patients taking paroxetine CR and fluoxetine.

<sup>e</sup> For patients taking paroxetine CR or fluoxetine, the maximum number of placebo tablets was 3 (corresponding to the decreased range of allowable aripiprazole doses).

Table 3.11:  
Analysis of C<sub>p</sub> = Average ADT Concentration

Obs	Analyte	Aripiprasole Treatment	Geom. Mean Ratio C <sub>p</sub>	CV C <sub>p</sub>	Ratio		number of subjects with ratios	degrees of freedom for conf. interval (NWR)
					Lower Bound 90% CI	Upper Bound 90% CI		
1	Citalopram	Ari	1.009	0.041	0.942	1.081	44	154
2	Citalopram	Placebo	0.926	0.050	0.853	1.006	45	167
3	Desmethylsertraline	Ari	0.988	0.045	0.915	1.062	30	107
4	Desmethylsertraline	Placebo	1.054	0.036	0.992	1.119	29	109
5	Fluoxetine	Ari	1.171	0.069	1.045	1.312	24	88.3
6	Fluoxetine	Placebo	1.047	0.083	0.912	1.202	22	88.3
7	Norfluoxetine	Ari	1.390	0.081	1.215	1.590	24	88.3
8	Norfluoxetine	Placebo	1.148	0.047	1.062	1.240	22	88.1
9	O-Desmethylvenlafaxi	Ari	0.940	0.048	0.868	1.019	37	139
10	O-Desmethylvenlafaxi	Placebo	1.007	0.040	0.942	1.076	47	170
11	Paroxetine	Ari	0.899	0.077	0.790	1.023	13	43.2
12	Paroxetine	Placebo	0.911	0.068	0.812	1.021	11	43.2
13	Sertraline	Ari	0.940	0.049	0.866	1.019	30	106
14	Sertraline	Placebo	0.966	0.054	0.883	1.057	29	109
15	Venlafaxine	Ari	0.968	0.067	0.864	1.078	37	138
16	Venlafaxine	Placebo	0.865	0.073	0.767	0.976	47	172

Algorithm For Scoring 4-hour Interval Centered at Time  $t_i$

Number of Points from Phase B within $\pm 2$ hours of timepoint $t_i$	Number of Points from Phase C within $\pm 2$ hours of timepoint $t_i$	Interval Score (choose $t_i$ which has maximal score)
1	1	1
1	2	2
2	1	2
1	3	3
3	1	3
2	2	4
3	2	5
2	3	5
3	3	6

Note that no interval could be chosen that did not have at least one time point from both Phase B and Phase C.

**Table 9.1** Number of Patients and Concentration-Time Points for Patients Randomized to Phase C Available for Statistical Analysis in Study CN138139

Treatment Randomized to in Phase C	Analyte	Number of Patients	Number of Concentration-Time Points by Study Week						Total Number of Concentration-Time Points
			Week 4	Week 6	Week 8	Week 12	Week 13	Week 14 or Discharge	
Aripiprazole	Citalopram	54	54	50	52	44	45	54	299
	Fluoxetine/Norfluoxetine	26	26	26	25	23	21	24	145
	Paroxetine	18	15	18	18	15	15	18	99
	Serrtraline/Desmethylserrtraline	36	33	34	35	28	29	32	191
	Venlafaxine/O-Desmethylvenlafaxine	47	47	47	45	36	36	42	249
	<b>Total</b>	<b>181</b>	<b>175</b>	<b>175</b>	<b>175</b>	<b>146</b>	<b>146</b>	<b>170</b>	<b>987</b>
Placebo	Citalopram	50	49	47	50	43	42	48	279
	Fluoxetine/Norfluoxetine	24	24	22	24	21	20	20	131
	Paroxetine	14	14	14	14	12	12	12	78
	Serrtraline/Desmethylserrtraline	35	35	31	35	29	29	32	191
	Venlafaxine/O-Desmethylvenlafaxine	51	48	50	51	46	43	50	288
	<b>Total</b>	<b>174</b>	<b>170</b>	<b>164</b>	<b>174</b>	<b>151</b>	<b>146</b>	<b>162</b>	<b>967</b>

**3.2.2. Title (CN138163):** Assessment of the potential for drug-drug interactions between aripiprazole and five antidepressants in a multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of aripiprazole as adjunctive therapy in the treatment of patients with major depressive disorder

**Objectives:** To assess the potential for drug-drug interactions between the ADTs and aripiprazole by comparing plasma concentrations of the ADTs administered alone (Phase B) with plasma concentrations of the ADTs co-administered with aripiprazole (Phase C) in Study CN138163.

**Study Design:** This was a multicenter, randomized, double-blind, placebo-controlled study of efficacy and safety in patients with major depressive disorder. Male and female outpatients, 18 - 65 years of age, with a diagnosis of major depressive disorder (MDD). Patients who met entrance criteria at the end of screening (Phase A) were enrolled into the 8-week Prospective Treatment Phase (Phase B) and were dispensed single-blind placebo plus an assigned open label marketed ADT (placebo-plus-ADT). The specific ADT (escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine) each patient was chosen by the Investigator by considering each patient's antidepressant treatment history. Patients who met criteria for an incomplete response at the end Phase B (Week 8 visit) were randomized into the 6 week double-blind Randomization Phase (Phase C) in a 1:1 ratio to receive either placebo-plus-ADT (ie, double-blind placebo plus the same open-label ADT taken during Phase B) or aripiprazole-plus-ADT (ie, double blind aripiprazole plus the same open-label ADT taken during Phase B). Patients who met criteria for a response at the end of Phase B (Week 8 visit) continued treatment with single-blind placebo-plus-

ADT for 6 additional weeks (defined as Phase B+). Blood samples were obtained for pharmacokinetics from all patients. Samples were obtained at study Weeks 4, 6, and 8 where the ADT was being administered alone (Phase B) and from patients randomized to aripiprazole or placebo at study Weeks 12, 13 and 14 (Phase C). The following information was recorded at each visit: date and time of sample collection, date and time of the patient's most recent ADT dose, strength of ADT dose in mg, and the time of the meal closest to that dose. In the Prospective Phase (Phase B), patients were assigned placebo plus an open-label marketed ADT that included either escitalopram, fluoxetine, paroxetine CR, sertraline or venlafaxine XR. In the Randomization Phase (Phase C), patients were randomized to receive 6 weeks of either (1) continued placebo-plus-ADT (double-blind adjunctive placebo plus the final dosage of the assigned open-label marketed ADT reached during Phase B) or, (2) aripiprazole-plus-ADT (double-blind adjunctive aripiprazole plus the final dosage of the assigned open-label marketed ADT reached during Phase B) according to a computer generated randomization schedule prepared by BMS.

Test product, dose and mode of administration, duration of treatment, batch numbers: Aripiprazole, 2 mg and 5 mg tablets, flexibly dosed (2 mg, 5 mg, 10 mg, 15 mg, and 20 mg once daily) for 6 weeks in Phase C, administered orally; batch numbers: 2 mg tablets: 4C83826; 5 mg tablets: 4C83828, 5A03459, 5A09327. Reference therapy, dose and mode of administration, duration of treatment, batch numbers: Placebo, matching tablets administered orally (between 1-4 tablets once daily) for 8 weeks in Phase B, 6 weeks in Phase C and 6 weeks in Phase B+, administered orally; batch numbers: 4C83829, 4G83537, 4M63881.

Analytical method: Plasma samples were analyzed by validated liquid chromatography-tandem mass spectroscopy (LC-MS/MS) or high performance liquid chromatography (HPLC) with fluorescence detection methods for concentrations of citalopram, fluoxetine and norfluoxetine, paroxetine, sertraline and desmethylsertraline or venlafaxine and O-desmethylvenlafaxine as appropriate for the ADT the individual was administered. The linear concentration range for citalopram was 1.00 to 500 ng/mL. Values for the between-run and within-run precision for analytical quality control samples were  $\leq 6.25\%$  and  $8.14\%$  coefficient of variation (CV), respectively, with deviations from the nominal concentrations within  $\pm 1.38\%$ . The between-run variability and within-run variability for the analytical QCs of fluoxetine were  $\leq 6.33\%$  CV and  $12.12\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 3.31\%$ . The between-run variability and within-run variability for the analytical QCs of norfluoxetine were  $\leq 7.29\%$  CV and  $16.90\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 3.14\%$ . The linear equation concentration range for norfluoxetine was 0.250 to 100 ng/mL. The between-run variability and within-run variability for the analytical QCs of paroxetine were  $\leq 12.33\%$  CV and  $23.86\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were no more than  $\pm 3.69\%$ . The linear concentration range for venlafaxine was 2.00 to 200 ng/mL. Values for the between-run and within-run precision for analytical quality control samples were  $\leq 5.41\%$  and  $12.39\%$  coefficient of variation (CV), respectively, with deviations from the nominal concentrations within  $\pm 2.13\%$ . Values for the between-run and within-run precision for analytical quality control samples of O-desmethylvenlafaxine were  $\leq 7.15\%$  and  $12.36\%$  coefficient of variation (CV), respectively, with deviations from the nominal concentrations within  $\pm 2.40\%$ . The between-run variability and within-run variability for the analytical QCs of sertraline were  $\leq 10.69\%$  CV and  $20.08\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 5.83\%$ . The between-run variability and within-run variability for the analytical QCs of desmethylsertraline were  $\leq 20.35\%$  CV and  $36.10\%$  CV, respectively. The

deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 5.33\%$ .

**Data Analysis:** In the study, the timing of the collection of the single blood sample for the pharmacokinetics assessment at each visit was not controlled with respect to the time of dosing of the ADT. Thus, it was possible that blood samples were collected at different times post-dose at each visit. Since plasma concentrations of the ADT (and metabolites) will vary with time post-dose, a direct comparison of all concentrations from each visit would not be a valid comparison in many cases due to the variation in post-dose collection times at each visit. The sponsor stated that a traditional population pharmacokinetic modeling approach to assess for the potential for a drug-drug interaction between aripiprazole and the ADTs was not possible, since only a single sample was collected at each visit. Accordingly, a pre-specified selection algorithm was employed to compare ADT concentrations from samples collected from randomized subjects (non-responders) at similar times in Phases B and C. A time window was algorithmically chosen for each individual subject to maximize the number of samples collected within a 4 h ( $\pm 2$  hr) time period with at least one sample in Phases B and C. A 4 hour ( $\pm 2$  hr) interval was chosen *a priori* as the most pragmatic compromise between the known changing plasma concentrations of all 5 ADTs and their active metabolites and maximizing the number of samples included in the analysis. The optimal window for each patient was selected by choosing a time for which the number of time points for Phase B and for Phase C was maximized; i.e., the algorithm (attached) was used to score a particular 4-hour time interval,  $t_i$ .

Point estimates and 90 % confidence intervals were calculated to assess the effect of aripiprazole exposure on the average concentration ( $C_p$ ) of each ADT or its metabolite in Phase C compared to Phase B. *A priori*, the point estimates for the Phase C to Phase B geometric mean plasma concentration ratio was to be summarized with a 95% CI. However, a 90% CI is more traditionally used to describe the variability in point estimates for pharmacokinetic data and the 90% CI was used to describe the current dataset. This change in the CI did not affect the statistical analysis to obtain the point estimates. For each patient,  $C_p$  was defined as the within-subject geometric mean concentration for a selected common optimal window (across Phase B and Phase C) for that subject. Since the comparison window times were only comparable within subject, within-subject mean ratios were estimated for this optimum window. That is, for each subject log-concentrations were calculated. The selected concentrations were then analyze using a linear mixed effects model with a random subject effect and a fixed phase effect. Point estimates and confidence intervals based on this analysis were calculated. The results were then summarized by treatment and the point estimates and confidence intervals were back transformed. The resulting estimated relative concentration ratios were summarized by treatment and aripiprazole status (placebo or aripiprazole).

**Results:** The results of the statistical analyses on antidepressant plasma concentrations in Phase C compared to Phase B are summarized in the following table.

Results of Statistical Analyses on Antidepressant Plasma Concentrations in Phase C Compared to Phase B

Antidepressant Therapy Analyte	Treatment in Phase C	Number of Subjects with Evaluable Data	Phase C to Phase B Geometric Mean Plasma Concentration Ratio	
			Point Estimate	90% Confidence Interval
Citalopram	Aripiprazole	42	0.931	(0.836, 1.037)
	Placebo	32	0.904	(0.826, 0.991)
Fluoxetine	Aripiprazole	4	1.301	(0.747, 2.266)
	Placebo	5	0.839	(0.685, 1.028)
Norfluoxetine	Aripiprazole	4	1.158	(0.906, 1.480)
	Placebo	5	1.080	(0.921, 1.266)
Paroxetine	Aripiprazole	6	0.693	(0.478, 1.005)
	Placebo	7	0.909	(0.822, 1.005)
Sertraline	Aripiprazole	15	0.994	(0.834, 1.185)
	Placebo	16	1.026	(0.800, 1.316)
Desmethylsertraline	Aripiprazole	15	1.071	(0.955, 1.202)
	Placebo	16	0.974	(0.855, 1.110)
Venlafaxine	Aripiprazole	35	0.965	(0.846, 1.101)
	Placebo	33	0.917	(0.786, 1.069)
O-Desmethylvenlafaxine	Aripiprazole	35	0.993	(0.913, 1.081)
	Placebo	33	0.981	(0.872, 1.103)

In general however, the point estimates for the geometric mean of the Phase C to Phase B plasma concentration ratios for parent ADTs and, where applicable, their active metabolites were close to and/or overlapped 1.0 and the ratios were similar in the patients randomized to aripiprazole compared to the patients randomized to placebo. Although this study was not designed or powered *a priori* to statistically test for pharmacokinetic differences in ADT concentrations between Phase C and Phase B, the 90% CIs for the parent ADT ratios for citalopram, sertraline and desmethylsertraline, venlafaxine and O-desmethylvenlafaxine in the aripiprazole-treated patients met the usual criteria to conclude bioequivalence (contained within the interval of 0.80, 1.25).

Summary: In this study, pharmacokinetic data were acquired to assess whether potential therapeutic benefits of aripiprazole correlated with increased ADT concentrations. Overall, the mean antidepressant concentrations remained substantially unchanged for both the aripiprazole and the placebo groups across treatment phases. For escitalopram, sertraline, and venlafaxine XR, the safety and efficacy findings from this aripiprazole study can now be

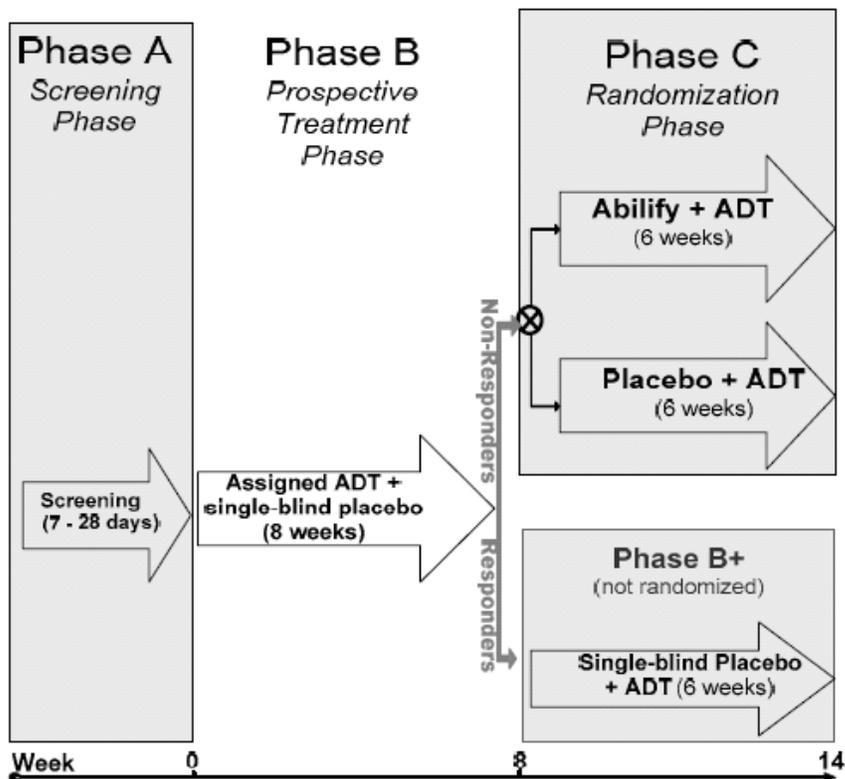
interpreted more definitively in light of the absence of any confounding drug-drug interaction that could have altered ADT exposure.

*Reviewer's comment: The study suggests aripiprazole does not affect the plasma concentrations of citalopram, sertraline, desmethylsertraline, venlafaxine and O-desmethylvenlafaxine. There is a suggestion that fluoxetine, norfluoxetine and paroxetine concentrations were affected, but there were not sufficient patients on these medications with evaluable plasma concentrations to draw definite conclusions. It must be noted that this study evaluated average concentrations within a sampling window. Therefore the result do not represent the effect on total exposure ((AUC) to these anti-depressant drugs. It must be noted that similar changes in fluoxetine, paroxetine and norfluoxetine concentrations were observed in patients who were administered placebo instead of aripiprazole. But the changes in the placebo administered patients were of a smaller magnitude. The study did not evaluate the effect of the anti-depressant drugs on aripiprazole.*

*The statistical method used by the sponsor to compare concentrations is reasonable and acceptable. However, it is recommended the sponsor performs a traditional population pharmacokinetic analysis to confirm the computed results. The changes in paroxetine, fluoxetine and norfluoxetine were not expected. The data collected should be sufficient to perform the traditional population pharmacokinetic analysis.*

*The sponsor stated that traditional population pharmacokinetic analysis was not performed because only one sample per patient per visit was collected, and the timing of the collection of the single blood sample for the pharmacokinetic assessment at each visit was not controlled with respect to the time of dosing of the ADT. After consultation with the pharmacometrics, the sponsor's rationale for not conducting a traditional population pharmacokinetic analysis is invalid. Therefore, it is recommended the sponsor conduct a traditional pharmacokinetic analysis.*

Schematic for Study CN138163



Source: CN138163 Clinical Study Report<sup>2</sup>

Note: Blood samples for ADT concentration analysis were obtained for all patients at study Week Visits 4, 6, and 8 (Phase B) and for non-responders at study Week Visits 12, 13 and 14 (Phase C)

**Table 4.1.4A: Daily Dosing Schedule for ADTs and Placebo in Phases B and C**

Study Week <sup>a</sup>	1	2	3	4	5	6	7	8
Escitalopram (mg)	10	10 or 20	10 or 20	10 or 20	10 or 20	10 or 20	10 or 20	10 or 20
Fluoxetine (mg)	20	20	20 or 40	20 or 40	20 or 40	20 or 40	20 or 40	20 or 40
Paroxetine CR (mg)	25	25 or 37.5	25, 37.5 or 50	37.5 or 50				
Sertraline <sup>a</sup> (mg)	50	50 or 100	100 or 150	100 or 150	100 or 150	100 or 150	100 or 150	100 or 150
Venlafaxine XR <sup>a</sup> (mg)	37.5 - 75 <sup>b</sup>	75 or 150	150 or 225	150 or 225	150 or 225	150 or 225	150 or 225	150 or 225
Placebo (tablets)	1	1	1	1	1	1	1	1

CN138163 Pharmacokinetic Report

Source: Table 3.4.4A of the CN138163 Clinical Study Report<sup>2</sup>

<sup>a</sup> The prescribed dose for a study week was made at the previous Study Visit (i.e. the prescribed dose for Week 1 is made at the Baseline Visit, the prescribed dose for Week 2 is made at the Week 1 Visit, etc.).

<sup>b</sup> For the first week, patients were prescribed 37.5 mg of venlafaxine XR for 3 days followed by 75 mg/day.

**Table 4.1.4B: Dosing Schedule for Aripiprazole and Placebo in Phase C**

Study Week <sup>a,b</sup>	9	10	11	12	13	14
Aripiprazole Dose (mg/day)	5	2, <sup>c</sup> 5 or 10	2, 5, 10 or 15	2, 5, 10, 15 or 20 <sup>d</sup>	2, 5, 10, 15 or 20 <sup>d</sup>	2, 5, 10, 15 or 20 <sup>d</sup>
Placebo (tablets / day)	1	1 - 2	1 - 3	1 - 4 <sup>e</sup>	1 - 4 <sup>e</sup>	1 - 4 <sup>e</sup>

CN138163 Pharmacokinetic Report

Source: Table 3.4.4B of the CN138163 Clinical Study Report<sup>2</sup>

<sup>a</sup> The prescribed dose for a study week is made at the previous Study Visit (ie, the prescribed dose for study week 9 is made at the Week 8 Visit, the prescribed dose for study week 10 is made at the Week 9 Visit, etc.).

<sup>b</sup> ADT doses remained unchanged in Phase C from Phase B (ie, patients remained on the same dose as at the end of Phase B).

<sup>c</sup> Dose decreases from 5 mg/day to 2 mg/day would entail continued dosing with one tablet per day; however, the tablet strength would be decreased (ie, 2 mg instead of 5 mg of aripiprazole).

<sup>d</sup> This dose was not an option for patients taking paroxetine CR and fluoxetine.

<sup>e</sup> For patients taking paroxetine CR or fluoxetine, the maximum number of placebo tablets was 3 (corresponding to the decreased range of allowable aripiprazole doses)

**Table 9a** Number of Patients and Concentration-Time Points for Patients Randomized to Phase C Available for Statistical Analysis in Study CN138163

Treatment Randomized to in Phase C	Analyte	Number of Patients	Number of Concentration-Time Points by Study Week						Total Number of Concentration-Time Points
			Week 4	Week 6	Week 8	Week 12	Week 13	Week 14 or Discharge	
Aripiprazole	Citalopram	47	44	46	47	43	38	44	262
	Fluoxetine/Norfluoxetine	4	4	4	4	2	3	4	21
	Paroxetine	10	9	10	10	6	5	10	50
	Sertraline/Desmethylsertraline	18	16	15	18	12	16	17	94
	Venlafaxine/O-Desmethylvenlafaxine	41	39	38	41	31	31	40	220
	<b>Total</b>	<b>120</b>	<b>112</b>	<b>113</b>	<b>120</b>	<b>94</b>	<b>93</b>	<b>115</b>	<b>647</b>
Placebo	Citalopram	39	35	37	36	34	34	35	211
	Fluoxetine/Norfluoxetine	5	5	5	5	4	5	5	29
	Paroxetine	8	7	8	8	8	8	8	47
	Sertraline/Desmethylsertraline	21	19	21	20	14	14	18	106
	Venlafaxine/O-Desmethylvenlafaxine	40	39	38	39	31	32	37	216
	<b>Total</b>	<b>113</b>	<b>105</b>	<b>109</b>	<b>108</b>	<b>91</b>	<b>93</b>	<b>103</b>	<b>609</b>

CN138163 Pharmacokinetic Report

Table-8.11:  
Analysis of Cp = Average ADT Concentration

Obs	Analyte	Aripiprasole Treatment	Geom.Mean Ratio Cp	CV Cp	Ratio	Ratio	number of subjects with ratios	degrees of freedom
					Lower Bound 90% CI	Upper Bound 90% CI		for conf.interval (90%)
1	Citalopram	Ari	0.931	0.065	0.836	1.037	42	147
2	Citalopram	Placebo	0.904	0.055	0.826	0.991	32	121
3	Desmethylsertraline	Ari	1.071	0.069	0.955	1.202	15	47.4
4	Desmethylsertraline	Placebo	0.974	0.078	0.855	1.110	16	57.2
5	Fluoxetine	Ari	1.301	0.319	0.747	2.266	4	12
6	Fluoxetine	Placebo	0.839	0.117	0.685	1.028	5	18.2
7	Norfluoxetine	Ari	1.158	0.138	0.906	1.480	4	11.4
8	Norfluoxetine	Placebo	1.080	0.092	0.921	1.266	5	18.7
9	O-Desmethylvenlafaxi	Ari	0.993	0.051	0.913	1.081	35	110
10	O-Desmethylvenlafaxi	Placebo	0.981	0.071	0.872	1.103	33	108
11	Paroxetine	Ari	0.693	0.218	0.478	1.005	6	20.2
12	Paroxetine	Placebo	0.909	0.058	0.822	1.005	7	21.1
13	Sertraline	Ari	0.994	0.105	0.834	1.185	15	49.1
14	Sertraline	Placebo	1.026	0.150	0.800	1.316	16	56.8
15	Venlafaxine	Ari	0.965	0.080	0.846	1.101	35	110
16	Venlafaxine	Placebo	0.917	0.093	0.786	1.069	33	108

**Table 6: Algorithm For Scoring 4-hour Interval Centered at Time  $t_i$** 

Number of Points from Phase B within $\pm 2$ hours of timepoint $t_i$	Number of Points from Phase C within $\pm 2$ hours of timepoint $t_i$	Interval Score (choose $t_i$ which has maximal score)
1	1	1
1	2	2
2	1	2
1	3	3
3	1	3
2	2	4
3	2	5
2	3	5
3	3	6

**Table 9a**      **Number of Patients and Concentration-Time Points for Patients Randomized to Phase C Available for Statistical Analysis in Study CN138163**

Treatment Randomized to in Phase C	Analyte	Number of Patients	Number of Concentration-Time Points by Study Week						Total Number of Concentration-Time Points
			Week 4	Week 6	Week 8	Week 12	Week 13	Week 14 or Discharge	
<b>Aripiprazole</b>	Citalopram	47	44	46	47	43	38	44	262
	Fluoxetine/Norfluoxetine	4	4	4	4	2	3	4	21
	Paroxetine	10	9	10	10	6	5	10	50
	Sertraline/Desmethylsertraline	18	16	15	18	12	16	17	94
	Venlafaxine/O-Desmethylvenlafaxine	41	39	38	41	31	31	40	220
	<b>Total</b>	<b>120</b>	<b>112</b>	<b>113</b>	<b>120</b>	<b>94</b>	<b>93</b>	<b>115</b>	<b>647</b>
<b>Placebo</b>	Citalopram	39	35	37	36	34	34	35	211
	Fluoxetine/Norfluoxetine	5	5	5	5	4	5	5	29
	Paroxetine	8	7	8	8	8	8	8	47
	Sertraline/Desmethylsertraline	21	19	21	20	14	14	18	106
	Venlafaxine/O-Desmethylvenlafaxine	40	39	38	39	31	32	37	216
	<b>Total</b>	<b>113</b>	<b>105</b>	<b>109</b>	<b>108</b>	<b>91</b>	<b>93</b>	<b>103</b>	<b>609</b>

### 3.2.3. Title (Protocol No. CN138462): Effects of Aripiprazole on the Steady-State Pharmacokinetics of Venlafaxine in Healthy Subjects

**Objective:** 1) To assess the effects of daily 10 to 20 mg oral doses of aripiprazole on the steady state pharmacokinetics (PK) of venlafaxine in healthy subjects. 2) To assess the safety and tolerability of aripiprazole when co-administered with venlafaxine to healthy subjects

**Study Design:** This was an open-label, non-randomized study in healthy subjects aged 18 to 45 years old. The mean ( $\pm$ SD) age and weight were  $35 \pm 7$  years and  $76.9 \pm 12.8$  kg, respectively. On the morning of Day -5, qualified subjects entered the clinical facility and were confined for the duration of the study (until Day 15). On Day -4, subjects began receiving a daily oral dose of 75 mg venlafaxine (Treatment A) after an overnight fasting of at least 10 hours and continued on this dose until Day 14. Subjects unable to tolerate daily doses of 75 mg venlafaxine were discontinued from the study. On Day 1, subjects were to be co-administered aripiprazole with 75 mg venlafaxine according to the following schedule: 3 days at 10 mg (Treatment B), 4 days at 15 mg (Treatment C), and 7 days at 20 mg (Treatment D). On Days 1, 4, and 8, when initiating or increasing the daily aripiprazole dose, a tolerability assessment was made prior to aripiprazole dose titration, including pre-dose supine and standing blood pressure (BP) and heart rate (HR). For subjects who underwent aripiprazole dose titration, physical activity was limited for 6 hours after study drug administration. If symptoms of orthostatic hypotension developed, the subject remained supine until orthostatic hypotension was resolved. If tolerability issues developed that did not resolve within 12 hours after dose titration, the subjects were down titrated to the prior highest tolerated aripiprazole dose. Lorazepam or benztropine could be given at the Investigator's discretion for severe akathisia or extra-pyramidal symptoms. On Days -1, 3, and 7, subjects were required to maintain a well-hydrated state by drinking at least 1 liter of water in addition to other fluids. Blood and urine samples were obtained at selected times (screening, Days -5, -1, 8, and study discharge) for clinical laboratory evaluations. A 12-lead electrocardiogram (ECG) was obtained at screening, Day -5, and study discharge. On Days -1 and 14, subjects underwent serial blood sample collection for a 24-hour period to characterize the PK of venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV). On Days 14 and 15, blood samples were collected pre-dose or at clock matched times to characterize the PK of aripiprazole and dehydro-aripiprazole. The lot number for venlafaxine 75 mg Tablet was B51123. The Lot numbers for Aripiprazole 10 mg, 15 mg and 20 mg were 6E15085, 6C17038 and 6F18960, respectively.

**Analytical Method:** Analysis of aripiprazole and dehydro-aripiprazole in human plasma by LC/MS/MS was performed using a validated method during the period of known analyte stability. The linear concentration range was 1 to 250 ng/mL. The between-run variability and within-run variability for the analytical QCs of aripiprazole were  $\leq 9.99\%$  CV and  $6.62\%$  CV, respectively, and were  $\leq 1.83\%$  CV and  $2.13\%$  CV, respectively, for dehydroaripiprazole. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 6.72\%$  for aripiprazole and within  $\pm 3.25\%$  for dehydroaripiprazole.

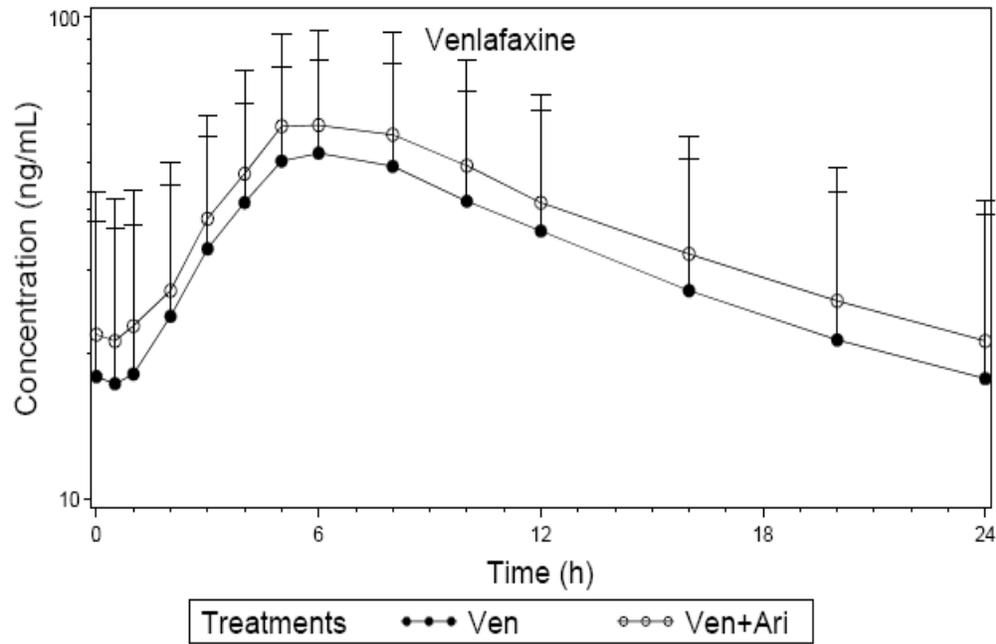
Samples for venlafaxine and O-desmethylvenlafaxine were analyzed using high performance liquid chromatography (HPLC) with fluorescence detection. The linear concentration range was 2 to 200 mg/mL. The between-run variability and within-run variability for the analytical QCs of venlafaxine were  $\leq 7.45\%$  CV and  $19.97\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 8.01\%$ . The between-run variability and within-run variability for the analytical QCs of O-desmethylvenlafaxine were  $\leq 18.08\%$  CV and  $56.90\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations within  $\pm 4.59\%$ . The results for the standard curves and QCs

indicated that the plasma assay method was precise and accurate for the analysis of venlafaxine and O-desmethylvenlafaxine in this study.

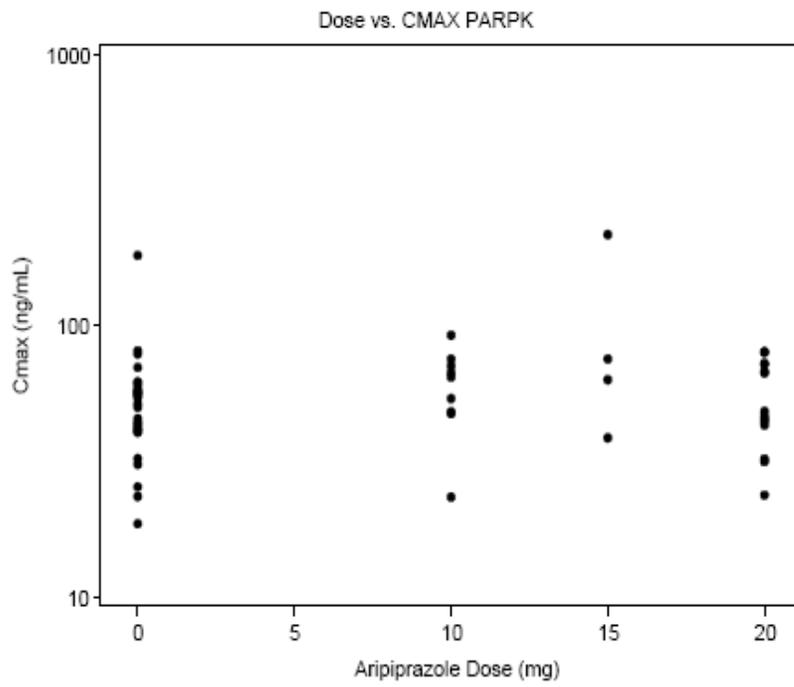
**Data Analysis:** Pharmacokinetic parameters for were computed using non-compartmental methods.

**Results:** The following figure contains the plasma concentration time profile of venlafaxine with and without aripiprazole.

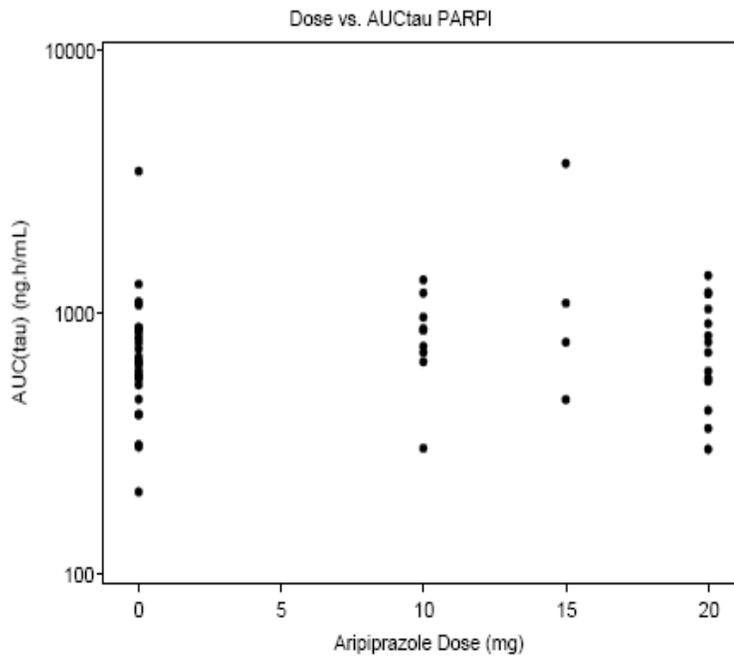
Mean ( $\pm$ SD) Plasma Concentration-Time Profiles for Venlafaxine Administered Alone and With Aripiprazole



The following figures are plots of individual Venlafaxine C<sub>max</sub> vs. Aripiprazole Dose in subjects given Venlafaxine XR 75 mg



Plot of individual Venlafaxine AUCtau vs. Aripiprazole Dose in Subjects given Venlafaxine XR 75 mg



The following table contains summary statistics for the pharmacokinetic parameters.

Summary Statistics for Venlafaxine Pharmacokinetic Parameters

Pharmacokinetic Parameter	Treatment	
	Venlafaxine XR 75 mg (N=27)	Venlafaxine XR 75 mg + Aripiprazole (N=27)
<b>C<sub>max</sub> (ng/mL)</b>		
Geom. Mean	48.82	56.06
(CV%)	(55)	(57)
<b>AUC(TAU) (ng•h/mL)</b>		
Geom. Mean	657.05	777.27
(CV%)	(77)	(70)
<b>T<sub>max</sub> (h)</b>		
Median	6.0	6.0
Min, Max	(5.0, 8.0)	(4.0, 10.0)

The summary of the statistical analyses for venlafaxine pharmacokinetic parameters are provided in the following table

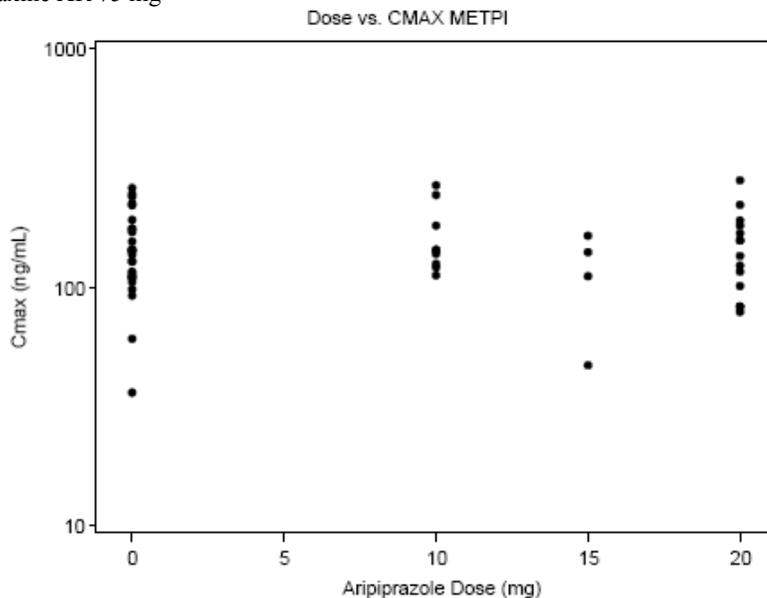
Results of Statistical Analyses for Venlafaxine Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Treatment	Geometric Mean	Point Estimate	90% Confidence Limits
C <sub>max</sub> (ng/mL)	venlafaxine	48.82	1.148	(1.083, 1.217)
	venlafaxine + aripiprazole	56.06		
AUC(TAU) (ng·h/mL)	venlafaxine	657.05	1.183	(1.130, 1.238)
	venlafaxine + aripiprazole	777.27		

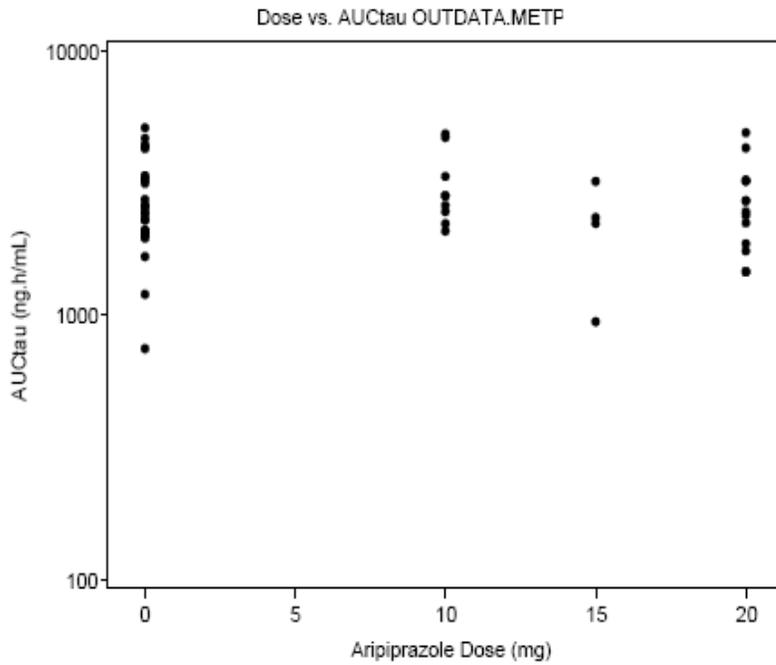
The geometric mean (%CV) of the C<sub>min</sub> for venlafaxine on Day 14 (t=0h) and Day 14 (t=24h) were 13.26 (110.25) and 13.31 (118.32) ng/mL, respectively. There was a small increase in venlafaxine C<sub>max</sub> and AUC(TAU) in the presence of aripiprazole. Under the usual definition of interaction effect (90% confidence limits for the geometric mean ratios contained entirely within 80%-125%), there was no meaningful increase in exposure to venlafaxine.

The following figure contain plots of the individual C<sub>max</sub> and AUC(Tau) versus treatment for O-desmethylvenlafaxine are provided in the following figures

Plots of Individual O-desmethylvenlafaxine C<sub>max</sub> vs Aripiprazole Dose in Subjects given Venlafaxine XR 75 mg



Plot of Individual O-desmethylvenlafaxine AUC(Tau) vs. Aripiprazole Dose in Subjects given Venlafaxine XR 75 mg



The effect of aripiprazole on O-desmethylvenlafaxine is summarized in the following table

Summary Statistics of O-desmethylvenlafaxine Pharmacokinetic Parameters

Pharmacokinetic Parameter	Treatment	
	Venlafaxine XR 75 mg (N=27)	Venlafaxine XR 75 mg + Aripiprazole (N=27)
<b>C<sub>max</sub> (ng/mL)</b>		
Geom. Mean	135.90	138.20
(CV%)	(38)	(38)
<b>AUC(TAU) (ng•h/mL)</b>		
Geom. Mean	2520.11	2580.18
(CV%)	(39)	(37)
<b>T<sub>max</sub> (h)</b>		
Median	8.0	8.0
Min, Max	(5.0, 12.0)	(5.0, 12.0)

Results of statistical analyses for O-desmethylvenlafaxine pharmacokinetic parameters are provided in the following table

Results of Statistical Analyses for O-desmethylvenlafaxine Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Treatment	Geometric Mean	Point Estimate	90% Confidence Limits
C <sub>max</sub> (ng/mL)	venlafaxine	135.90	1.017	(0.964, 1.073)
	venlafaxine + aripiprazole	138.20		
AUC(TAU) (ng•h/mL)	venlafaxine	2520.11	1.024	(0.973, 1.077)
	venlafaxine + aripiprazole	2580.18		

There were no increases in O-desmethylvenlafaxine C<sub>max</sub> and AUC(TAU) when increasing doses of aripiprazole were co-administered with venlafaxine.

Blood samples were taken predose and 24 hours post-dose of Aripiprazole on days 14 and 15. The following table contains aripiprazole C<sub>min</sub> values on days 14 and 15

Summary Statistics for Aripiprazole C<sub>min</sub> on Days 14 and 15

Pharmacokinetic Parameter	Treatment					
	aripiprazole 10 mg + venlafaxine XR 75 mg		aripiprazole 15 mg + venlafaxine XR 75 mg		aripiprazole 20 mg + venlafaxine XR 75 mg	
	Day 14 (N=9)	Day 15 (N=9)	Day 14 (N=2)	Day 15 (N=4)	Day 14 (N=16)	Day 15 (N=14)
C <sub>min</sub> (ng/mL)						
Geom. Mean	120.26	118.99	267.64	196.03	190.62	206.65
(CV%)	(42.32)	(41.43)	(46.64)	(53.70)	(27.98)	(26.80)

The following table contains summary statistics for dehydro-aripiprazole C<sub>min</sub> on days 14 and 15

Summary Statistics for dehydro-aripiprazole C<sub>min</sub> on Days 14 and 15

Pharmacokinetic Parameter	Treatment					
	aripiprazole 10 mg + venlafaxine XR 75 mg		aripiprazole 15 mg + venlafaxine XR 75 mg		aripiprazole 20 mg + venlafaxine XR 75 mg	
	Day 14 (N=9)	Day 15 (N=9)	Day 14 (N=2)	Day 15 (N=4)	Day 14 (N=16)	Day 15 (N=14)
<b>C<sub>min</sub> (ng/mL)</b>						
Geom. Mean	51.34	53.98	56.12	64.15	74.20	85.04
(CV%)	(45.17)	(48.29)	(25.41)	(14.28)	(20.67)	(21.48)

The trough concentration of aripiprazole was similar on days 14 and 15 when it was coadministered with venlafaxine.

**Safety Summary:** The most frequently reported (ie,  $\geq 20\%$  of subjects) adverse events (AE) in subjects who received aripiprazole were insomnia (39.5%), akathisia (34.2%), dizziness (26.3%) and anxiety (23.7%). All the AEs were of mild or moderate intensity and were considered by the Investigator to be either possibly or probably related to study drug. Other AEs that occurred in  $\geq 10\%$  of subjects who received aripiprazole were constipation (18.4%), dystonia (18.4%), nausea (13.2%) and headache (10.5%). There was 1 reported AE of orthostatic hypotension and 1 AE of syncope. All the events were of mild or moderate intensity and were considered by the Investigator to be either possibly or probably unrelated to study drug. The sponsor reported that as observed in previous studies with aripiprazole, 10 to 20 mg oral doses of aripiprazole (co-administered with venlafaxine) were poorly tolerated in healthy subjects. No novel safety concerns were identified. There were no serious or severe adverse events.

**Pharmacokinetic Summary:** This study was performed to evaluate the effect of aripiprazole at doses of 10 - 20 mg on the steady-state pharmacokinetics of venlafaxine and its major active metabolite O-desmethylvenlafaxine in healthy subjects. Aripiprazole co-administered with venlafaxine did not affect the overall systemic exposure to venlafaxine or O-desmethylvenlafaxine. The median T<sub>max</sub> for venlafaxine and O-desmethylvenlafaxine were similar with or without aripiprazole co-administration. A pharmacokinetic drug-drug interaction is not expected to occur for venlafaxine and O-desmethylvenlafaxine when aripiprazole is co-administered with venlafaxine.

**Reviewer comments:** *Aripiprazole does not affect the pharmacokinetics of Venlafaxine and its active metabolite, O-desmethylvenlafaxine. The effect of venlafaxine on aripiprazole was not statistically evaluated. However, trough concentrations of aripiprazole and dehydro-aripiprazole were similar on days 14 and 15 when they were co-administered with venlafaxine.*

TABLE 3.0.2.10.  
Summary Statistics of Venlafaxine Pharmacokinetic Parameters

Part1: Venlafaxine Monotherapy

Aripiprazole Yes/No	STATISTIC	C <sub>MAX</sub> (ng/mL)	AUC(tau) (ng <sup>2</sup> h/mL)	T <sub>MAX</sub> (h)	C <sub>MIN1</sub>	C <sub>MIN2</sub>
					at Time 0 hrs (ng/mL)	at Time 24 hrs (ng/mL)
No	N	27	27	27	27	27
	MEAN	54.01	769.43	6.00	17.94	17.77
	S.D.	29.65	592.83	0.96	19.78	21.02
	GEO.MEAN	48.82	657.05	5.93	13.26	13.31
	C.V.	54.90	77.05	16.01	110.25	118.32
	MEDIAN	51.50	642.16	6.00	13.70	12.00
	MIN	18.60	206.74	5.00	2.90	3.53
	MAX	181.00	3461.54	8.00	108.00	116.00

Summary Statistics of Venlafaxine Pharmacokinetic Parameters

Part2: Venlafaxine and Aripiprazole

Aripiprazole Yes/No	STATISTIC	C <sub>MAX</sub> (ng/mL)	AUC(tau) (ng <sup>2</sup> h/mL)	T <sub>MAX</sub> (h)	C <sub>MIN1</sub>	C <sub>MIN2</sub>
					at Time 0 hrs (ng/mL)	at Time 24 hrs (ng/mL)
Yes	N	27	27	27	27	27
	MEAN	62.49	903.02	6.19	21.94	21.27
	S.D.	35.72	636.47	1.42	21.30	20.43
	GEO.MEAN	56.06	777.27	6.04	17.07	16.94
	C.V.	57.16	70.48	22.88	97.08	96.04
	MEDIAN	63.00	771.54	6.00	17.90	15.30
	MIN	23.30	300.66	4.00	4.05	6.18
	MAX	216.00	3702.00	10.00	118.00	114.00

Summary Statistics for 0-desmethylvenlafaxine Pharmacokinetic Parameters

Part 1: Venlafaxine Monotherapy

Aripiprazole Yes/No	STATISTIC	C <sub>MAX</sub> (ng/mL)	AUC(tau) (ng <sup>2</sup> h/mL)	T <sub>MAX</sub> (h)	C <sub>MIN1</sub>	C <sub>MIN2</sub>
					at Time 0 hrs (ng/mL)	at Time 24 hrs (ng/mL)
No	N	27	27	27	27	27
	MEAN	147.06	2725.33	8.78	80.83	81.23
	S.D.	55.56	1066.41	1.67	34.32	35.72
	GEO.MEAN	135.90	2520.11	8.61	73.83	74.41
	C.V.	37.78	39.13	19.05	42.46	43.98
	MEDIAN	142.00	2439.65	8.00	69.70	71.20
	MIN	36.10	746.60	5.00	25.20	26.80
	MAX	260.00	5102.43	12.00	157.00	164.00

Summary Statistics for 0-desmethylvenlafaxine Pharmacokinetic Parameters

Part 2: Venlafaxine and Aripiprazole

Aripiprazole Yes/No	STATISTIC	C <sub>MAX</sub> (ng/mL)	AUC(tau) (ng <sup>2</sup> h/mL)	T <sub>MAX</sub> (h)	C <sub>MIN1</sub>	C <sub>MIN2</sub>
					at Time 0 hrs (ng/mL)	at Time 24 hrs (ng/mL)
Yes	N	27	27	27	27	27
	MEAN	148.46	2756.95	8.33	85.80	84.68
	S.D.	56.28	1009.28	1.54	35.81	34.30
	GEO.MEAN	138.20	2580.18	8.19	79.09	78.95
	C.V.	37.91	36.61	18.53	41.74	40.51
	MEDIAN	140.00	2600.65	8.00	81.80	74.40
	MIN	47.00	944.23	5.00	31.20	33.10
	MAX	280.00	4894.85	12.00	189.00	175.00

Summary Statistics for Aripiprazole Cmin

Part 1: Day 13-Day 14 trough

Treatment Description	STATISTIC	CMINNEW Cmin Trough Concentration (ng/ml)
Venlafaxine XR 75mg+Aripiprazole 10mg	N	9
	MEAN	132.11
	S.D.	55.91
	GEO.MEAN	120.26
	C.V.	42.32
	MEDIAN	123.00
	MIN	45.60
MAX	227.00	
Venlafaxine XR 75mg+Aripiprazole 15mg	N	2
	MEAN	283.50
	S.D.	132.23
	GEO.MEAN	267.64
	C.V.	46.64
	MEDIAN	283.50

Summary Statistics for Aripiprazole Cmin

Part 1: Day 13-Day 14 trough

Treatment Description	STATISTIC	CMINNEW Cmin Trough Concentration (ng/ml)
Venlafaxine XR 75mg+Aripiprazole 15mg	MIN	190.00
	MAX	377.00
Venlafaxine XR 75mg+Aripiprazole 20mg	N	16
	MEAN	197.19
	S.D.	55.17
	GEO.MEAN	190.62
	C.V.	27.98
	MEDIAN	188.00
	MIN	127.00
MAX	318.00	

TABLE 3072.02.01  
 Summary Statistics for Aripiprazole C<sub>min</sub>

Part 2: Day 14-Day 15 trough

Treatment Description	STATISTIC	CMINNEW C <sub>min</sub> Trough Concentration (ng/ml)
Venlafaxine XR 75mg+Aripiprazole 10mg	N	9
	MEAN	130.89
	S.D.	54.23
	GEO.MEAN	118.99
	C.V.	41.43
	MEDIAN	128.00
	MIN	42.00
	MAX	210.00
Venlafaxine XR 75mg+Aripiprazole 15mg	N	4
	MEAN	215.50
	S.D.	115.73
	GEO.MEAN	196.03
	C.V.	53.70
	MEDIAN	177.00

Summary Statistics for Aripiprazole C<sub>min</sub>

Part 2: Day 14-Day 15 trough

Treatment Description	STATISTIC	CMINNEW C <sub>min</sub> Trough Concentration (ng/ml)
Venlafaxine XR 75mg+Aripiprazole 15mg	MIN	125.00
	MAX	383.00
Venlafaxine XR 75mg+Aripiprazole 20mg	N	14
	MEAN	213.43
	S.D.	57.20
	GEO.MEAN	206.65
	C.V.	26.80
	MEDIAN	208.00
	MIN	138.00
	MAX	327.00

TABLE 3.3.2.4A:  
Summary Statistics for Dehydro-aripiprazole Cmin

Part 1: Day 13-Day 14 trough

Treatment Description	STATISTIC	CMINNEW Cmin Trough Concentration (ng/ml)
Venlafaxine XR 75mg+Aripiprazole 10mg	N	9
	MEAN	56.54
	S.D.	25.54
	GEO.MEAN	51.34
	C.V.	45.17
	MEDIAN	51.00
	MIN	27.70
	MAX	98.40
Venlafaxine XR 75mg+Aripiprazole 15mg	N	2
	MEAN	57.05
	S.D.	14.50
	GEO.MEAN	56.12
	C.V.	25.41
	MEDIAN	57.05

TABLE 3.3.2.4B:  
Summary Statistics for Dehydro-aripiprazole Cmin

Part 1: Day 13-Day 14 trough

Treatment Description	STATISTIC	CMINNEW Cmin Trough Concentration (ng/ml)
Venlafaxine XR 75mg+Aripiprazole 15mg	MIN	46.80
	MAX	67.30
Venlafaxine XR 75mg+Aripiprazole 20mg	N	16
	MEAN	75.62
	S.D.	15.63
	GEO.MEAN	74.20
	C.V.	20.67
	MEDIAN	73.45
	MIN	55.50
	MAX	112.00

Summary Statistics for Dehydro-aripiprazole Cmin

Part 2: Day 14- Day 15 trough

Treatment Description	STATISTIC	CMINNEW Cmin Trough Concentration (ng/ml)
Venlafaxine XR 75mg+Aripiprazole 10mg	N	9
	MEAN	60.41
	S.D.	29.17
	GEO.MEAN	53.98
	C.V.	48.29
	MEDIAN	59.30
	MIN	26.10
MAX	108.00	
Venlafaxine XR 75mg+Aripiprazole 15mg	N	4
	MEAN	64.65
	S.D.	9.23
	GEO.MEAN	64.15
	C.V.	14.28
	MEDIAN	64.75

Summary Statistics for Dehydro-aripiprazole Cmin

Part 2: Day 14- Day 15 trough

Treatment Description	STATISTIC	CMINNEW Cmin Trough Concentration (ng/ml)
Venlafaxine XR 75mg+Aripiprazole 15mg	MIN	54.70
	MAX	74.40
Venlafaxine XR 75mg+Aripiprazole 20mg	N	14
	MEAN	86.81
	S.D.	18.65
	GEO.MEAN	85.04
	C.V.	21.48
	MEDIAN	82.70
	MIN	61.50
	MAX	126.00

**3.2.4. Title (Study No. CN138463):** Effects of Aripiprazole on the Steady State Pharmacokinetics of Escitalopram in Healthy Subjects.

**Objectives:** 1) To assess the effects of daily 10 mg oral doses of aripiprazole on the steady-state pharmacokinetics of escitalopram in healthy subjects. 2) To assess the safety and tolerability of aripiprazole when co-administered with escitalopram to healthy subjects.

**Study Design:** This was an open-label, non-randomized study in healthy subjects. Healthy subjects, ages 18 to 45 years, as determined by medical history, physical examination, 12-lead ECG, vital signs and clinical laboratory evaluations, were eligible to participate in the study. The mean age and weight were  $29 \pm 8$  years and  $79.5 \pm 8.7$  kg, respectively. In the morning on Days -7 to 14, after fasting for at least 10 hours, each subject received an oral dose of 10 mg escitalopram. On Days 1 to 14, each subject was co-administered an oral dose of 10 mg aripiprazole. The time of dose administration was called "0" hour. On Day -7, subjects began receiving a daily oral dose of 10 mg escitalopram and continued on this dose until Day 14. If subjects were unable to tolerate daily doses of 10 mg escitalopram, they were discontinued from the study. On Day 1, subjects began receiving 10 mg aripiprazole once daily for 14 days. A tolerability assessment was made prior to the aripiprazole dose initiation, including predose supine and standing blood pressure (BP) and heart rate (HR) and physical activity was limited for 6 hours after study drug administration. If vomiting developed, aripiprazole dosing was considered tolerable only if the vomiting occurred prior to Day 4 and resolved within 12 hours post aripiprazole dosing. On Days -1 and 14, subjects underwent serial blood sample collection for a 24 hour period to characterize the PK of escitalopram. On Days 14 and 15, blood PK samples were also collected pre-dose to characterize the PK of aripiprazole and dehydro-aripiprazole. The lot number for aripiprazole 10 mg used in the study was 6F20934 and for escitalopram were M0619F and P11500.

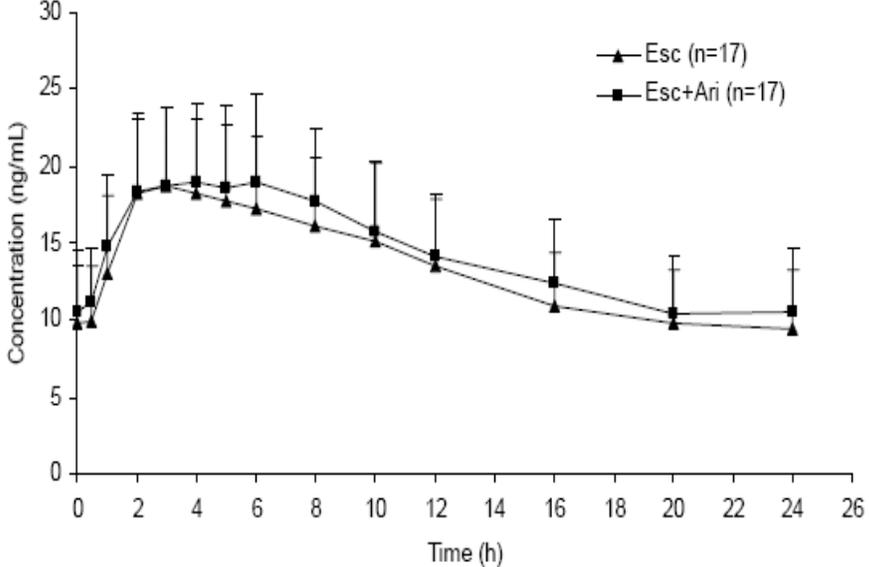
**Analytical Method:** Analysis of escitalopram in human plasma by LC/MS/MS was performed using a validated method during the period of known analyte stability. The lower limit of quantitation (LLOQ) was established at 1 ng/mL. The linear range was 1 to 500 ng/mL. The between-run variability and within-run variability for the analytical QCs of escitalopram were  $\leq 8.25\%$  CV and  $19.06\%$  CV, respectively. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 1.73\%$ . The results for the standard curves and QCs indicated that the plasma assay method was precise and accurate for the analysis of escitalopram in this study.

Samples were analyzed for aripiprazole and dehydroaripiprazole using liquid chromatography tandem mass spectrometry (LC-API/MS/MS) detection. The LLOQ was established at 1 ng/mL. The linear concentration range was 1 to 250 ng/mL. The between-run variability and within-run variability for the analytical QCs of aripiprazole were  $\leq 7.45\%$  CV and  $5.27\%$  CV, respectively, and the between-run variability was  $\leq 2.67\%$  CV for dehydroaripiprazole. The deviations of the mean observed concentrations from the nominal concentrations were within  $\pm 8.50\%$  for aripiprazole and within  $\pm 6.17\%$  for dehydroaripiprazole. The results for the standard curves and QCs indicated that the human plasma assay method was precise and accurate for the analysis of aripiprazole and dehydroaripiprazole in this study.

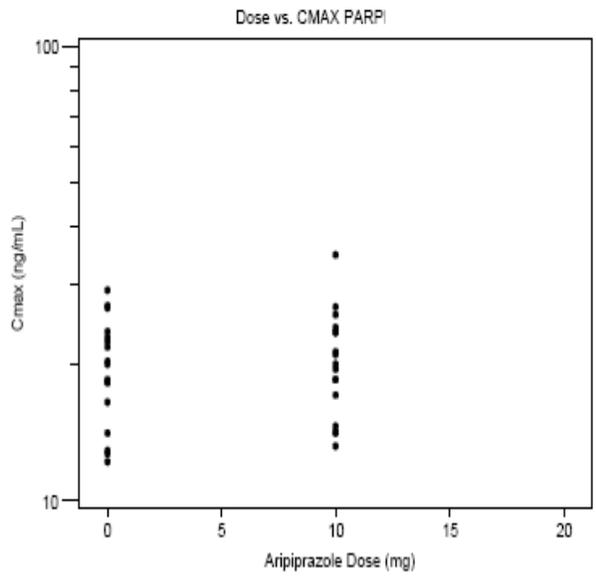
**Data Analysis:** Pharmacokinetic parameters were computed using non-compartmental methods.

**Results:** The mean plasma concentration time profile for escitalopram administered alone and co-administered with aripiprazole is contained in the following figure

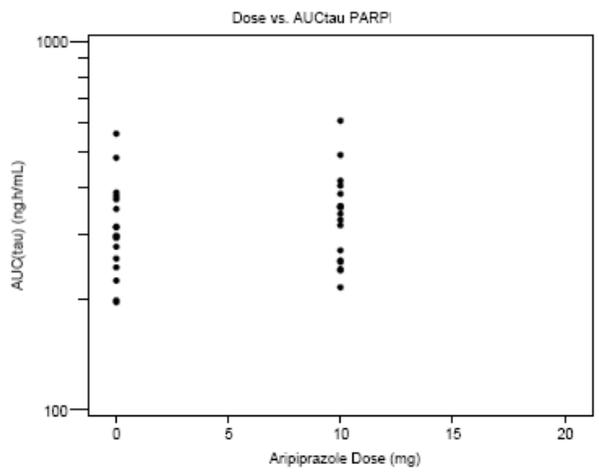
Mean  $\pm$ SD Steady-State Plasma Concentration-Time Profiles for Escitalopram Administered Alone and Co-Administered with Aripiprazole in Healthy Subjects



Plot of Individual Escitalopram Cmax vs. Aripiprazole Dose in Subjects given 10mg Escitalopram



Plot of Individual Escitalopram AUC(TAU) vs. Aripiprazole Dose in Subjects given 10mg Escitalopram



The following tables contain the summary statistics for the pharmacokinetic parameters of escitalopram.

Summary Statistics for Escitalopram Pharmacokinetic Parameters

Pharmacokinetic Parameter	Treatment	
	Escitalopram (N=17)	Escitalopram + Aripiprazole (N=17)
<b>C<sub>max</sub> (ng/mL)</b>		
Geom. Mean	19.17	19.95
(CV%)(between subject)	(25.96)	(26.89)
<b>AUC(TAU) (ng•h/mL)</b>		
Geom. Mean	308.16	330.89
(CV%)(between subject)	(30.23)	(29.58)
<b>T<sub>max</sub> (h)</b>		
Median	3.0	3.0
Min, Max	(1.0, 8.0)	(1.0, 6.0)

CN138463

Results of Statistical Analyses for Escitalopram Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Treatment	Geometric Mean	Point Estimate	90% Confidence Limits
<b>C<sub>max</sub> (ng/mL)</b>	escitalopram	19.173		
	escitalopram + aripiprazole	19.946	1.04	(0.99,1.09)
<b>AUC(TAU) (ng•h/mL)</b>	escitalopram	308.16		
	escitalopram + aripiprazole	330.89	1.07	(1.04,1.11)

CN138463

The geometric mean (CV%) of the C<sub>min</sub> of escitalopram on Day 14 (t=0h) and Day 14 (t=24h) were 9.29 (37.18) and 8.86 (40.10) ng/mL, respectively.

Pharmacokinetics of Aripiprazole

Pharmacokinetic samples for Cmin of aripiprazole and dehydro-aripiprazole were obtained pre-dose on Day 14 and 24 h later. The results are contained in the following table.

Summary Statistics for Aripiprazole Cmin on Days 14 and 15

Pharmacokinetic Parameter	Treatment B (10 mg escitalopram + 10 mg aripiprazole) (N=17)	
	Day 14	Day 15
Cmin (ng/mL)		
Geom. Mean	135.24	133.67
CV (%)	32.86	32.88

CN138463

Summary Statistics for Dehydro-Aripiprazole Cmin on Days 14 and 15

Pharmacokinetic Parameter	Treatment B (10 mg escitalopram + 10 mg aripiprazole) (N=17)	
	Day 14	Day 15
Cmin (ng/mL)		
Geom. Mean	38.99	40.98
CV (%)	20.59	21.37

CN138463

There does not appear to be any difference in the dehydro-aripiprazole Cmin between the two timepoints.

**Safety summary:** The sponsor reported that overall, a total of 166 AEs occurred in 22 (95.7%) of the 23 subjects who received aripiprazole. The most frequently reported (ie,  $\geq 20\%$  of subjects) AEs in subjects who received aripiprazole were sleep disorder (47.8%), nausea (43.5%), postural dizziness (43.5%), akathisia (39.1%), disturbance in attention (39.1%), dystonia (34.8%), extrapyramidal disorder (30.4%), orthostatic hypotension (30.4%), headache (26.1%), nasal congestion (26.1%), increased heart rate (21.7%) and decreased appetite (21.7%). There were a total of 19 orthostatic hypotensive events. The sponsor reported that there was 1 SAE of syncope of moderate intensity and a fall on Day 1 of aripiprazole dosing. All AEs were mild or moderate in intensity. The sponsor reported that the safety and side effect profile of escitalopram is similar to that of other SNRIs and SSRIs. During the acute phase of treatment, these side effects include reduced appetite, tremor, akathisia, sleep disorders, agitation and postural dizziness.

**Pharmacokinetic Summary:** Aripiprazole co-administered with escitalopram did not significantly alter the systemic exposure of escitalopram. The mean C<sub>min</sub> plasma aripiprazole concentrations on Day 14 (134 and 135 ng/mL at pre-dose and 24 h post-dose on Day 14, respectively) were similar to previously reported steady-state C<sub>min</sub> concentrations of 103 ng/mL in healthy subjects following daily 10 mg dose for 14 days (study 31-93-201). Based on the C<sub>min</sub> of escitalopram on Day 14 (t=0h) and Day 14 (t=24h), plasma concentration of escitalopram seemed to be at steady-state. Compared to when escitalopram was administered alone, the geometric mean ratios of C<sub>max</sub> and AUC<sub>τ</sub> of escitalopram following co-administration of aripiprazole satisfied the usual criterion (90% confidence intervals of geometric mean ratios between 0.8 and 1.25) for concluding absence of effect. The median T<sub>max</sub> of escitalopram was similar with or without aripiprazole co-administration.

**Reviewer conclusions:** *The reviewer agrees with the sponsor's conclusion that aripiprazole co-administered with escitalopram did not significantly alter the systemic exposure of escitalopram. The study did not evaluate the effect of escitalopram on aripiprazole.*

PROTOCOL: CN138-463

PAGE: 1

Table S.8.2.1B:  
Summary Statistics of Escitalopram Pharmacokinetic Parameters

Part I: Escitalopram Monotherapy

Subject Received Aripiprazole	STATISTIC	C <sub>MAX</sub> (ng/mL)	AUC (tau) (ng <sup>2</sup> h/mL)	T <sub>MAX</sub> (h)	C <sub>MIN1</sub> C <sub>MIN</sub> at Profile Start t = 0hrs (ng/mL)	C <sub>MIN2</sub> C <sub>MIN</sub> at Profile End t= 24hrs (ng/mL)
No	N	17	17	17	17	17
	MEAN	19.82	320.67	3.35	9.82	9.46
	S.D.	5.15	96.95	1.80	3.65	3.79
	GEO.MEAN	19.17	308.16	2.95	9.29	8.86
	C.V.	25.96	30.23	53.71	37.18	40.10
	MEDIAN	20.00	297.14	3.00	9.13	8.63
	MIN	12.20	196.13	1.00	5.50	5.10
	MAX	29.10	562.12	6.00	19.50	19.90

Note: See Section 5.2 of the CSR for a listing of data/subjects excluded

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Table S.8.2.1B:  
Summary Statistics of Escitalopram Pharmacokinetic Parameters

Part2: Escitalopram and Aripiprazole

Subject Received Aripiprazole	STATISTIC	C <sub>MAX</sub> (ng/mL)	AUC(tau) (ng <sup>h</sup> /mL)	T <sub>MAX</sub> (h)	C <sub>MIN1</sub> C <sub>MIN</sub> at Profile Start t = 0hrs (ng/mL)	C <sub>MIN2</sub> C <sub>MIN</sub> at Profile End t= 24hrs (ng/mL)
Yes	N	17	17	17	17	17
	MEAN	20.61	343.62	3.35	10.58	10.59
	S.D.	5.54	101.63	1.66	3.91	4.00
	GEO.MEAN	19.95	330.89	2.92	9.99	9.99
	C.V.	26.89	29.58	49.39	37.00	37.78
	MEDIAN	20.00	340.83	3.00	10.80	11.00
	MIN	13.20	215.20	1.00	6.04	6.02
	MAX	34.80	609.83	6.00	21.70	21.90

TABLE 3.6.2.2A:  
Summary Statistics for Aripiprazole Cmin

Part 1

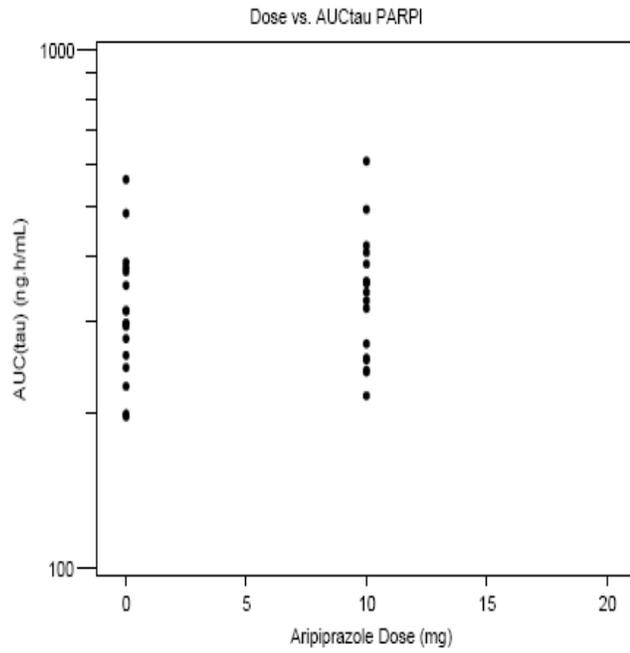
Subject Received Aripiprazole	STATISTIC	CMIN1 CMIN at Profile Start t = 0hrs (ng/mL)	CMIN2 CMIN at Profile End t= 24hrs (ng/mL)
Yes	N	17	17
	MEAN	141.88	140.27
	S.D.	46.62	46.12
	GEO.MEAN	135.24	133.67
	C.V.	32.86	32.88
	MEDIAN	140.00	136.00
	MIN	81.30	72.20
	MAX	247.00	243.00

Summary Statistics for Dehydro-aripiprazole Cmin

Part 1

Subject Received Aripiprazole	STATISTIC	CMIN1	CMIN2
		at Profile Start t = 0hrs (ng/mL)	at Profile End t= 24hrs (ng/mL)
Yes	N	17	17
	MEAN	39.79	41.87
	S.D.	8.19	8.95
	GEO.MEAN	38.99	40.98
	C.V.	20.59	21.37
	MEDIAN	37.90	40.10
	MIN	26.00	27.60
	MAX	55.20	58.30

Plot of Individual Escitalopram AUC(TAU) vs. Aripiprazole Dose in Subjects given 10mg Escitalopram



Appendix 8.2.1C:  
Listing of Escitalopram Pharmacokinetic Parameters

SUBJECT	STUDY DAY	TREATMENT GROUP	C <sub>MAX</sub> (ng/mL)	T <sub>MAX</sub> (h)	AUC (tau) (ng <sup>h</sup> /mL)	C <sub>MIN1</sub> at Time t=0 (ng/mL)	C <sub>MIN2</sub> at Time t=24 (ng/mL)
CNL38463-1-1	-1	Escitalopram 10 mg	18.30	2.00	257.53	6.32	6.43
	14	Escitalopram 10mg + Aripirazole 10mg	18.50	2.00	254.52	6.04	6.09
CNL38463-1-10	-1	Escitalopram 10 mg	26.60	2.00	380.72	11.80	10.30
	14	Escitalopram 10mg + Aripirazole 10mg	24.10	2.00	356.34	11.40	11.20
CNL38463-1-11	-1	Escitalopram 10 mg	14.10	6.00	243.81	7.46	6.78
	14	Escitalopram 10mg + Aripirazole 10mg	14.60	5.00	252.12	7.89	7.51
CNL38463-1-12	-1	Escitalopram 10 mg	21.80	2.00	313.57	9.23	8.30
	14	Escitalopram 10mg + Aripirazole 10mg	25.70	2.00	406.40	12.20	11.80
CNL38463-1-14	-1	Escitalopram 10 mg	20.30	3.00	297.14	9.13	8.63
	14	Escitalopram 10mg + Aripirazole 10mg	18.50	5.00	317.06	9.22	9.70
CNL38463-1-16	-1	Escitalopram 10 mg	20.00	4.00	295.73	8.01	7.05
	14	Escitalopram 10mg + Aripirazole 10mg	20.00	5.00	328.17	9.39	8.39
CNL38463-1-19	-1	Escitalopram 10 mg	22.40	2.00	351.23	11.30	11.00
	14	Escitalopram 10mg + Aripirazole 10mg	19.50	4.00	357.78	12.20	11.00
CNL38463-1-2	-1	Escitalopram 10 mg	26.90	5.00	483.77	16.10	14.60
	14	Escitalopram 10mg + Aripirazole 10mg	26.70	3.00	492.11	14.70	16.10
CNL38463-1-20	-1	Escitalopram 10 mg	22.90	4.00	389.24	12.10	13.50

Appendix 8.2.1C:  
Listing of Escitalopram Pharmacokinetic Parameters

SUBJECT	STUDY DAY	TREATMENT GROUP	C <sub>MAX</sub> (ng/mL)	T <sub>MAX</sub> (h)	AUC (tau) (ng <sup>4</sup> h/mL)	C <sub>MIN1</sub>	C <sub>MIN2</sub>
						at Time t=0 (ng/mL)	at Time t=24 (ng/mL)
CN138463-1-20	14	Escitalopram 10mg + Aripirazole 10mg	23.50	6.00	419.13	14.20	13.70
CN138463-1-21	-1	Escitalopram 10 mg	23.60	1.00	373.14	11.70	11.10
	14	Escitalopram 10mg + Aripirazole 10mg	23.50	1.00	386.12	11.50	11.40
CN138463-1-22	-1	Escitalopram 10 mg	12.70	5.00	196.13	7.20	5.17
	14	Escitalopram 10mg + Aripirazole 10mg	14.10	4.00	239.26	7.06	7.53
CN138463-1-23	-1	Escitalopram 10 mg	12.90	2.00	198.52	5.50	5.10
	14	Escitalopram 10mg + Aripirazole 10mg	13.20	2.00	215.20	6.57	6.02
CN138463-1-3	-1	Escitalopram 10 mg	18.50	3.00	277.26	7.76	7.97
	14	Escitalopram 10mg + Aripirazole 10mg	17.10	1.00	271.13	7.04	7.36
CN138463-1-5	-1	Escitalopram 10 mg	12.20	8.00	224.42	6.63	6.47
	14	Escitalopram 10mg + Aripirazole 10mg	14.20	4.00	241.05	7.05	7.71
CN138463-1-7	-1	Escitalopram 10 mg	16.50	2.00	292.97	8.09	9.41
	14	Escitalopram 10mg + Aripirazole 10mg	21.00	3.00	354.53	10.90	11.00
CN138463-1-8	-1	Escitalopram 10 mg	18.20	3.00	314.15	9.14	9.17
	14	Escitalopram 10mg + Aripirazole 10mg	21.30	2.00	340.83	10.80	11.70
CN138463-1-9	-1	Escitalopram 10 mg	29.10	3.00	562.12	19.50	19.90
	14	Escitalopram 10mg + Aripirazole 10mg	34.80	6.00	609.83	21.70	21.90

Appendix 8.2.2A:  
Listing of Aripiprazole C<sub>min</sub> values

SUBJECT	STUDY DAY	TREATMENT GROUP	PEAKNAME	C <sub>MIN1</sub> C <sub>MIN</sub> at Time t=0 (ng/mL)	C <sub>MIN2</sub> C <sub>MIN</sub> at Time t=24 (ng/mL)
CN138463-1-1	14	ESC+ARI	BMS-337039	185.00	178.00
CN138463-1-10	14	ESC+ARI	BMS-337039	142.00	136.00
CN138463-1-11	14	ESC+ARI	BMS-337039	152.00	153.00
CN138463-1-12	14	ESC+ARI	BMS-337039	153.00	139.00
CN138463-1-14	14	ESC+ARI	BMS-337039	98.90	111.00
CN138463-1-16	14	ESC+ARI	BMS-337039	247.00	230.00
CN138463-1-19	14	ESC+ARI	BMS-337039	117.00	115.00
CN138463-1-2	14	ESC+ARI	BMS-337039	172.00	165.00
CN138463-1-20	14	ESC+ARI	BMS-337039	159.00	167.00
CN138463-1-21	14	ESC+ARI	BMS-337039	140.00	144.00
CN138463-1-22	14	ESC+ARI	BMS-337039	117.00	115.00
CN138463-1-23	14	ESC+ARI	BMS-337039	103.00	103.00
CN138463-1-3	14	ESC+ARI	BMS-337039	83.80	72.20

Appendix 8.2.2A:  
Listing of Aripiprazole C<sub>min</sub> values

SUBJECT	STUDY DAY	TREATMENT GROUP	PEAKNAME	CMIN1 CMIN at Time t=0 (ng/mL)	CMIN2 CMIN at Time t=24 (ng/mL)
CNL38463-1-5	14	ESC+ARI	BMS-337039	81.30	87.40
CNL38463-1-7	14	ESC+ARI	BMS-337039	110.00	108.00
CNL38463-1-8	14	ESC+ARI	BMS-337039	123.00	118.00
CNL38463-1-9	14	ESC+ARI	BMS-337039	228.00	243.00

Appendix 8.2.3A:  
Listing of Dehydro-Aripiprazole Cmin value

SUBJECT	STUDY DAY	TREATMENT GROUP	PEAKNAME	CMIN1	CMIN2
				at Time t=0 (ng/mL)	at Time t=24 (ng/mL)
CN138463-1-1	14	ESC+ARI	BMS-337044	33.80	35.60
CN138463-1-10	14	ESC+ARI	BMS-337044	45.80	44.30
CN138463-1-11	14	ESC+ARI	BMS-337044	26.40	28.80
CN138463-1-12	14	ESC+ARI	BMS-337044	35.50	35.60
CN138463-1-14	14	ESC+ARI	BMS-337044	46.00	55.50
CN138463-1-16	14	ESC+ARI	BMS-337044	40.20	43.20
CN138463-1-19	14	ESC+ARI	BMS-337044	26.00	27.60
CN138463-1-2	14	ESC+ARI	BMS-337044	55.20	48.10
CN138463-1-20	14	ESC+ARI	BMS-337044	49.50	58.30
CN138463-1-21	14	ESC+ARI	BMS-337044	53.20	56.70
CN138463-1-22	14	ESC+ARI	BMS-337044	37.90	40.10
CN138463-1-23	14	ESC+ARI	BMS-337044	42.00	42.50
CN138463-1-3	14	ESC+ARI	BMS-337044	37.10	35.80

Appendix 8.2.3A:  
Listing of Dehydro-Aripiprazole Cmin value

SUBJECT	STUDY DAY	TREATMENT GROUP	PKPARAM	CMIN1 CMIN at Time t=0 (ng/mL)	CMIN2 CMIN at Time t=24 (ng/mL)
QN138463-1-5	14	ESC+ARI	EMS-337044	35.80	38.70
QN138463-1-7	14	ESC+ARI	EMS-337044	40.10	40.00
QN138463-1-8	14	ESC+ARI	EMS-337044	34.90	35.60
QN138463-1-9	14	ESC+ARI	EMS-337044	37.00	45.40

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Andre Jackson  
10/19/2007 06:43:11 AM  
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics  
New Drug Application Filing and Review Form

**General Information About the Submission**

Information		Information	
NDA Number	21436	Brand Name	Abilify
OCPB Division (I, II, III)	I	Generic Name	Aripiprazole
Medical Division	Psychiatry	Drug Class	
OCPB Reviewer	Andre Jackson	Indication(s)	(b) (4)
OCPB Team Leader	Ray Baweja	Dosage Form	Tablet
		Dosing Regimen	2-20 mg/day
Date of Submission	May 16, 2007	Route of Administration	Oral
Estimated Due Date of OCPB Review	September 11, 2007	Sponsor	Otsuka
PDUFA Due Date	November 11, 2007	Priority Classification	P
Division Due Date	October 11, 2007		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				

In-vivo effects of primary drug:		2		<p>1. Study CN138462 The effect of the co-administration of 2 - 20 mg/day of aripiprazole On the steady-state pharmacokinetics of venlafaxine. Study done in 38 subjects. 90% CI estimated for PK parameters</p> <p>2. Study CN138463 The effect of the co-administration of 2 - 20 mg/day of aripiprazole On the steady-state pharmacokinetics of escitalopram . Study done in 17 subjects. 90% CI estimated for PK parameters</p>
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				

Data sparse In-vivo effects of primary drug:		2		<p>3. Study CN138139 The effect of the co-administration of 2 - 20 mg/day of aripiprazole as an adjunctive therapy. on the steady-state pharmacokinetics of the antidepressants escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine was investigated. Compared concentrations from subjects collected at similar times.</p> <p>4. Study CN138163 The effect of the co-administration of 2 - 20 mg/day of aripiprazole as an adjunctive therapy. on the steady-state pharmacokinetics of the antidepressants escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine was investigated. Compared concentrations from subjects collected at similar times.</p>
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>4</b>		

<b>Filability and QBR comments</b>		
	"X" if yes	Comments
<b>Application fileable ?</b>	<b>Yes</b>	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
<b>Comments sent to firm ?</b>		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
<b>QBR questions (key issues to be considered)</b>	1.What is the effect of aripiprazole on the steady state plasma levels/pharmacokinetics of the antidepressants escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine	
<b>Other comments or information not included above</b>		
<b>Primary reviewer Signature and Date</b>		
<b>Secondary reviewer Signature and Date</b>		

**CC: NDA 21436 S018 HFD-850 (Electronic Entry or Lee), HFD-130 (CSO), HFD-860 (Jackson, Mehta, Baweja ), CDR (Biopharm-CDR)**

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Andre Jackson  
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Mehul Mehta  
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BIOPHARMACEUTICS