Permeability – Permeability studies were conducted with the Caco-2 cell monolayers cultured between 14 and 21 days and the cell passage numbers were between 20 and 40. The results are shown in Table 12:

Table 14. Permeability Across Caco-2 Cell Monolayer (Apical to Basolateral, N=3)

	Aripiprazole		Metoprolol		Mannitol	
Apical pH	Initial C	Pc (nm/sec)	Initial C	Pc (nm/sec)	Initial C	Pc (nm/sec)
5.5	83μM	26±15	195 μM	74±1	5 μM	20±2
6.5	43 μM	47±12	201 μM	71±3	5 μM	18±2
7.4	4 μM	ND	195 μM	154±12	5 μM	20±1

ND Pc value cannot be determined due to limited solubility and significant nonspecific binding to Caco-2 cell device (poor recovery<5%).

Aripiprazole is a base. Other basic drugs like acebutalol, timolol and cimetidine all had similar permeability values (47-49 nm/sec) with absorption ranging from 40 to 95% in humans. The permeability of aripiprazole at an apical pH of 6.5 (47 nm/sec) is consistent with moderate absorption-87% for the absolute bioavailability of aripiprazole tablet.

Dissolution – [redacted]

Conclusion: Based on its solubility, permeability and dissolution performance, aripiprazole can be classified as BCS Class IV drugs.

2. ***What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure? Is there a biowaiver request?***

For NDA registration, 2-, 5-, 10-, 15-, 20-, and 30-mg tablets are proposed for marketing. Of these six tablet strengths, 5-, 10- and 15-mg tablets have been used in clinical trials in the U.S. The 2-, 20- and 30-mg strengths tablets have not been used in any clinical trials. The 5-, 10- and 15-mg tablets are designed based on their corresponding clinical formulations, with a minor change in shape and addition of colorants for aesthetic and commercial purposes. The differences in composition, when comparing the 5-, 10- and 15-mg trade and clinical tablet formulations, are considered minor and comparable dissolution profiles in three pH ranging media were provided.

Bioequivalence: Bioequivalence has been established between the 30-mg commercial tablet and 3x10 mg commercial tablets but not between the 1x15 mg and 3x5 mg tablets. The AUC of aripiprazole was comparable between 1x15 mg commercial tablet and 3x5 mg commercial tablets, but the C_{max} was 18% lower following 1x15 mg tablet with 90% CI of 0.73 and 0.93. Biowaiver is requested for strengths lower than the 30 mg tablet.

Formulation composition: Formulas of aripiprazole tablets are shown in Table 15:

Table 15. Formulas of Aripiprazole 2-, 5-, 10-, 15-, Original 20- and 30-mg Tablets (mg with %w/w)

Ingredient	2-mg	5-mg	10-mg	15-mg	20-mg	30-mg
Aripiprazole	2.0 (2.11)	5.0 (5.26)	10.0 (10.53)	15.0 (15.79)	20.0 (15.79)	30.0 (15.79)
Lactose monohydrate						
Starch (Corn) (NF)						
Microcrystalline cellulose						
Hydroxypropyl cellulose						
Magnesium Stearate						
Coloring agent						
Total						
Tablet color	Green	Blue	Pink	Yellow	Red	White
Shape	Rectangular	Rectangular	Rectangular	Round	Round	Round

The 2-, 5-, 10- and the 15-mg tablets are essentially proportionally similar; i.e., the total tablet weight is the same with the only change being the amount of drug with a corresponding change in the amount of lactose and the presence of a different colorant in the range of

The formulations of the 20- and 30-mg tablets were originally developed to be basically proportionally similar to the 15-mg tablet. However, the original 20- and 30-mg tablets exhibited less than complete and slower dissolution than other aripiprazole tablet strengths in pH 1.2 medium. To improve the dissolution at pH 1.2, the 20- and 30-mg tablets have been re-designed to be proportionally similar to the 10-mg tablets. As a result, the dissolution of the current 20- and 30-mg tablets at pH 1.2 is markedly improved. Formulas of aripiprazole 10-, 20- and 30-mg tablets are shown below:

Table 16. Formulas of Aripiprazole 10-mg, Current 20-mg and 30-mg Tablets

Ingredient	Function	10-mg	20-mg	30-mg
Aripiprazole (NC)	Active Ingredient			
Lactose monohydrate (NF)	Diluent			
Starch (Corn) (NF)	Diluent			
Microcrystalline cellulose (NF)	Diluent			
Hydroxypropyl cellulose (NF)	Binder			
Magnesium Stearate (NF)	Lubricant			
Coloring agent				
Total weight (mg)				
Tablet color				

The 10-, 20- and 30-mg tablets are proportionally similar; i.e., all the ingredients are in the same proportion between the three strengths except for the colorant, which is in the range of 0% to 0.02% w/w. The percentage of the other ingredients (microcrystalline cellulose, corn starch, hydroxypropyl cellulose and magnesium stearate) are identical across the entire range of the tablet strengths from 2-mg to 30-mg.

Dissolution Profile Comparison: Because the low solubility of aripiprazole in pH >5, less than of the drug released in the pH 6.8 dissolution medium. The solubility of aripiprazole reaches its at pH 4.0, therefore, was observed for all tablet strengths. The sponsor proposed this medium for the NDA method. The supportive evidence is that when aripiprazole tablets are stored under conditions of high temperature and high humidity, aripiprazole anhydrous form is converted to the monohydrate form

over time and increased level of monohydrate showed a decrease in dissolution rate in this dissolution medium.

However, the pH 4.0 buffer is considered nondiscriminative by the OCPB reviewer and gastric pH is recommended for aripiprazole dissolution test. In gastric pH, the original 20- and 30-mg tablets showed slower dissolution, which is likely to be due to higher drug concentration (—) in these tablets. The higher surface concentration of aripiprazole in these tablets, facilitates rapid formation of an insoluble sticky layer/HCl salt on the surface of disintegrating particles, that inhibits dissolution of drug. To enhance dissolution of the original 20- and 30-mg tablets, a direct scale-up of 10-mg tablet ( ) was used and the dissolution of the current 20- and 30-mg tablets at pH 1.2 is markedly improved. Due to limited solubility at pH 1.2 medium, it is necessary to increase paddle speed from 50 rpm to 60 rpm to reach — drug release in 30 minutes.

Figure 3. Dissolution profiles of 2-, 5-, 10-, 15-, 20- and 30-mg trade tablets at pH 1.2/60rpm

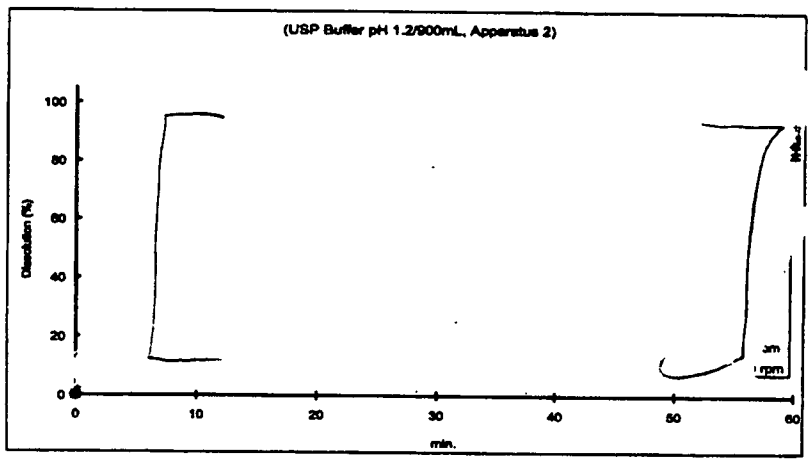
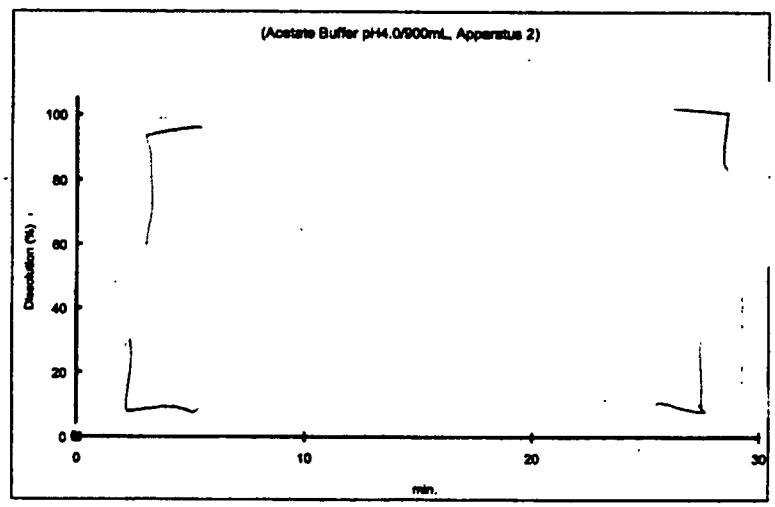


Figure 4. Dissolution profiles of 2-, 5-, 10-, 15-, 20- and 30-mg trade tablets at pH 4.0/50 rpm



Conclusion: Since the following criteria are met for aripiprazole, the sponsor's biowaiver request can be granted:

- the pharmacokinetics of aripiprazole is linear (5-30 mg);
- the 30-mg aripiprazole trade tablet is bioequivalent to 3x10 mg trade tablets;
- the lower strengths are compositionally proportional to the 30-mg strength;
- the lower strengths have dissolution performance comparable to that of the 30-mg tablet in three dissolution media (i.e., pH 1.2, pH 4.0 and pH 6.8).

3. ***What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?***

Food Effect: Following a single 15 mg dose, a high fat meal increased C_{max} and AUC of aripiprazole and OPC-14857 by less than 20% and delayed their T_{max} by 3 hours and 7 hours, respectively. The sponsor concludes that aripiprazole can be administered without regard to meals. However, due to the limited solubility of aripiprazole drug substance and nonrapid dissolving nature of the tablet in gastric pH, food effect should be conducted on the highest strength (30 mg). The sponsor was requested to conduct this study during pre-NDA meeting.

4. What is the effect of gastric pH on aripiprazole bioavailability?

Gastric pH Effect: The effect of increased gastric pH by concomitant famotidine administration (40 mg single dose) on aripiprazole pharmacokinetics (15 mg single dose) was studied in 16 healthy subjects. Changes in major pharmacokinetic parameters of aripiprazole and its metabolites are:

Table 17. Changes (%) in Pharmacokinetic Parameters after Concomitant Aripiprazole and Famotidine Administration Compared to Aripiprazole Alone

	Aripiprazole			OPC-14857		OPC-3373	
Parameter	C_{max}	AUC_∞	CL/F	C_{max}	AUC_∞	C_{max}	AUC_t
Arip+Famotidine (n=12)	-37%	-13%	+15%	-21%	-15%	-57%	-51%

The solubility of aripiprazole is pH-dependent, its solubility decreasing with increasing pH. The results of this study suggest that the increase in gastric pH by famotidine was prolonged enough to influence the solubility of aripiprazole and hence its absorption.

5. What is the effect of polymorphic form change on aripiprazole bioavailability?

When aripiprazole tablets are stored under conditions of high temperature and high humidity, aripiprazole anhydrous form is converted to the monohydrate form over time, which has a lower solubility. Bioavailability study showed that tablets containing 20-30% monohydrate were bioequivalent to tablets containing 100% anhydrous (reference) with respect to C_{max} and AUC demonstrating that formation of less than 20% monohydrate in aripiprazole tablets has no effect on *in vivo* performance. When tablets containing 100%

monohydrate form were compared to tablets containing the anhydrous form, only the 90% confidence interval for C_{max} (0.73, 0.93) failed meeting BE criteria.

6. What are the proposed dissolution method and dissolution specifications?

The proposed dissolution method is as follows:

Apparatus: USP Apparatus 2 (paddles) at 60 rpm
Medium: 0.1 N HCL (pH 1.2) at 37±0.5 C°
Specification: — in 30 min

Since the mean dissolution rate reached — for all strengths, the FDA specification of NLT — in 30 min is appropriate.

4.6 Analytical

The analytical methods used for the determination of aripiprazole were highly sensitive and specific.

All methods were fully validated in accordance with FDA Bioanalytical Validation Guidelines and regulatory requirements. They are acceptable.

Number of Pages Redacted 28

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Draft Labeling
(not releasable

Individual Study Review

Bioavailability and Bioequivalence Studies

Study 96-203 (Vol. 6-10): ***Single Dose Evaluation of the Safety and Relative Bioavailability of OPC-14597 [redacted], and Tablet in Normal Subjects***

The objectives of this study were to assess the safety profile of OPC-14597 (aripiprazole) administered as an [redacted] and to determine the relative bioavailability of OPC-14597 [redacted], and tablet in order to choose a formulation for a subsequent radiolabeled study.

The study had two phases. Phase I was an open label, sequential dose ascending (1, 5, 10 and 20 mg) study in which OPC-14597 in [redacted] (OPC-14597 bulk powder Lot #97B71M) was administered to 9 healthy male subjects orally after an overnight fast. Phase 2 was an open label, randomized, single-dose, two-way crossover study in which 20 mg of OPC-14597 was administered orally to another 6 male healthy volunteers as a [redacted] (20 mg, Lot #93H79M) or tablet (2x10 mg, Lot #5K75A010) in each dosing period. There was a 5-day washout period between dosing with the [redacted] and tablet. Blood samples were collected for 12 days and urine samples were collected for 48 hours following the administration of study drug for determination of OPC-14597 in plasma and urine and its metabolites in urine. All participants were Caucasians. The PK parameters for OPC-14597 following single oral doses [redacted], Tablet (T) and [redacted] to healthy subjects (n=3 in each dosing) are as follows:

Table 1. Pharmacokinetic Parameters after Single Doses of [redacted] Tablet and [redacted] (N=3)

Dose (mg)	C_{max} (ng/ml)	AUC_∞ (ng.h/ml)	T_{max} (h)	$t_{1/2}$ (h)	CL/F (ml/h/kg)	Vz/F (L/kg)
[redacted]						
T-20						

Data represent Mean±SD

Table 2. Urine OPC-14597 and Its Metabolites Excretion

	A_{e48} (μg)				
Dose (mg)	OPC-14597	OPC-14857	OPC-3373	DM-1451	OPC-1533
[redacted]					
T-20	2.72±6.67	26.58±24.67	670.8±217.4	2.86±3.26	47.78±117.02
Parent drug	f_{e48} 0.003-0.014%		CL_R 0.0034-0.014 ml/h/kg.		
[redacted] e/Tablet					

No pharmacodynamic measurements were performed in this study. Safety measures included physical examinations, vital signs, AEs, hematology, clinical chemistry, urinalysis, and ECGs.

Summary

- Overall, plasma concentration of OPC-14597 increased approximately proportional to the dose.
- The C_{max} was similar between the [redacted] and tablet, whereas the AUC for the [redacted] was approximately 74% of that for the tablet.
- The dose normalized AUC for the tablet is similar to that from an [redacted] of OPC-14597.
- OPC-14597 has minimal renal clearance.
- OPC-14597 was better tolerated at the lower dose [redacted] than at the higher doses (5 and 10 mg [redacted] and [redacted] and tablet) among volunteers. Although AEs were experienced by most of the subjects, the AEs were generally mild to moderate and were not completely unexpected.
- There were no clinically significant changes in laboratory values, ECGs, vital signs, or physical examination findings.

Study 138-016 (Vol. 11-12): ***Open-Label, Randomized, Three-way Crossover Study of the Absolute Bioavailability of Aripiprazole 5 mg Commercial Tablet and Aripiprazole [redacted] with Reference to [redacted] in Healthy Subjects***

[redacted]

Table 1. Summary of Aripiprazole PK Parameters (Mean with CV %)

[redacted]

Table 2. Summary of Statistical Analysis for Dose-Normalized Aripiprazole PK Parameters

Treatment	Adjusted Geometric Mean, Ratio-Point Estimate (90% CI), AUC_{inf} (ng.h/ml)	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	AUC_{0-2h} (ng.h/ml)
5 mg Tablet	265, **0.87** (0.79, 0.95)	227, **1.02** (0.93-1.11)	3.9	3.37

Table 3. Summary of PK Parameters for the Active Metabolite OPC-14857

Treatment	Geometric Mean (CV%) AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h) (Median with range)
5 mg Tablet	264 (39)	1.97 (38)	60 (24-144)

Summary

- The absolute oral bioavailability of aripiprazole was 87%, indicating aripiprazole is nearly completely absorbed and undergoes minimal presystemic metabolism after oral administration.
-
- In this study the aripiprazole formulation was well tolerated with no adverse events leading to the discontinuation of any subjects. All AEs reported were mild to moderate in intensity. The safety results were consistent with the safety profile of aripiprazole in other studies conducted in healthy subjects.

Study 138-018 (Vol. 13-15): ***The Effect of a High Fat Meal and Intrasubject Variability on the Pharmacokinetics of Aripiprazole in Healthy Subjects***

The primary objective of this study was to assess the effect of high fat meal on the pharmacokinetic parameters of aripiprazole in healthy subjects. The secondary objective was to assess the intrasubject variability in aripiprazole PK in healthy subjects.

This was an open-label, randomized, three-period, two-treatment crossover study in healthy young adult subjects. A total of 45 subjects (31 males and 14 females; 35 Caucasians, 7 Blacks and 3 Hispanic/Latinos) were enrolled in the study and 37 subjects completed the study as designed. A single dose of 15 mg aripiprazole tablet (Batch #00D95A015A) was administered in a fasted condition (Treatment A) and within 5 minutes of consuming a high-fat breakfast (Treatment B) with a washout period of at least 21 days between each dose. Each subject was administered Treatment A, Treatment B, and a repetition of either A or B. Blood samples were collected for pharmacokinetic analysis up to 384 hours (0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48, 72, 96, 144, 192, 240, 288, 336, and 384 hours) post-dose. Subjects were monitored closely for adverse events throughout the study.

Table 1. Summary of Aripiprazole PK Parameters

Treatment 15 mg	C_{max} (ng/ml)	AUC_{∞} (ng.h/ml)	T_{max} (h)	$t_{1/2}$ (h)
Fasted Mean±SD (N=58)	53.2±14.0	3522±1803	4.0±2.4	75.3±29.0
Geometric Mean (CV%)	51.7 (26)	3291(51)		70.0 (38)
Fed Mean±SD (N=57)	59.2±13.0	4403±1986	6.8±3.2	83.8±31.4
Geometric Mean (CV%)	57.2 (22)	3895 (45)		77.7 (37)
Ratio of GM (90% CI)	**1.107** (1.048, 1.169)	**1.184** (1.143, 1.227)		
Intrasubjects CV%				
Fasted	18.0%	10.8%		
Fed	14.3%	7.7%		

Table 2. Summary of PK Parameters for the Active Metabolite OPC-14857

Treatment 15 mg	C_{max} (ng/ml)	AUC_{∞} (ng.h/ml)	T_{max} (h)	$t_{1/2}$ (h)
Fasted Mean±SD (N=58)	7.0±1.8	1461±508	64.1±27.5	101.9±46.9
Geometric Mean (CV%)	6.9 (26)	1381 (35)		94.2 (46)
Fed Mean±SD (N=57)	8.0±2.3	1829±749	71.6±29.2	118.3±64.6
Geometric Mean (CV%)	7.7 (29)	1695 (41)		106.5 (55)
Ratio of GM (90% CI)	**1.112** (1.0698, 1.157)	**1.141** (1.096, 1.189)		
Intrasubjects CV%				
Fasted	9.8%	10.7%		
Fed	11.5%	11.9%		

Summary

- A high fat meal increased the C_{max} and AUC_{inf} of aripiprazole or OPC-14857 by <20% and delayed T_{max} by 3 hours and 7 hours for the parent drug and its active metabolite, respectively following administration of a single 15 mg aripiprazole commercial tablet in healthy subjects.

- Following administration of a single 15 mg aripiprazole commercial tablet in healthy subjects, the intrasubject variability of aripiprazole and OPC-14857 for C_{max} were 18% and 10% (fasted) and 14% and 11% (fed), respectively. The intrasubject variability of aripiprazole and OPC-14857 for AUC were 11% and 11% (fasted) and 8% and 12% (fed), respectively.

- There were no serious adverse events (SAEs) in this study. There were a total of 125 AEs. The most frequently reported treatment-emergent AEs were mild to moderate nausea, headache, vomiting, sweating, lightheadedness and mild asthenia. Vomiting led to the discontinuation of study therapy in 3 subjects. There were no laboratory abnormalities in this study.

Study 138-015 (Vol. 16): ***Study of the Effects of Aripiprazole Monohydrated Content on the Bioavailability of Aripiprazole in Healthy Subjects (920008950 3.0)***

This was a bioequivalent study designed to assess the effects of aripiprazole monohydrate content on the pharmacokinetics of aripiprazole in healthy volunteers. In this 3-way

crossover study a total of 46 subjects received single-doses of aripiprazole as a reference formulation (Lot #99L77A015), prototype formulation 1 (containing 20% monohydrate, Lot #99L91A015A1) or prototype formulation 2 (containing 100% monohydrate, Lot #99L91A015B1). This study was terminated at the end of the first treatment period due to poor tolerability of the 15 mg dose of aripiprazole in healthy subjects (19 subjects withdrew consents).

Demographic Characteristics

N	Age (Yrs)	Gender		Race		
		Male	Female	Caucasian	Black	Hispanic/Latino
46	26±8.1 (18-45)	35 (76.1%)	11 (23.9%)	41 (89.1%)	1 (2.2%)	1 (2.2%)
				Asian/Pacific Islanders 3 (6.5%)		

Due to the high incidence of nausea and vomiting reported following administration of a single 15 mg dose of aripiprazole irrespective of formulation, a decision was made to terminate this study and initiate a new study at a lower dose of aripiprazole (10 mg, Protocol CN138-034).

Study 138-034 (Vol. 16-20): ***The Effect of Aripiprazole Monohydrate Content on the Bioavailability of Aripiprazole in Healthy Subjects***

The current tablet formulation of aripiprazole makes use of anhydrous form I drug substance. Upon exposure of these tablets to 45°C at 75% relative humidity for six weeks or more, drug form in these tablets converts to 100% monohydrate. Conversion to the monohydrate form is also seen at less extreme temperatures. Both anhydrous and monohydrate forms of aripiprazole are quite soluble in aqueous solution at pH less than 4.0. However, at pH 4.5, solubility of the anhydrous form is 144 mg/900 ml and that of monohydrate is 32.4 mg/900 ml. Thus, it is possible that the anhydrous and monohydrate forms of aripiprazole could have different *in vivo* dissolution rates and bioavailability.

The primary objective of this study was to determine whether 2 prototype forms of aripiprazole which contain different fractions of the monohydrate form were bioequivalent to a reference product prepared by the commercial process. A 15 mg dose was employed in the previous study, administered following an overnight fast. This study was terminated prematurely due to frequent nausea and vomiting. The current study was designed to assess the relative bioavailability of the same three formulations of aripiprazole at a reduced dose of 10 mg. In addition, in a further effort to improve tolerability, volunteers were asked to consume 8 oz of — (lemon-lime soda) 2 h prior to dosing and again at 2 h post-dose. It was anticipated that these changes would improve the tolerability. The lemon-lime soda at 2 h post-dose actually appeared to induce nausea and vomiting, so it was removed after 18 subjects had completed Period 1.

In this 3-way crossover study a total of 66 subjects received single-doses of aripiprazole as a reference formulation (anhydrous, 10 mg tablet, Batch #99C77A010C), prototype formulation 1 (containing 20%-30% monohydrate, 10 mg tablet, Batch #00C82A010B1) or prototype formulation 2 (containing 100% monohydrate, 10 mg tablet, Batch

#00C82A010A). Of 66 subjects, 47 subjects completed the protocol as designed and 19 subjects discontinued from the study early.

Demographic Characteristics

N	Age (Yrs)	Gender		Race		
		Male	Female	Caucasian	Black	Hispanic/Latino
66	27±8.0 (18-44)	36 (54.5%)	30 (45.5%)	60 (90.9%)	4 (6%)	2 (3%)

Table 1. Summary of Aripiprazole PK Parameters

Treatment 10 mg N=47	C_{max} (ng/ml)	AUC_{∞} (ng.h/ml)	AUC_{0-t} (ng.h/ml)	T_{max} (h)
(Mean±SD)				
A-Anhydrate	44.1±13.1	2975±1391	2692±1075	4.0±3.6
B-20% Monohydrate	40.6±13.4	2889±1296	2615±1031	4.2±2.8
C-100% Monohydrate	38.2±13.3	2793±1241	2495±1045	4.7±4.1
Geometric Mean (CV%)				
Anhydrate	42.7 (30)	2784 (45)	2542 (40)	3.0 (1.0, 24.0)
20% Monohydrate	38.9 (33)	2697 (45)	2468 (39)	3.0 (1.0-12.0)
100% Monohydrate	35.9 (35)	2558 (44)	2292 (42)	4.0 (1.0-24.0)
Ratio of GM (90% CI)				
B/A	0.91 (0.83, 1.01)	0.97 (0.91, 1.03)	0.97 (0.91, 1.04)	
C/A	0.84 (0.76, 0.93)	0.92 (0.87, 0.98)	0.90 (0.84, 0.96)	

Table 2. Summary of Pharmacokinetic Parameters for the Active Metabolite OPC-14857

Treatment 10 mg N=47	C_{max} (ng/ml)	AUC_{0-t} (ng.h/ml)	T_{max} (h)
(Mean±SD)			
A-Anhydrate	5.0±1.7	933±341	64.8±21.8
B-20% Monohydrate	4.9±1.7	898±328	67.4±23.3
C-100% Monohydrate	4.8±1.8	889±324	70.5±28.0
Geometric Mean (CV%)			
Anhydrate	4.8 (34)	891 (37)	60.9 (24-96)
20% Monohydrate	4.6 (35)	844 (36)	64.2 (48-144)
100% Monohydrate	4.4 (38)	817 (36)	65.9 (24-144)
Ratio of GM (90% CI)			
B/A	0.96 (0.90, 1.03)	0.95 (0.89, 1.01)	
C/A	0.92 (0.86, 0.99)	0.92 (0.86, 0.98)	

Table 3. Summary of Aripiprazole PK Parameters for Subjects without Emesis

Treatment 10 mg	C_{max} (ng/ml)	AUC_{∞} (ng.h/ml)	AUC_{0-t} (ng.h/ml)	T_{max} (h)
(Mean±SD)				
A-Anhydrate (N=40)	45.1±13.3	3009±1373	2720±1107	4.1±3.8
B-20% Monohydrate (N=39)	41.2±13.6	2825±1227	2570±964	4.3±3.0
C-100% Monohydrate (N=37)	38.8±14.3	2753±1270	2475±1093	4.5±4.3
Geometric Mean (CV%)				
Anhydrate	43.8 (29)	2754 (46)	2522 (41)	3.0 (1.0-24.0)
20% Monohydrate	39.3 (33)	2660 (43)	2444 (37)	3.0 (1.0-12.0)
100% Monohydrate	36.2 (37)	2504 (46)	2244 (44)	3.0 (1.0-24.0)
Ratio of GM (90% CI)				
B/A	0.90 (0.80, 1.00)	0.97 (0.91, 1.03)	0.97 (0.85, 1.01)	
C/A	0.82 (0.73, 0.93)	0.91 (0.85, 0.97)	0.89 (0.82, 0.96)	

Table 4. Summary of Pharmacokinetic Parameters for the Active Metabolite OPC-14857 for Subjects without Emesis

Treatment 10 mg	C_{max} (ng/ml)	AUC_{0-t} (ng.h/ml)	T_{max} (h)
(Mean±SD)			
A-Anhydrate	5.1±1.6	943±310	61.8±21.0
B-20% Monohydrate	4.9±1.7	878±278	64.0±20.1
C-100% Monohydrate	4.9±1.9	899±325	68.8±27.8
Geometric Mean (CV%)			
Anhydrate	4.9 (32)	880 (33)	48 (24-96)
20% Monohydrate	4.7 (34)	836 (32)	72 (48, 144)
100% Monohydrate	4.4 (39)	804 (36)	72 (24, 144)
Ratio of GM (90% CI)			
B/A	0.95 (0.88, 1.02)	0.95 (0.89, 1.02)	
C/A	0.91 (0.84, 0.98)	0.91 (0.85, 0.98)	

The criteria for bioequivalence were satisfied all comparisons except that of C_{max} for parent drug between the 100% monohydrate and the anhydrous (reference) formulations. Some subjects had pre-dose concentration values greater than 5% of the C_{max} value. However, these pre-dose concentration values were equally distributed among the three treatments. These subjects were included in the bioequivalence evaluation and there were no statistically significant sequence or formulation carryover effects detected in the analyses of variance. Therefore, these pre-dose concentration values are not expected to affect the results of the study.

Summary

- Tablets containing 20-30% monohydrate (prototype Formulation 1) were bioequivalent to tablets containing anhydrate (reference) with respect to C_{max} and AUC.

- The criteria for BE were satisfied all comparisons except that of C_{max} for parent drug between the 100% monohydrate (prototype Formulation 2) and the reference formulations.

- There was a 23 to 25% incidence of nausea and 9% (Prototype 2) to 19% (reference treatment) incidence of vomiting.

Study 138-035 (Vol. 21-23): ***Bioequivalence of Aripiprazole in Healthy Subjects when Administered as a 15 mg Commercial Tablet as Compared with 3x5 mg Commercial Tablet***

This was an open-label, randomized, two-period, two-treatment, crossover study in healthy subjects. A total of 60 subjects were enrolled and received aripiprazole tablets. Of these, 49 subjects completed the protocol as designed and 11 subjects discontinued from the study early. Each subject received two single doses of 15 mg aripiprazole, either as a 15 mg tablet or as 3x5 mg tablets, separated by 21 days. Blood samples were collected for pharmacokinetic analysis up to 384 hours (17 days) post-dose.

Demographic Characteristics

N	Age (Yrs)	Gender		Race		
		Male	Female	Caucasian	Black	Hispanic/Latino
60	30±8.5 (19-45)	32 (53.3%)	28 (46.6%)	53 (88.3%)	2 (5.0%)	3 (5.0%)
			American Indian 1 (3.3), Asian/ Pacific Islander 1 (3.3%)			

Table 1. Summary of Aripiprazole Pharmacokinetic Parameters

Treatment N=49	C_{max} (ng/ml)	AUC_{∞} (ng.h/ml)	AUC_{0-t} (ng.h/ml)	T_{max} (h)
(Mean±SD)				
3x5 mg	67.5±17.6	4296±1848	4084±1720	4.2±2.1
1x15 mg	58.1±18.7	3996±1833	3773±1669	4.8±2.2
Geometric Mean (CV%)				
3x5 mg	65.4 (26)	3970 (43)	3785 (42)	4.0 (1.0, 12.0)
1x15 mg	54.4 (32)	3577 (46)	3381 (44)	5.0 (2.0-12.0)
Ratio of GM (90% CI)				
1x15 mg/3x5mg	0.83 (0.75, 0.92)	0.90 (0.84, 0.97)	0.89 (0.83, 0.97)	

Table 2. Summary of PK Parameters for the Active Metabolite OPC-14857

Treatment N=48	C_{max} (ng/ml)	AUC_{0-t} (ng.h/ml)	T_{max} (h)
(Mean±SD)			
3x5 mg	8.6±3.0	1578±689	62.0±21.5
1x15 mg	7.7±2.7	1427±531	67.5±32.3
Geometric Mean (CV%)			
3x5 mg	8.0 (35)	1453 (44)	48.0 (24.0-96.0)
1x15 mg	7.3 (35)	1339 (36)	48.0 (24.0-192.0)
Ratio of GM (90% CI)			
1x15 mg/3x5mg	0.90 (0.84, 0.97)	0.92 (0.87, 0.98)	

Table 3. Summary of Aripiprazole Pharmacokinetic Parameters (Supplemental Analysis*)

Treatment N=41	C_{max} (ng/ml)	AUC_{∞} (ng.h/ml)	AUC_{0-t} (ng.h/ml)	T_{max} (h)
(Mean±SD)				
3x5 mg	67.7±18.5	4365±1878	4166±1776	4.2±2.1
1x15 mg	57.7±18.8	3975±1739	3767±1606	4.9±2.4
Geometric Mean (CV%)				
3x5 mg	64.9 (27)	3984 (43)	3806 (43)	4.0 (1.0-12.0)
1x15 mg	53.2 (33)	3539 (44)	3346 (43)	5.0 (2.0-12.0)
Ratio of GM (90% CI)				
1x15 mg/3x5mg	0.82 (0.73, 0.93)	0.89 (0.82, 0.97)	0.88 (0.80, 0.96)	

*Excluding subjects with emesis or significant pre-dose plasma concentration

Table 4. Summary of PK parameters for the Active Metabolite OPC-14857 (Supplemental Analysis*)

Treatment N=34	C_{max} (ng/ml)	AUC_{0-t} (ng.h/ml)	T_{max} (h)
(Mean±SD)			
3x5 mg	8.3±2.8	1439±480	56.5±19.5
1x15 mg	7.5±2.8	1312±403	60.0±19.8
Geometric Mean (CV%)			
3x5 mg	7.7 (33)	1340 (33)	48.0 (24.0-96.0)
1x15 mg	7.1 (37)	1245 (31)	48.0 (24.0-96.0)
Ratio of GM (90% CI)			
3/5 mg/1x15 mg	0.92 (0.84, 1.00)	0.93 (0.86, 1.00)	

*Excluding subjects with emesis or significant pre-dose plasma concentration

Summary

- The C_{max} of aripiprazole was 18% lower following 1x15 mg commercial tablet and did not meet the criteria for bioequivalence when compared to the C_{max} following 3x5 mg commercial tablets. The AUC values were comparable between 3x5 mg and 1x15 mg tablets.

- The safety results were consistent with the safety profile of aripiprazole in other studies conducted in healthy subjects.

- A total of 20 vital sign abnormalities were reported for 13 subjects in the study. Ten were low supine pulse rates, 4 were elevated standing pulse rate, 5 were low standing blood pressure, and 1 was low supine blood pressure.

Study 138-054 (Vol. 24): ***Bioequivalence of Aripiprazole in healthy Subjects when Administered as a 15 mg Commercial Tablet as Compared with a 15 mg Clinical Trial Tablet***

The primary objective of this study was to demonstrate the bioequivalence of the 15 mg commercial tablet to the 15 mg clinical trial tablet. The secondary objectives were to assess the safety and the pharmacokinetics of the active metabolite, OPC-14857.

This was an open-label, randomized, two-period, two-treatment, crossover study in 80 healthy subjects. Each subject received Treatment A (clinical trial 15 mg tablet, Lot #99L77A015) and Treatment B (Commercial 15 mg tablet, Lot #00D95A015A) with at least 21 days between each treatment. Blood samples for pharmacokinetic analysis were collected up to 384 hours (17 days) post-dose. Subjects were monitored closely for adverse events throughout the study.

Demographic Characteristics

N	Age (Yrs)	Gender		Race		
		Male	Female	Caucasian	Black	Hispanic/Latino
80	34±7.4 (18-45)	50 (62.5%)	30 (37.5%)	40 (50%)	16 (20%)	24 (30%)

Eighty (80) subjects were randomized to treatment sequences and received a single dose during Treatment Period I. Due to early termination of the study by the Sponsor, no subjects completed the protocol as designed. Pharmacokinetic data were not analyzed for this study since only one leg of the study was completed. In this study there were no deaths, discontinuations for adverse events or serious adverse events.

Study CN138-065 (Vol. 1-4, 2/27/02 Submission): ***Bioequivalence of Aripiprazole When Administered as 30 mg Proposed Commercial Tablet Compared with 3x10 mg Proposed Commercial Tablets in Healthy Subjects***

The primary objective of this study was to demonstrate bioequivalence of a single 30 mg dose of aripiprazole (proposed commercial tablets) when administered as 1x30 mg tablet as compared with 3x10 mg tablets. The secondary objectives were to assess the intrasubject variability in aripiprazole pharmacokinetics, the safety and the pharmacokinetics of the active metabolite, OPC-14857 in healthy subjects.

This was an open-label, randomized, three-period, two-treatment, crossover study in 48 healthy subjects. Each subject received Treatment A (30 mg aripiprazole as 3x10 mg, Batch #00D88A010A) and Treatment B (30 mg aripiprazole as 1x30 mg, Batch #01F80A030A) and a repetition of either Treatment A or Treatment B according to a randomization schedule with at least 28 days between each dose. Blood samples for pharmacokinetic analysis were collected up to 384 hours (17 days) post-dose. Subjects were monitored closely for the occurrence of adverse events, physical examination, vital signs, clinical laboratory results and ECGs.

Demographic Characteristics

N	Age	Gender		Race		
	(Yrs)	Male	Female	Caucasian	Black	Hispanic/Latino
48	35±7 (20-45)	11 (23%)	37 (77%)	27 (56%)	3 (6%)	18 (38%)

A total of 48 subjects were enrolled and received aripiprazole tablets. Of these, 35 subjects completed the protocol and 13 subjects discontinued from the study early. Thirty-seven (37) subjects received both Treatment A and Treatment B and had pharmacokinetic parameters available. As suggested by the FDA Guidance for Industry, data from studies where subjects experienced emesis within two times the median T_{max} after dosing are to be excluded from the summary statistics and bioequivalence analyses. Subjects 2, 12, 27, 33, 34, 36, and 47 had emesis within 10 h after dosing (median T_{max} for aripiprazole is 5 hours) and therefore were excluded from the statistical analysis.

Table 1. Summary of Aripiprazole Pharmacokinetic Parameters (N=30)

PK Parameter	3x10 mg	1x30 mg	3x10 mg	1x30 mg
	Arithmetic Mean±SD		Geometric Mean (CV%)	
C_{max} (ng/ml)	128.6±35.6	119.8±35.1	123.1 (28%)	115.1 (29%)
AUC_{inf} (ng.hr/ml)	7591±3528	7260±3070	6760 (46%)	6596 (42%)
AUC_{0-t} (ng.hr/ml)	7350±3296	7008±2840	6568 (45%)	6392 (41%)
T_{max} (h) Median (range)	3.75 (1.0-9.0)	3.75 (2.0-7.0)		
$T_{1/2}$ (h)	69.4±18.0	71.7±22.8		

Table 2. Summary of Statistical Analysis for Aripiprazole Pharmacokinetic Parameters (N=30)

	Geometric Mean (CV%)[a]		1x30 mg/3x10 mg	
Parameter	A: 3x10 mg	B: 1x30 mg	Pt. Estimate	90% CI
C_{max} (ng/ml)	122.8 (20)	115.0 (16)	0.94	0.87, 1.01
AUC_{inf} (ng.hr/ml)	6763.6 (10)	6636 (13)	0.98	0.93, 1.04
AUC_{0-t} (ng.hr/ml)	6571 (10)	6432 (13)	0.98	0.92, 1.04

[a] Intra-subject CV based on 15 subjects for 1x30 mg treatment and on 17 subjects for 3x10 mg treatment.

According to the sponsor, there were no statistically significant carryover, sequence or period effects. The intra-subject CVs for C_{max} AUC in both Treatments A and B were comparable.

Table 3. Summary of OPC-14857 Pharmacokinetic Parameters (N=30)

PK Parameter	3x10 mg	1x30 mg	3x10 mg	1x30 mg
	Arithmetic Mean±SD		Geometric Mean (CV%)	
C_{max} (ng/ml)	19.1±6.6	18.4±5.9	17.9 (34%)	17.4 (32%)
AUC_{inf} (ng.hr/ml)	3519±1181	3444±1156	3289 (34%)	3235 (34%)
AUC_{0-t} (ng.hr/ml)	3194±1051	3117±1013	2995 (33%)	2939 (33%)
T_{max} (h) Median (range)	48 (4.0-84)	48 (9.0-96)		
$T_{1/2}$ (h)	93.6±37.8	94.4±43.4		

Safety and Tolerability: A total of 190 adverse events (AEs) occurred during the study. All AEs were considered mild to moderate in intensity by the Investigator. Over 20% of the healthy subjects participating in this study experienced at least one episode of vomiting, illustrating the poor tolerability of the 30 mg dose of aripiprazole in healthy subjects. There were no deaths in this study. Two subjects were discontinued due to AEs, one with flu syndrome which was considered unrelated to study and the other due to a car accident which was considered serious and unlikely related to study drug.

ECG: According to the sponsor, there were no ECGs that met the Sponsor-defined criteria for potentially clinically significant changes from baseline (≥120 bpm or increase of ≥15 bpm - tachycardia, ≤50 bpm or decrease of ≥15 bpm - bradycardia; QT_c≥450 msec or ≥10% increase from baseline).

Summary

- Aripiprazole 30 mg proposed commercial tablets are bioequivalent to 3x10 mg proposed commercial tablets.
- The intrasubject variability for aripiprazole C_{max} and AUC in both 3x10 mg and 1x30 mg treatments were comparable.
- Single doses of 30 mg aripiprazole were poorly tolerated in healthy subjects.

Human Pharmacokinetic (PK) Studies

Study 96-201 (Vol. 25-29): ***A Study of the Absorption, Distribution, Metabolism and Excretion following Oral Administration of [^{14}C]-OPC-14597 (Aripiprazole) in Healthy Volunteers***

The objective of this study was to determine the absorption, distribution, metabolism and excretion of radioactivity and intact drug following a single 20 mg dose of [^{14}C]-OPC-14597 (aripiprazole) in healthy volunteers. In this open-label study, 20 mg dose of OPC-14597 (capsule, Lot #MD8344, specific activity=10 μCi/mg), radiolabeled with [^{14}C] on the quinolone ring, were administered orally to 12 healthy volunteers. All subjects were Caucasian males with mean age of 29 yrs (21-44 yrs). Blood, urine and fecal samples were collected prior dosing and for at least 192 hours post-dosing. A physical examination, 12-lead electrocardiogram (ECG), and laboratory safety tests were performed at screening, prior to dosing, and upon exiting the study. No pharmacodynamics were measured in this study.

Blood, plasma, urine and fecal radioactivity were measured by a ——— analysis was performed on urine and fecal samples with the ——— detectors. Plasma concentrations were determined by a ——— method.

Pharmacokinetics Results

Table 1. Summary of Pharmacokinetic Parameters for Total Radioactivity (mean±SD)

	C^*_{max} (ng /ml)	AUC^*_{∞} (ng.h/ml)	T_{max} (h)	$t_{1/2}$ (h)	CL/F (ml/h/kg)	V_z/F (L/kg)
Total	89±28	8384±3143	5 (2-24)	149±95	NC	NC
Parent	74±19	4738±2067	5 (2-12)	79±29	72±26	5546±4162
OPC-14857	9±3	1689±593	48 (24-168)	72±24	151±71	5546±4162?

*C_{max} is in units of ng-equiv/ml, and AUC is in units of ng-equiv.h/ml only for total radioactivity in plasma. NC-not calculated. Median with range for T_{max}.

Table 2. Mean Blood/Plasma (B/P) Ratio Based on Total Radioactivity Corrected for Hematocrit

N=12	Hematocrit	Mean B/P Ratio	Adjusted Mean B/P Ratio
	45.09±2.84	0.56±0.05	1.03±0.08

Table 3. Summary of Recoveries from Urine and Feces (% of Radioactive Dose)

Urine (total)	OPC-3373	OPC-3952	U-1	U-2		
25.52±3.98	19.2±4.07	5.18±0.91	0.82±0.50	0.33±0.18		
Feces (total)	Parent	OPC-14857	DM-1451	OPC-3952	U-4	U-5	U-6
55.18±6.60	18.32±10.9	3.28±1.92	14.93±5.67	14.68±5.37	0.44±0.80	4.88±2.98	0.41±0.40

Assay Performance

Table 4. Performance of Quality Control (QC) Samples during Liquid Scintillation Counting

QC Samples	Plasma (n=32)		Urine (n=36)		Whole Blood (n=40-44)		Feces (n=64-70)	
	dpm/ml	%Accuracy	dpm/ml	%Accuracy	dpm/ml	% Accuracy	dpm/ml	%Accuracy
H	10074	101.9±3.8	187753	107.7±2.3	9618	95.1±3.2	795960	95.3±7.3
M	4850	101.0±5.1	18775	100.3±2.2	4914	97.2±3.3	39790	95.8±7.2
L	779	98.2±4.9	1596	90.8±2.0	807	96.6±4.8	1861	96.3±7.2
LL	99	98.7±9.7	184	91.3±3.6	200	97.9±13.4	1020	101.1±8.5

Table 5. HPLC/MS/MS Assay Performance

Analyte	Retention Time (min)	Linear Range (ng/ml)	Intra-Day (% Accuracy) 3	15	200	Inter-Day (% Accuracy) 3	15	200 (ng/ml)
OPC-14597	8.4	1.00-250.00	96 (7.2)	101 (5.4)	89 (9.0)	99 (9.4)	100 (6.3)	89 (6.7)
OPC-14857	8.0	1.00-250.00	100 (12.6)	101(12.0)	92 (8.6)	100(9.8)	101 (9.2)	92 (6.7)
DM-1451	5.5	1.00-250.00	100 (9.8)	99 (12.9)	90 (7.2)	100 (10.2)	99 (10.7)	90 (6.3)
OPC-3373	6.4	2.50-250.00	100 (11.8)	101 (11.6)	92 (6.3)	103 (12.0)	100 (7.7)	93 (7.5)
DCPP	6.3	2.50-250.00	106 (14.4)	99 (15.3)	92 (11.1)	106 (9.6)	99 (10.1)	92 (7.6)
OPC-14714	7.3	NA						

Aripiprazole was the predominant species found in plasma, followed by its active metabolite, OPC-14857. Plasma concentrations of OPC-3373, DM-1451 and DCPP exceeded the lower limit of quantitation at only a few sampling times; therefore, PK analysis of these data was not performed. Radiochromatographic profiling in blood and plasma could not be done due to lack of sensitivity. In urine, OPC-3373 and U-3 were found to be the predominant species and two other metabolites: U-1 and U-2 were also found. Structural identification of U-3 was performed, and it was found to be a structural analog of OPC-3373 and assigned the name OPC-3952. Results of hydrolysis of urine and fecal samples indicated that there were no detectable glucuronide or sulfate conjugates present in either matrix.

Safety: Sixty-seven (67%) percent of the subjects experienced potentially drug-related treatment-emergent AEs that were mild to moderate in severity and resolved spontaneously. These AEs included dizziness, somnolence, nervousness, abnormal dreams, nausea, flatulence, constipation, dyspepsia, abdominal pain, chest pain, neck rigidity, and vasodilatation. Shifts in serum chemistry parameters from normal at baseline to low or high at the last visit were observed in a number of subjects (one to low SAT, one to high cholesterol, one to low urea nitrogen, and four to high triglyceride). These abnormalities were not judged to be clinically significant. There were no clinically significant changes in hematology or urinalysis, or in ECGs, vital signs, or physical examination findings.

Summary

- There was no preferential binding of [^{14}C]-OPC-14597 to red blood cells.
- Of the total radioactivity in plasma, 57% was due to the parent (OPC-14597) and 20% due to OPC-14857.

- Approximately 60% of the radiolabeled dose were recovered in the feces and 27% in the urine.

- Neither the parent (OPC-14597) nor the active metabolite (OPC-14857) was excreted in the urine; OPC-3373 and OPC-3952 were the major species present in urine.

- The parent (OPC-14597) drug, and OPC-3952 were the major species present in feces.

- Neither glucuronide nor sulfate conjugates of the parent drug or its metabolites were found in the urine or feces.

- A single 20 mg dose of aripiprazole was tolerated by normal volunteers with AEs being mild to moderate in severity and resolving spontaneously. There were no SAEs.

- There were no clinically significant changes in ECGs, vital signs, physical examination findings, or laboratory values.

Study 138-028 (Vol. 30-31): ***Disposition of Dual Labeled ^{14}C-Aripiprazole in Healthy Male Subjects following Single Oral Administration***

The objective of this study was to assess the pharmacokinetics, metabolism, and routes and extent of elimination of a single oral dose of dual labeled ^{14}C-aripiprazole in healthy male subjects. One of the [^{14}C] labels was introduced at the same position as that in the previous study; the additional [^{14}C] label in this study was introduced on the dichlorophenyl piperazine portion of the molecule. This was an open-label, single-dose study. Single doses of ^{14}C-aripiprazole (5 mg oral ethanol solution, 77.5 μC_i, Batch #N00235) were administered to 9 healthy male subjects (8 Blacks and 1 Caucasian) and 6 subjects completed the study. Blood was collected for pharmacokinetic and biotransformation analyses at selected time points over a 17-day period. Complete urinary and fecal output was collected over 17-day period, or until discharge, and analyzed for total radioactivity.

Table 1. Summary of Pharmacokinetic Parameters for Total Radioactivity
(Geometric mean with %CV, Median with range for T_{max}, Mean±SD for $t_{1/2}$)

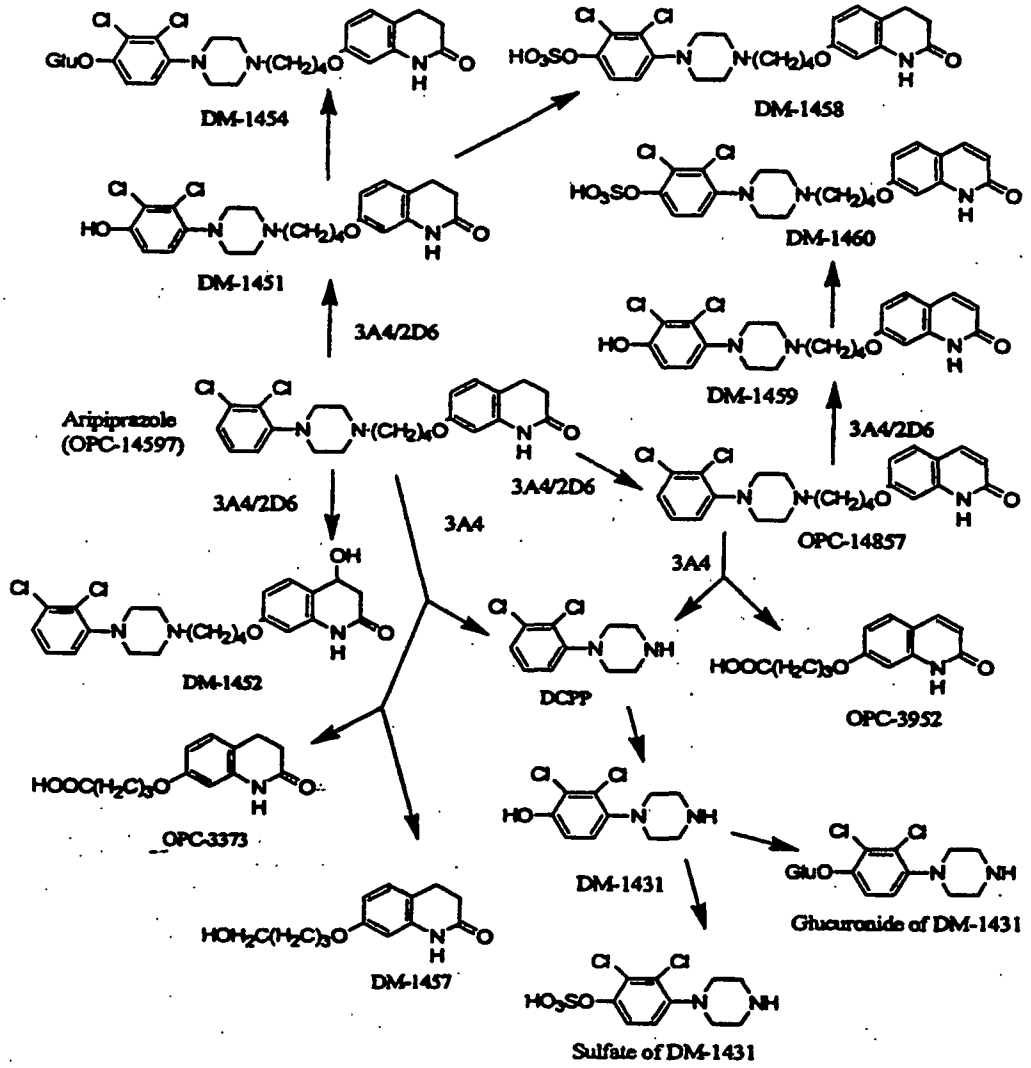
N=9	C^*_{max} (ng/ml)	AUC^*_{∞} (ng.h/ml)	AUC^*_{0-t} (ng.h/ml)	T_{max} (h)	$t_{1/2}$ (h)
Total	34.3 (25.2)	6349 (36.3)	4979 (32.4)	4.0 (1.5-24.0)	159.3±48.0
Parent	19.0 (38.5)	1142 (43.0)	950 (41.1)	4.0 (1.5-24.0)	117.7±83.7
OPC-14857	2.3 (30.2)		215 (61.2)	48.0 (5.0-96.0)	ND

C_{max} is in units of ng-equiv/ml, and AUC is in unit of ng-equiv.h/ml only for total radioactivity in plasma.

Table 2. Relative Distribution of Radioactivity Percent among Various Peaks in the Radiochromatographic Profiles of Pooled Urine and Feces from Humans

	Urine (0-384 h)		Feces (0-384 h)
Total %UR (N=6)	35.7±3.5	%FE (N=6)	43.9±18.1
OPC-3373	42%	DM-1451	53%
Glucuronide of DM-1431	14%	DM-1459	19%
OPC-3952	10%	OPC-14857	9%
Sulfate of DM-1431	8%	Aripiprazole	8%
DM-1431	5%	DM-1452	trace
DM-1454, DM-1457	1%, 1%	Others	8%
DCPP	trace		
Others	14%		
Total	95%	Total	97%

Figure 1. Proposed Aripiprazole metabolic Pathways



Summary

- During 384 hours collection period following a 5 mg oral dose of dual label ^{14}C-aripiprazole, the mean total recovery of radioactivity in urine and feces combined was 80% (36% in urine and 44% in feces) of the administered radioactivity dose.

- The C_{max}, AUC_{inf} and AUC_{0-t} for aripiprazole in plasma were approximately 55%, 18%, and 19%, respectively, of the corresponding C_{max}, AUC_{inf} and AUC_{0-t} for radioactivity in plasma.

- The AUC_{0-t} values for the active metabolite OPC-14857, relative to aripiprazole and radioactivity, corrected for molecular weight, were 23% and 4%, respectively.

- After oral administration of single 5-mg oral dose of dual C-14 labeled aripiprazole to healthy male volunteers, the parent drug was found to be the predominant drug-related component in plasma. The major metabolites in plasma was the biologically active, dehydro analog of aripiprazole (OPC-14857). Other metabolites were a minor part of the plasma radioactivity.

- Aripiprazole was eliminated mainly by metabolism, as only 8% of the radioactivity in feces was recovered unchanged. Aripiprazole was not detected in urine. Urinary metabolites included N-dealkylation, dehydrogenation products and DCPP-derived metabolites. The fecal metabolites resulted from aromatic hydroxylation and dehydrogenation of the parent drug. The active dehydro analog also appeared to be eliminated by N-dealkylation and aromatic hydroxylation.

- The primary metabolic pathways identified in this study, together with the results of the previous *in vitro* metabolic studies, show that the P450 isoforms CYP3A4 and CYP2D6 are the primary enzymes responsible for the elimination of aripiprazole in humans.

- Direct glucuronide or sulfate conjugation of aripiprazole or OPC-14857 was not observed in humans.

- The DCPP-derived metabolites as well as other minor unknown metabolites in the urine and feces were either not found or were insignificant (about 1%) in human plasma, indicating that the systemic exposure to DCPP and DCPP-derived metabolites in humans was insignificant.

- In this study the 5-mg aripiprazole oral ethanol solution was well tolerated with no adverse events leading to the discontinuation of any subject. All AEs reported were mild to moderate in intensity.

Study 138-061 (Vol. 32-34): ***Assessment of the Biliary Excretion of DM-1454, DM-1458 and Dehydro-DM-1458 during Multiple Dose Administration of Aripiprazole to healthy Subjects***

The primary objective of this study was to determine the presence of DM-1454 (DM1451 glucuronide), DM1458 (DM-1451 sulfate) and dehydro DM-1458 (DM-1460) in the bile of healthy subjects administered aripiprazole 15 mg on Day 1 and 30 mg QD for the next 6 days under fasted conditions. Plasma concentrations of aripiprazole and these metabolites were also determined.

Sixteen healthy subjects (11 male and 5 female; 5 Caucasians, 3 Blacks, 7 Hispanic/Latino and 1 Arabic) were enrolled in this open-label, multiple dose study. On Day 1, all subjects received a single 15 mg aripiprazole tablet (Batch #00F90A015B). The first 8 subjects received 2x15 mg tablets in the morning of Day 2-7. Due to the poor tolerability, the next 8 subjects received 1x15 mg aripiprazole tablet on Day 2-7. Approximately an hour after the administration of the dose, an oral-gastric tube was inserted and advanced by the volunteer. Placement near the ampulla of Vater was confirmed via fluoroscopy. Bile samples were collected continuously as multiple fractions using suction from 4 to 6 hours following the dose. Cholecystokinin at 20 ng/kg was given to stimulate gall bladder concentration at 5 hr following the dose. The oral-gastric tube was removed at 6.25 hr post-dose. Blood samples were collected for pharmacokinetic analysis up to 24 hours post-dose on Day 7. Subjects were monitored closely for adverse events throughout the study.

Table 1. Summary of Pharmacokinetic Parameters (Geometric Mean with CV%)

Dose	Gender	DM-1454		DM-1458		DM-1460	
		C_{min}	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}
Bile		(ng/ml)		(ng/ml)		(ng/ml)	
30 mg	All (N=8)	201 (118)	9346 (66)	64.7 (104)	4254 (81)	21.2 (113)	1269 (71)
	Male (n=6)	112 (104)	9064 (57)	43 (144)	4868 (78)	11.6 (90)	1219 (79)
	Female (n=2)	1157 (27)	10245 (98)	220 (37)	2840 (44)	128 (22)	1429 (44)
15 mg	All (N=8)	82.4 (196)	6679 (82)	31.3 (234)	3632 (49)	10.3 (264)	608 (82)
	Male (n=5)	150.4 (161)	5272 (76)	54.0 (186)	4045 (40)	19.0 (211)	599 (92)
	Female (n=3)	30.2 (80)	9908 (80)	12.6 (82)	3035 (76)	3.8 (26)	625 (66)
Plasma							
30 mg		LLQ		1.0-4.4		1.2-1.3 (Subject 6 only)	
15 mg		LLQ except 2 subjects		1.0-2.9 (few subjects)		LLQ	

Table 2. Summary of Plasma Pharmacokinetic Parameters (Geometric Mean with CV%)

Dose	Gender	T_{max} (h)	C_{max} (ng/ml)	AUC_t (ng.h/ml)	AUC Ratio (Met/Parent)
Aripiprazole					
30 mg	All (N=8)	1.5 (1.0-3.0)	292.3 (23)	4578 (25)	
	Male (n=6)	2.0 (1.0-3.0)	278.0 (24)	4470 (28)	
	Female (n=2)	1.0 (1.0-1.0)	339.8 (21)	4918 (23)	
DM-1458					
30 mg	All (N=7)	4.0 (2.0-10.0)	2.4 (43)	47.5 (41)	0.009 (16)
	Male (n=5)	4.0 (3.0-10.0)	2.2 (49)	44.2 (42)	0.009 (13)
	Female (n=2)	3.0 (2.0-4.0)	3.0 (40)	54.6 (49)	0.009 (28)

Table 3. Summary of Plasma Pharmacokinetic Parameters (Geometric Mean with CV%)

Dose	Gender	T_{max} (h)	C_{max} (ng/ml)	AUC_t (ng.h/ml)	AUC Ratio (Met/Parent)
Aripiprazole					
15 mg	All (N=8)	2.5 (0.5-3.0)	189 (17)	3359 (13)	
	Male (n=5)	3.0 (2.0-3.0)	174 (8)	3167 (13)	
	Female (n=3)	1.0 (0.5-2.0)	218 (17)	3707 (7)	
DM-1458					
15 mg	All (N=5)	6.0 (1.0-6.0)	1.6 (45)	39.1 (24)	0.009 (16)
	Male (n=2)	4.0 (3.0-6.0)	1.0 (48)	NC	NC
	Female (n=3)	6.0 (1.0-6.0)	2.1 (29)	39.1 (24)	0.009 (16)

Safety and tolerability: There were no deaths or other serious adverse events. There were no discontinuations due to adverse events. However, since 30 mg dose on Days 2-7 was poorly tolerated by first 8 subjects enrolled, the next 8 subjects received 15 mg aripiprazole QD for 7 days. The most frequently reported treatment-emergent AEs were insomnia, anxiety, somnolence, agitation, asthenia, nervousness, arthralgia, disorder lacrimation, salivation and dyspnea. The oral-gastric-tube and bile collection procedures were well tolerated.

Summary

- Metabolites DM-1454, DM-1458, and DM-1460 were present in bile of healthy subjects administered 15 or 30 mg aripiprazole QD for 1 week.

- Aripiprazole and its metabolite DM-1458 were present in plasma of healthy subjects administered 15 or 30 mg aripiprazole QD for one week; DM-1454 and DM-1460 were below the limits of quantitation in most subjects.

- The highest bile concentrations of these three metabolites in healthy subjects were no more than 6% of the lowest bile concentrations found in monkeys administered 25-75 mg/day for 39 weeks.

- The highest bile concentrations of these three metabolites in healthy subjects were below (<6%) of their limits of *in vitro* solubility in human bile.

- The safety results were consistent with the safety profile of aripiprazole in other 15-30 mg multiple dose studies conducted in healthy subjects.

Study 93-201 (Vol. 35-39): ***Multiple Ascending Dose Tolerability and Pharmacokinetic Study of OPC-14597 in Healthy Young Male Volunteers***

The objective of this study was to evaluate the tolerability and pharmacokinetic characteristics of multiple ascending doses of OPC-14597 (aripiprazole) up to 20 mg/day for 14 days in healthy male young volunteers. This was a single-center, double-blind, randomized, placebo-controlled study.

Disposition of Subjects (N) and Dosing Schedule

Dosing (mg/day) For 14 days	5 (Lot 3D82-5)	10 (Lot 3D82-10)	15 (Lot 3D82-15)	20 5+15	Placebo (Lot 3D82-P)
Randomized	6	8	6	6	13
Completed	6	6+2	6	5	12
Race					
Caucasian	5	5	5	4	11
Black	1	2	0	1	0
Hispanic	0	1	0	1	1

In the 10 mg/day treatment group, 2 subjects withdrew from the study due to personal reasons and they were replaced. In the 20 mg/day group, one subject withdrew due to adverse events.

Full pharmacokinetic profile on Days 1, 8 and 14 was obtained. Trough concentrations were collected in the morning of Days 3 through 7 and Days 10 through 13. Half-life determination was made by measurements on Days 15 through 20. Safety measurements included adverse events, clinical laboratory tests, prolactin, vital signs, EEG, ECG, and physical examination.

Table 1. Summary of Main Pharmacokinetic Parameters (Mean±SD)

Parameter	Day	5 mg/day (N=6)	10 mg/day (N=6)	15 mg/day (N=6)	20 mg/day (N=5)
C_{max} (ng/ml)	1	27.3±4.9	38.9±6.4	70.8±6.3	65.6±16.5
	14	98.2±28.1	162.5±53.4	242.0±36.0	392.7±180.9
T_{max} (h)	1	3.4±0.9	5.0±2.2	3.5±1.5	6.8±3.0
	14	3.3±1.2	2.8±1.2	3.0±0.6	3.8±1.1
$t_{1/2}$ (h)	14	56.1±8.8	52.9±10.4	47.4±9.6	68.1±22.9

Summary

Pharmacokinetics

- The kinetic processes of OPC-14597 were linear for the plasma concentrations resulting from daily dosing as high as 20 mg/day for 14 days.

- The elimination half-life ranged from about 50 to about 100 hours among subjects with the apparent systemic clearance (CLs/F) of about 3.45 L/hr.

- Most subjects achieved a steady state before Day 14 of dosing, and those which did not achieved at least 90% of steady state by Day 14.

- The pharmacokinetics of OPC-14597 for daily doses as high as 20 mg/day were described by a two compartment open model with first order absorption. The results in parameter estimates were similar to those found by a model independent analysis.
- The relative variance in the elimination kinetics appeared to increase as the dose level increased. However, this does not appear to be an apparent saturation or induction of the elimination pathways.

- The metabolites (DM-1451, hydroxylated metabolite and OPC-3373, cleaved carboxylic acid moiety) observed in rats did not appear to exist at a measurable level in these normal human subjects for the dose levels administered.

Safety

- OPC-14597 exhibits adverse effects which are generally mild to moderate in nature and disappear with continued use of the drug.

- The incidence of orthostatic hypotension was high in both placebo and OPC-14597 treatment groups, but was higher in the OPC-14597 treatment group with no clear dose-related relationship.

- There were no clinically significant changes in clinical chemistry, hematology, urinalysis, ECG and EEG results.

- Prolactin levels were not increased by OPC-14597 treatment.

- OPC-14597 appears to be safe when given in doses up to 20 mg to normal male volunteers over a period of 14 consecutive days.

Study 93-204 (Vol. 40-43): ***Multiple Dose Tolerability and Pharmacokinetic Study of Titrated Doses of OPC-14597 in Healthy Male Volunteers***

The objective of this study was to evaluate the tolerability and pharmacokinetic characteristics of multiple doses of OPC-14597 titrated from 10 mg to 30 mg per day for 14 days. Eleven (11) healthy male volunteers (91% Caucasian and 9% Black, aged from 18 to 40 years) were randomized to receiving either an active treatment or placebo. The subjects were dosed daily at 10 mg/day for Days 1 and 2, 20 mg/day for Days 3 and 4, and 30 mg/day for Day 5-14. Two subjects dropped out and did not complete the trial. Blood samples were obtained on Days 1, 10, and 14 at pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours post-dose. Trough blood samples prior to dosing were collected on Days 3-9 and 11-13. Additional blood samples were collected at 48, 72, 96, 120, and 144 hours after the last dose on Day 14 to determine the terminal half-life of OPC-14597.

Table 1. Summary of Model Independent PK Parameters (Mean±SD)

Day	Dose	Day	C_{max} (ng/ml)	AUC_{0-24} h (ng.hr/ml)	T_{max} (hr)
1-2	10 mg/day	1	39.8±5.6	621.6±112.5	4.2±2.3
3-4	20 mg/day				
5-14	30 mg/day	10	405.7±124.5	7430.0±2428.4	2.8±1.1
		14	452.2±132.3	8360.0±3402.6	3.0±0.7
			$t_{1/2}$ (hr)	CL/F (L/hr)	
			59.1±24.4 (37-97)	4.0±1.2 (2.13-5.21)	

Summary

Pharmacokinetics

- When the results from this study are compared to those of Study 31-93-201, the pharmacokinetics of OPC-14597 appear linear for the plasma concentrations resulting from daily dosing as high as 30 mg/day for 10 days.

- The elimination half-life ranged from about 37 to about 97 hours among subjects with the apparent systemic clearance (CLs/F) being about 4.0 L/hr.

- Most subjects achieved a steady state before Day 14 of dosing, and those who did not are at least 90% toward achieving steady state by Day 14.

- The pharmacokinetics of OPC-14597 for daily doses as high as 30 mg/day were described by a two compartment open model with first order absorption, which results in parameter estimates similar to those found by a model independent analysis.

- The relative variance in the elimination kinetics appeared to increase as the dose level increased. However, this does not appear to be an apparent saturation or induction of the elimination pathways.

- The metabolites (DM-1451, hydroxylated metabolite and OPC-3373, cleaved carboxylic acid moiety) observed in rats did not appear to exist at a measurable level in these normal human subjects for the dose levels administered.

Safety profile: OPC-14597 appears to be safe when given in doses up to 30 mg to normal volunteers over a period of 10 consecutive days, following 10 mg/day for 2 days and 20 mg/day for 2 days. The drug exhibits AEs that are generally mild to moderate in nature and decrease in frequency with continued use of the drug. Orthostatic hypotension and the inability to collect vital signs because of postural dizziness occurred early in the study in the active treatment only. There were no clinically significant changes in clinical chemistry, hematology, urinalysis, ECG and EEG results. Prolactin levels were not increased by OPC-14597.

Study 98-202 (Vol. 44): ***A Pilot Study to Determine the Tolerability of Aripiprazole Doses Higher Than 30 mg Administered Orally in Patients with a Diagnosis of Schizophrenia or Schizoaffective Disorder***

The objective of this study was to investigate the tolerability and safety of aripiprazole at doses higher than 30 mg per day, up to 90 mg per day. Secondary objectives were (1) to evaluate the pharmacokinetic parameters after steady state was achieved and during the washout phase using the doses of 45, 60, 75, and 90 mg/day, and (2) to evaluate, on preliminary basis, the ability of aripiprazole at these higher dose levels to maintain a stable symptom profile in patients with schizophrenia or schizoaffective disorder.

The diagnosis and main criteria for patient inclusion was non-hospitalized men or women between 18 and 45 years of age, with a diagnosis of schizophrenia or schizoaffective disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), on stable dose of an oral antipsychotic drug (used as monotherapy) for at least one month prior to study screening. The test product used was 15 mg tablet (Lot #97K87A015B).

This was a double-blind inpatient pilot study designed to determine the tolerability and safety of aripiprazole at doses of 45 mg, 60 mg, 75 mg and 90 mg per day compared to 30 mg per day in patients with stable schizophrenia or schizoaffective disorder. Doses were evaluated as four consecutive steps, proceeding to the next step only after the tolerability of the previous dose was ascertained. An independent cohort of 5 patients was enrolled at each step with 2 receiving 30 mg dose as a control and 3 receiving either 45 mg, 60 mg, 75 mg, or 90 mg dose, escalated by 15 mg from the maximum dose received by the previous cohort. Patients were on the same dose for 14 days.

Disposition of Patients Enrolled in Study

Dose	30 mg	45 mg	75 mg	90 mg
Randomized to Active Treatment	9	3	3	3
Completed Study	8	3	3	2[a]

[a] One patient completed study treatment through Study Day 15, then withdrew consent. This patient's discontinuation was not recorded as being due to an adverse event.

Criteria for Evaluation

Efficacy - Rating scales completed during this study included Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI).

Safety - Safety was evaluated through medical review of reports of adverse events (AEs), vital sign measurements, electrocardiograms (ECGs), the results of physical examinations and clinical laboratory tests. Serum prolactin concentrations, and extrapyramidal symptoms (EPS) rating scales including Simpson-Angus Scale (SAS), Barnes Akathisia Scale (Barnes), and Abnormal Involuntary Movement Scale (AIMS). Electrocardiograms were centrally read by eResearch Technology (Philadelphia, PA).

Pharmacokinetics - Blood samples were collected for determination of plasma concentrations of aripiprazole, its principal metabolite, OPC-14857, and other metabolites (OPC-3373, DM-1451, and 2,3-DCPP), during steady state (prior to dosing on Day 1, 12, 13, 14, and 15) and during the post-treatment stabilization period (Day 15 post-dose through 21 at 1, 2, 4, 6, 8, 24, 36, 48, 72, 96, 120, and 144 hours after the last dose of aripiprazole).

Table 1. Patients with Potentially Clinically Significant Vital Sign Abnormalities

Subject	Dose	Study Day	SBP, Standing	Supine	DBP, Standing (mm Hg)	Supine
#9	30 mg	3	from 112 to 88			
#23		6/4	from 112 to 90	from 110 to 90		
#8	60 mg	6				from 80 to 48
#11	75 mg	14			from 84 to 50	
#18	90 mg	7, 9, 10	from 120 to 90			
#19		12	from 112 to 80			

One patient receiving 75 mg/day experienced tachycardia (from 95 bpm to 142 bpm), and increasing in QT_{cB} (from 421 to 475 msec) on Day 15. **See Pharmacometrics review.**

PK: only aripiprazole plasma concentrations for individual patient at each time point were provided. No PK analysis has been done.

Study 99-224 (Vol. 45-48): ***A Pilot Study to Determine the Tolerability of Aripiprazole Doses Higher than 30 mg Administered Orally in Adult Patients with a Diagnosis of Schizophrenia or Schizoaffective Disorder***

The objective of this study was to investigate the tolerability and safety of aripiprazole at doses higher than 30 mg per day, up to 90 mg per day. Secondary objectives were (1) to evaluate the pharmacokinetic parameters at steady state and in the washout phase for the doses of 45, 60, 75, and 90 mg/day, and (2) to evaluate, on preliminary basis, the ability of aripiprazole at these higher dose levels to maintain a stable symptom profile in patients with schizophrenia or schizoaffective disorder.

This was a randomized, double-blind, inpatient, pilot study addressing the safety and tolerability of 30 mg (control), 45, 60, 75, and 90 mg/day doses of aripiprazole over a 15-day treatment period for each dose, in adult patients with schizophrenia or schizoaffective disorder. Patients were genotyped to exclude poor metabolizers via CYP2D6 pathway. Ten-patient cohorts entered the double-blind therapy with three patients in each cohort randomized to the 30 mg (control) dose and seven patients randomized to a dose escalated by 15 mg from the maximum dose received by the previous cohort. For each patient, the study consisted of 5 days of placebo washout and 15 days of treatment followed by at least 6 days of washout.

Disposition of Patients Enrolled in the Study
(Only 15-mg tablet strength was used in this study: Batch # 99C77A015A)

Dose		30 mg	45 mg	60 mg	75 mg	90 mg
Active Treatment		12	7	7	7	7
Gender	Men	9	7	5	6	5
	Women	3	0	2	1	2
Race	Caucasian	5	2	2	4	2
	Black	6	1	5	1	4
	Hispanic	1	4	0	1	0
	Asian	0	0	0	1	0
	Other	0	0	0	0	1

Pharmacokinetic Results

Table 1. Summary of Pharmacokinetic Parameters for Aripiprazole (Day 15)

Variable	30 mg (n=9)	45 mg (n=4)	60 mg (n=4)	75 mg (n=7)	90 mg (n=5)
C^{ss}_{min} (ng/ml)	252±113	501±76	489±110	645±173	1102±517
C^{ss}_{max} (ng/ml)	419±116	719±17	767±122	959±240	1697±524
AUC_τ (ng.hr/ml)	7561±2883	14309±878	14741±1764	19105±5109	32712±13725
t_{max} (hr)	2.0 (1.0-6.0)	3.0 (1.0-6.0)	4.0 (2.0-4.0)	6.0 (4.0-24.0)	2.0 (2.0-6.0)
$t_{1/2}$ (ng/ml)	51.7±17.6	43.0±23.5	52.2±ND (n=2)	52.0±33.4	104.1±108.4?
CL^{ss}/F (ml/hr/kg)	52.0±30.7	34.5±4.4	43.7±10.8	46.2±15.8	35.6±12.5

Table 2. Summary of Pharmacokinetic Parameters for OPC-14857 (Day 15)

Variable	30 mg (n=9)	45 mg (n=4)	60 mg (n=4)	75 mg (n=7)	90 mg (n=5)
C^{ss}_{min} (ng/ml)	107.6±36.3	203.1±19.6	198.7±28.9	282.5±51.6	412.0±110.9
C^{ss}_{max} (ng/ml)	138.5±53.8	286.0±32.0	251.6±48.4	329.2±56.6	499.4±116.1
AUC_{τ} (ng.hr/ml)	2981±1246	5765±573	5208±709	7449±1261	10589±2580
t_{max} (hr)	4.0 (0-8.0)	5.0 (1.0-24.0)	6.0 (2.0-24.0)	6.0 (2.0-24.0)	6.0 (0-24.0)
$t_{1/2}$ (ng/ml)	66.2±16.7	50.7±18.5	77.2±ND (n=2)	84.5±31.3	78.9±30.2

Table 3. Summary of Pharmacokinetic Parameters for OPC-3373 (Day 15)

Variable	30 mg (n=9)	45 mg (n=4)	60 mg (n=4)	75 mg (n=7)	90 mg (n=5)
C^{ss}_{max} (ng/ml)	10.2±4.1	18.1±10.6	16.7±3.2	23.0±7.0	43.1±11.0
AUC_{τ} (ng.hr/ml)	101±59	178±107	172±25	320±104	464±110
t_{max} (hr)	2.0 (1.0-4.0)	2.0 (1.0-2.0)	1.5 (1.0-12.0)	2.0 (2.0-4.0)	2.0 (1.0-4.0)

Table 4. Summary of Pharmacokinetic Parameters for DM-1451 (Day 15)

Variable	30 mg (n=9)	45 mg (n=4)	60 mg (n=4)	75 mg (n=7)	90 mg (n=5)
C^{ss}_{max} (ng/ml)	3.1±2.4	2.9±0.9	4.6±1.6	6.7±3.3	7.2±3.9
AUC_{τ} (ng.hr/ml)	44±28	56±20	85±32	124±69	136±63
t_{max} (hr)	4.0 (2.0-6.0)	5.0 (2.0-24.0)	5.0 (2.0-8.0)	6.0 (2.0-24.0)	2.0 (2.0-6.0)

The pharmacokinetics of Aripiprazole and its active metabolite OPC-14587 appeared to be linear following multiple oral doses in the range of 30-75 mg (15 mg increments) except for the 45 mg group which had similar exposure as the 60 mg group. The 90 mg dose resulted in higher than proportional increase in exposure.

Safety Results

Table 5. Patients with Potentially Clinically Significant Vital Sign Abnormalities

Dose Group	30 mg (N=12)	45 mg (N=7)	60 mg (N=7)	75 mg (N=7)	90 mg (N=7)
SBP, Standing Supine					1↓
DBP, Standing	1↑, 2↓	1↓	1↓	1↓	2↓
Supine	1↓		1↓		
Heart Rate, Standing	4↑	3↑	2↑	5↑ 1↓	6↑
Weight		1↑	1↑		1↑ 1↓
QT_{cB} interval				one from 395 to 451 msec	
Sinus tachycardia	one from 82 to 120 bpm (on Study Day 8)				(on Study Day 8)
Ventricular arrhythmia	from 0 to 1 (on Study Day 15)				

Efficacy Results

Table 6. Efficacy Data (Mean Change from Baseline by Week)

Week	30 mg	45 mg	60 mg	75 mg	90 mg
			PANSS Total Score (ranges from 30-210)		
Baseline	55.6±16.1 (N=12)	64.4±19.7 (N=7)	43.3±9.6 (N=7)	51.1±16.2 (N=7)	52.6±13.0 (N=7)
1	-1.9±16.3 (N=12)	-1.9±8.0 (N=7)	10.4±13.8 (N=7)	-3.6±6.7 (N=7)	5.9±16.3 (N=7)
2	-3.3±19.7 (N=9)	-8.9±8.0 (N=7)	2.0±6.3 (N=7)	1.7±6.9 (N=7)	-1.0±10.2 (N=7)
3	-7.6±24.4 (N=9)	-16.1±12.9 (N=7)	-3.2±3.8 (N=5)	2.4±8.3 (N=7)	-6.3±11.4 (N=6)
Last Visit	-7.7±21.5(N=12)	-16.1±12.9 (N=7)	0.4±7.0 (N=7)	2.4±8.3 (N=7)	-3.6±12.7 (N=7)
			PANSS Positive Subscale Score (ranges from 7 to 49)		
Baseline	15.1±3.8 (N=12)	16.3±5.2 (N=7)	10.6±2.6 (N=7)	12.4±4.9 (N=7)	14.0±3.4 (N=7)
1	0.2±5.3 (N=12)	-0.1±3.8 (N=7)	3.4±4.6 (N=7)	0.9±1.7 (N=7)	2.1±5.7 (N=7)
2	0±5.6 (N=9)	-2.0±1.4 (N=7)	1.6±5.3 (N=5)	2.4±2.6 (N=7)	-0.3±4.6 (N=7)
3	-1.8±6.5 (N=9)	-3.7±3.2 (N=7)	-0.4±3.4 (N=5)	1.7±1.9 (N=7)	-2.2±3.7 (N=6)
Last Visit	-1.8±5.9 (N=12)	-3.7±3.2 (N=7)	1.0±3.7 (N=7)	1.7±1.9 (N=7)	-1.7±3.6 (N=7)
			PANSS Negative Subscale Score (ranges from 7 to 49)		
Baseline	13.4±7.1 (N=12)	15.4±6.6 (N=7)	10.0±2.7 (N=7)	13.0±6.2 (N=7)	13.0±7.3 (N=7)
1	-0.9±5.4 (N=12)	-0.9±1.1 (N=7)	3.3±4.0 (N=7)	-1.9±3.1 (N=7)	-0.6±8.9 (N=7)
2	-2.2±6.9 (N=9)	-2.6±4.2 (N=7)	0.6±3.7 (N=7)	0.1±3.2 (N=7)	-0.7±4.6 (N=7)
3	-2.6±10.0 (N=9)	-4.4±4.6 (N=7)	-0.2±1.3 (N=5)	-1.7±4.4 (N=7)	-1.5±7.4 (N=6)
Last Visit	-2.2±8.6 (N=12)	-4.4±4.6 (N=7)	0.7±2.2 (N=7)	-1.7±4.4 (N=7)	-0.6±7.2 (N=7)
			CGI Severity of Illness Score (ranges from 1 to 7)		
Baseline	3.3±1.0 (N=12)	3.2±0.8 (N=7)	2.7±1.0 (N=7)	2.9±1.1 (N=7)	2.9±0.9 (N=7)
1	0±1.1 (N=12)	-0.4±0.5 (N=7)	0.1±0.9 (N=7)	0±0.6 (N=7)	-0.3±0.8 (N=7)
2	0.1±0.8 (N=9)	-0.6±0.5 (N=7)	-0.4±0.9 (N=7)	0.4±0.5 (N=7)	-0.6±1.0 (N=7)
3	-0.2±1.4 (N=9)	-0.9±0.7 (N=7)	-1.0±0.7 (N=5)	0.4±0.5 (N=7)	-0.8±0.8 (N=6)
Last Visit	-0.3±1.4 (N=12)	-0.9±0.7 (N=7)	-0.6±1.0 (N=7)	0.4±0.5 (N=7)	-0.6±1.0 (N=7)

*A negative change score signifies improvement.

Over the short term of the study, patients in all dose groups maintained a stable symptom profile. No analysis was conducted to explore PK/PD relationship.

Summary

- Aripiprazole daily doses of 30 mg, 45 mg, 60 mg, 75 mg, and 90 mg were generally safe and tolerated in this 15-day dosing study. While increased incidences of akathisia and tachycardia were seen for the 90 mg dose group, there were no discontinuations due to adverse events or serious adverse events that occurred in this dose group.

- Twenty-five (55%) of the 40 patients reported an EPS-related AE, with the highest incidence occurring in the 90 mg treatment group (6 patients, 86%).

- Three patients experienced potentially clinically significant (>7%) increases in body weight and one with >7% decrease in BW. Changes in body weight did not appear to correspond with dose level.

- Mean changes in serum prolactin concentrations showed slightly decreased values in the 30 mg and 45 mg treatment groups, whereas the 60 mg, 75 mg and 90 mg groups showed modest increases from baseline, the highest of which was at 90 mg.

- The pharmacokinetics of Aripiprazole and its active metabolite OPC-14587 appeared to be linear following multiple oral doses in the range of 30-75 mg (15 mg increments) except for the 45 mg group which had similar exposure as the 60 mg group. The 90 mg dose resulted in higher than proportional increase in exposure.

- Summary statistics in this 15-day pilot study showed that patients in all dose group maintained a stable symptom profile, as measured by the PANSS Total Score, the PANSS Positive Subscale Score, and the PANSS Negative Subscale Score, and the CGI Severity of Illness Score.

Study 98-201 (Vol.49-52): ***An Open-Label Study of the Effects of Diurnal Variation on the Pharmacokinetic Disposition of a Single Dose of OPC-14597 in Healthy Volunteers***

The purpose of this study was to evaluate the influence of diurnal variation on the pharmacokinetic disposition of aripiprazole (OPC-14597) and its metabolites. This was an open-label, parallel group study in 32 healthy volunteers who received a single dose of 20 mg aripiprazole (2x10 mg, Lot #5K75A010) between 8:00 AM and 9:00 AM (16 subjects; 8 Hispanic females, Males including 4 Hispanics, 2 Caucasians, 1 Black and 1 Indian) or between 10:00 PM and 11:00 PM (16 subjects; 8 Hispanic females, Males including 4 Hispanics, 4 Caucasians). Blood samples were collected for 24 hours post-dose on Day 1 and through 336 hours (14 days) post-dose. Urine samples were also collected through 168 hours (7 days) post-dose. Laboratory safety tests, a physical exam and 12-lead ECG were performed at screening, prior to dosing and upon exiting the study on Day 15. A 12-lead ECG was also performed at four hours post-dose and on Day 8 prior to discharge from the unit.

Table 1. Mean Plasma Pharmacokinetic Parameters for Aripiprazole (N=16 in each group))

Time of Dose	T^a_{max} (h)	C^b_{max} ng/ml)	$t_{1/2}$ (h)	AUC^b_t (ng.h/ml)	AUC^b_∞	CL/F (ml/h/kg)	Vz/F (L/kg)	CL_r (ml/h/kg)
8:00-9:00 AM	5.5	101.7	61.6	6179	6308	49.7	4.1	0.0260
	(3, 12)	(19.30)	(17.0)	(2453)	(2652)	(20.3)	(1.2)	(0.0221)
10:00-11:00 PM	12	78.6	57.2	5428	5558	52	4.2	0.0237
	(2, 24)	(14.8)	(9.2)	(1148)	(1194)	8.2)	(0.6)	(0.0182)
P-values from Two-way analysis of variance								
Time of Dose	0.030	<0.001	0.580	0.257	0.241	0.31	0.423	0.643
Gender	0.272	0.522	0.688	0.629	0.631	0.254	0.040	0.748

[a]Median (min, max), [b]Geometric mean, The values for the rest parameters are Mean with SD.

Table 2. Mean Plasma Pharmacokinetic Parameters for Active Metabolite OPC-14857

Time of Dose	T^a_{max} (h)	C^b_{max} ng/ml)	$t_{1/2}$ (h)	AUC^b_t (ng.h/ml)	AUC^b_∞	CL/F (ml/h/kg)	CL_r (ml/h/kg)
8:00-9:00 AM	60	13.5	94.4	2117	2438	128.2	0.3899
	(24, 144)	(7.0)	(36.1)	(651)	(763)	(57.3)	(0.1583)
10:00-11:00 PM	72	12.3	81.8	2048	2258	130.7	0.2856
	(24, 96)	(4.1)	(15.3)	(702)	(721)	(32.5)	(0.1348)
P-values from Two-way analysis of variance							
Time of Dose	0.216	0.435	0.432	0.763	0.046	0.637	0.046
Gender	0.378	0.006	0.722	0.002	0.002	0.097	0.477

Summary

- When a single 20 mg dose of aripiprazole was administered orally to healthy subjects in the morning or evening, C_{max} was 23% lower AUC was 12% lower when administered during the evening.

- There were no differences in plasma exposure to the active metabolite OPC-14857 between morning and evening dosing except for renal clearance which was 27% lower following evening dosing compared to AM dosing.

- For the inactive metabolite OPC-3373, due to the low circulating concentrations, only C_{max} and T_{max} (mean 3-5 hrs) could be determined and there were no differences between morning and evening dosing.

- Greater variability was observed in the AUC values (CV of 37%) of aripiprazole following AM dosing compared to PM dosing (CV of 21%). This was not observed in its C_{max}, which had similar variability across the two treatments (CV of 19%).

- With regard to gender, C_{max}, T_{max} and AUC of aripiprazole were not different but the Vz/F adjusted for body weight was significantly higher in females (4.4 L/kg) compared to males (3.6-4.0 L/kg). C_{max} and AUC of the active metabolite (OPC-14857) were significantly higher in females (43% after AM dose, 39% after PM dose for C_{max}, and 46% after AM dose and 40% after PM dose for AUC) compared to males.

- Based on the results of this study, aripiprazole may be dosed regardless of the time of day.

Safety: Two subjects had QT_c interval increases which met the criteria for potential clinical significance: one had an increase of 105 msec above baseline at 4 h post-dose on Day 1 based on the machine-generated ECG interval determination. Upon manual re-calculation of the interval, no increase over baseline was observed. The other subject had an increase of 49 msec above baseline at discharge. The investigator did not report either interval as an AE. One subject had a low hematocrit and one subject had a high bilirubin which met the criteria for potential clinical significance. However, none of these abnormal laboratory values were reported as AEs by the Investigator.

Study 00-225 (Vol. 53-59): ***An Open-Label Study of the Effects of Age and Gender on Single Dose Aripiprazole Pharmacokinetics in Healthy Subjects***

The primary objective of this study was to assess the effects of age and gender on single oral dose aripiprazole pharmacokinetics. This was an open-label, two center, three-by-two factorial design study. A total of sixty (60) male and female subjects (10 subjects of each gender per age group), in 3 age groups of 18 to 40 years, 41 to 64 years, and greater than or equal to 65 years received a single oral 15 mg aripiprazole dose (Lot #99C77A015A).

Demographic Characteristics

	Male			Female		
	18-40 yrs	41-64 yrs	≥65 yrs	18-40 yrs	41-64 yrs	≥65 yrs
Age	28 (23-36)	55 (41-63)	73 (67-78)	31 (20-40)	54 (44-61)	70 (66-75)
BW (kg)	80.1±10.1	86.5±7.4	84.7±14.9	63.4±11.5	65.1±7.3	72.3±10.4
Race, n (%)						
White	7 (70%)	8 (80%)	10 (100%)	5 (50%)	8 (80%)	9 (90%)
Black	2 (20%)	0	0	1 (10%)	0	0
Hispanic/ Latino	1 (10%)	2 (20%)	0	3 (30%)	2 (20%)	1 (10%)
American Indian	0	0	0	1 (10%)	0	0

According to the sponsor (Vol. 53), all subjects had CYP2D6 and CYP2C19 extensive metabolizer genotypes (Information on the phenotype and genotype testing results for CYP2D6 and CYP2C19 are provided in Appendices 8.3B and 8.3C, respectively)

Subjects had blood specimens collected for drug and metabolite analysis within 0.5 hour prior to aripiprazole dosing and, 1, 3, 4, 5, 6, 7, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 264, 312, and 360 hours post-dose. Additional samples were collected at pre-dose and at 6 hours post-dose for protein binding analysis. Each subject had urine specimens collected for drug and metabolites analysis at the following intervals: pre-dose, 0-24, 24-48, 48-72, and 72-96 hours post-dose. Assays were done at [redacted] methods with internal standard (OPC-14714). Protein binding of radiolabeled aripiprazole was determined in subject samples using [redacted] counting at [redacted]

Pharmacokinetic Results

Table 1. Summary of Aripiprazole Pharmacokinetic Parameters (Gender Differences)

Parameter ***Gender***	C_{max} (ng/ml)	AUC_∞ (ng.h/ml)	CL/F (ml/h/kg)	$t_{1/2}$ (h)	T_{max} (h)
Males (N=30)	54.7±12.5	4112±1861	53.1±24.8	91.6±39.6	5.0 (3.0-12.0)
Females (N=30)	72.4±14.6	5634±1984	46.3±18.9	96.1±28.6	3.6 (3.0-24.0)
Geometric mean (CV%)					
Males (N=30)	53.2 (22.9)	3738 (45.2)	48.3 (46.7)	85.6 (43.3)	
Females (N=30)	70.9 (20.2)	5303 (35.2)	46.3 (40.7)	96.1 (29.7)	
F/M	**1.33**	**1.42**	**0.96**		

Table 2. Summary of Other Aripiprazole Pharmacokinetic Parameters (Gender Differences)

Parameter ***Gender***	V_z/F (L/kg)	$A_{e,96h}$ (μg)	CLr (ml/h/kg)	f_u (%)
Males (N=30)	6.19±1.82	10.6±7.1	0.056±0.049	0.793±0.146
Females (N=30)	5.79±1.21	9.4±7.6	0.047±0.036	0.778±0.151
Geometric mean (CV%)				
Males (N=30)	5.96 (29.4)	9.51 (67.3)	0.0466 (86.6)	0.7808 (18.50
Females (N=30)	5.67 (20.9)	8.80 (81.2)	0.0448 (75.9)	0.7647 (19.3)
F/M	**0.95**	**0.92**	**0.96**	**0.98**

Table 3. Summary of OPC-14857 and OPC-3373 Pharmacokinetic Parameters (Gender Differences)

	OPC-14857			*OPC-3373*		
Parameter *Gender*	C_{max} (ng/ml)	AUC_t (ng.h/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_t (ng.h/ml)	T_{max} (h)
Males (N=30)	7.4±2.5	1483±463	72 (24-216)	6.7±3.4	40.6±36.2	1.0 (1.0-24.0)
Females (N=30)	10.1±2.9	2108±428	72 (6-216)	9.4±4.6	50.5±38.8	1.0 (1.0-5.0)
Geometric mean (CV%)						
Males (N=30)	7.0 (34.1)	1413 (31.2)		5.8 (50.7)	29.9 (89.2)	
Females (N=30)	9.7 (72.0)	2064 (20.3)		8.2 (49.1)	38.9 (76.7)	
F/M	**1.38**	**1.46**		**1.41**	**1.30**	

Figure 1. Mean plasma aripiprazole concentration-time profiles following oral administration of 15 mg aripiprazole tablets in healthy male and female subjects (N=30 in each group)

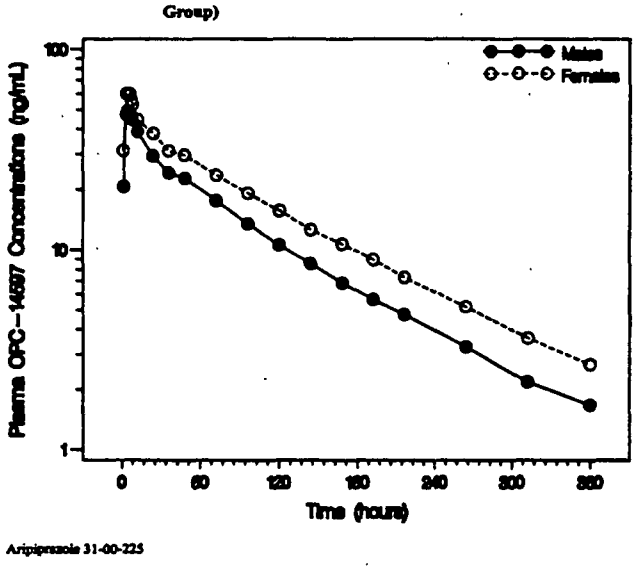


Table 4. Summary of Aripiprazole Pharmacokinetic Parameters after 15 mg Dose to Healthy Volunteers (Age Differences)

Parameter *Age*	C_{max} (ng/ml)	AUC_∞ (ng.h/ml)	CL/F (ml/h/kg)	$t_{1/2}$ (h)	T_{max} (h)
18-40 yrs (N=20)	65.4±10.9	4816±1999	51.4±20.7	84.0±27.0	4.5 (3.0-8.0)
41-64 yrs (N=20)	62.4±21.9	4661±2409	55.8±28.3	89.4±22.4	5.0 (3.0-8.0)
≥65 yrs (N=20)	63.0±14.4	5141±1787	42.0±13.7	108.3±45.0	3.0 (3.0-24.0)
Geometric mean (CV%)					
18-40 yrs (N=20)	64.5 (16.7)	4476 (41.5)	47.6 (40.3)	79.6 (33.3)	
41-64 yrs (N=20)	58.5 (35.2)	4036 (51.7)	49.8 (50.7)	86.2 (25.10	
≥65 yrs (N=20)	61.5 (22.8)	4885 (34.8)	39.7 (32.7)	101.4 (41.6)	
Elderly/Young	**0.95**	**1.09**	**0.83**		
Elderly/Middle	**1.05**	**1.21**	**0.80**		

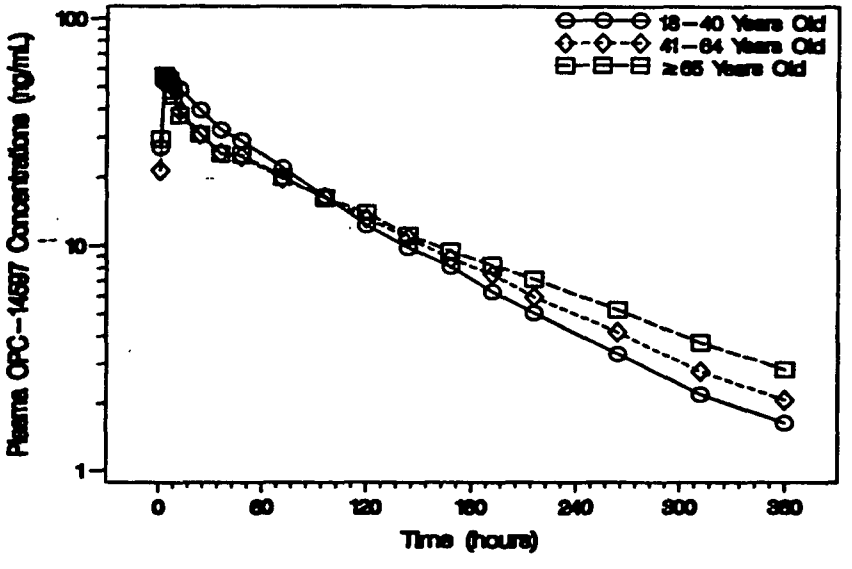
Table 5. Summary of Other Aripiprazole Pharmacokinetic Parameters after 15 mg Dose to Healthy Volunteers (Age Differences)

Parameter *Age*	V_z/F (L/kg)	$A_{e,96h}$ (μg)	CLr (ml/h/kg)	f_u (%)
18-40 yrs (N=20)	5.57±1.0.9	7.2±6.8	0.034±0.028	0.811±0.146
41-64 yrs (N=20)	6.49±2.11	9.5±6.4	0.056±0.055	0.747±0.142
≥65 yrs (N=20)	5.91±1.15	13.1±7.7	0.065±0.037	0.799±0.154
Geometric mean (CV%)				
18-40 yrs (N=20)	5.46 (19.5)	6.04 (94.5)	0.0299 (81.3%)	0.7993 (18.0)
41-64 yrs (N=20)	6.19 (32.5)	8.49 (67.5)	0.0451 (98.4)	0.7360 (19.0)
≥65 yrs (N=20)	5.81 (19.4)	14.41 (59.0)	0.0724 (57.1)	0.7845 (19.3)
Elderly/Young	**1.06**	**2.39**	**2.42**	**0.98**
Elderly/Middle	**0.94**	**1.70**	**1.60**	**1.06**

Table 6. Summary of OPC-14857 and OPC-3373 Pharmacokinetic Parameters after 15 mg Dose to Healthy Volunteers (Age Differences)

	OPC-14857			*OPC-3373*		
Parameter *Gender*	C_{max} (ng/ml)	AUC_t (ng.h/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_t (ng.h/ml)	T_{max} (h)
18-40 yrs (N=20)	9.3±3.0	1701±450	60 (24-168)	7.4±4.8	48.0±44.0	1.0 (1.0-24.0)
41-64 yrs (N=20)	8.4±3.0	1768±646	72 (24-144)	7.2±4.1	34.4±24.8	1.0 (1.0-5.0)
≥65 yrs (N=20)	8.4±3.1	1918±520	96 (6-216)	9.6±3.5	54.2±40.1	1.0 (1.0-5.0)
Geometric mean (CV%)						
18-40 yrs (N=20)	8.9 (31.8)	1638 (26.5)		6.05 (64.1)	33.68 (91.5)	
41-64 yrs (N=20)	8.0 (72.0)	1654 (36.5)		6.04 (57.5)	27.53 (34.4)	
≥65 yrs (N=20)	7.8 (96.0)	1838 (27.1)		8.97 (36.7)	42.82 (74.1)	
Elderly/Young	**0.88**	**1.12**		**1.48**	**1.27**	
Elderly/Middle	**0.98**	**1.11**		**1.48**	**1.56**	

Figure 2. Mean plasma aripiprazole concentration-time profiles following oral administration of 15 mg aripiprazole tablets in young, middle and elderly subjects (N=20 in each group)



Summary

- Aripiprazole CL/F (ml/h/kg) were not significantly influenced by subject gender.
- Gender differences in C_{max} and AUC (30-40% higher in women compared to men) of aripiprazole and its metabolites (OPC-14857 and OPC-3373) were explained by differences in body weight (BW is 25% higher in men compared to women).
- Elderly (>65 yrs) had 20% decrease in aripiprazole clearance and 20 hours longer elimination half-life compared to young subjects.
- There were no apparent differences in the frequency of adverse events between healthy young (18-40 years) and elderly (aged 65 and older) subjects.
- Healthy young women (18-40 years) had a greater incidence of AEs, including postural hypotension, than did young men (18-40 years).

Study 98-203 (Vol. 60): ***An Open-Label, Pilot Study of the Safety and Tolerability of Aripiprazole Administered Orally in Elderly Demented Patients with Psychosis and Behavioral Disturbances***

The objective of this study was to obtain preliminary data concerning the safety, tolerability, and efficacy of aripiprazole, at daily doses ranging from 5 to 30 mg, in an elderly demented population with psychosis and behavioral disturbances. This was an open-label, inpatient, pilot study addressing safety and tolerability over a 21 days treatment period in patients with possible Alzheimer's disease.

Treatment Schedule (Age ≥65 yrs)

Treatment	Step 1	Step 2	Step 3	Step 4	Step 5
First Week Dose	5 mg/day	10 mg/day	15 mg/day	20 mg/day	25 mg/day
Next 2 Weeks Dose	10 mg/day	15 mg/day	20 mg/day	25 mg/day	30 mg/day
N	5	5	5	10	5

Aripiprazole 5 mg (Batch #97K87A005), 10 mg (Batch #97F99A010) and 15 mg (Batch #97F99A015) one or two tablets QD were administered orally.

Blood samples were obtained predose on Day 1, 18, 19, 20 and 21 (or last visit), as well as 4-6 hours after dosing on Days 1 and 21 (or last visit) to determine plasma concentrations of aripiprazole and its active metabolite, OPC-14857 in this patient population.

Table 1. Plasma Concentrations for Elderly Patients Receiving Various Regimens of Aripiprazole

Dose Regimen[a]	Day 18[b]	Day 19[b]	Day 20[b]	Day 21[b]	Day 21[c]
Aripiprazole (ng/ml)					
5/10mg/day (n=5)	129±34	133±34	131±35	147±48	174±39
10/15mg/day (n=4)	171±79	183±99	184±96	204±126	260±117
15/20mg/day (n=5)	190±119	194±125	191±126	194±122	204±126
20/25mg/day (n=8)	335±108	328±97	321±105	341±104	467±121
25/30mg/day (n=5)	379±210	330±138	344±167	431±198	464±177
OPC-14857 (ng/ml)					
5/10mg/day (n=5)	45±12	48±18	48±16	54±13	53±15
10/15mg/day (n=4)	88±26	95±30	95±23	107±37	104±30
15/20mg/day (n=5)	64±9	70±6	66±7	71±11	74±8
20/25mg/day (n=8)	135±27	131±22	127±21	141±21	146±25
25/30mg/day (n=5)	161±65	142±50	143±47	150±48	160±49

[a] Dose on Day 1-7 followed by dose from Day 8-21. [b] Pre-dose samples; [c] 4 hours post-dose sample.

No formal pharmacokinetic analysis was performed on the concentration data since the sampling was not adequate to characterize pharmacokinetic parameters of aripiprazole or its metabolite.

Summary

- In this small, open-label, pilot study of elderly, demented patients with Alzheimer's disease and behavioral disturbances, aripiprazole, at doses from 5 mg/day to 20 mg/day was generally safe and well tolerated. The higher doses tested in this study, 25 mg/day to 30 mg/day, were generally safe, but marginally tolerated due to persistent somnolence that extended even beyond the dosing period in some patients.

- Summary statistics of efficacy in this small, open-label pilot study showed a small improvement on the BPRS Core score, AMMSE Total Score, and CGI-severity of Illness Score for patients receiving doses up to 20 mg/day. Patients in all dose groups showed a small improvement in the CGI-Improvement Score.

- Three patients exhibited potentially clinically significant increases in QT_c when the Bazett correction factor was utilized ($QT/RR^{0.5}$), but each instance occurred at a different Treatment Step (one patient in each of Treatment Steps 1, 4, and 5) and thus no relationship to aripiprazole dose was evident. The QT_c was normalized for these patients when the correction factor utilized by the Neuropharmacological Division of the FDA was applied ($QTcN=QT/RR^{0.37}$).

- Two patients had a >7% increase in body weight, one in Treatment Step 4 and the other in Treatment Step 5.

- Overall, the pre-dose aripiprazole plasma concentrations appeared to be at steady state by Day 18 for all the groups. The pre-dose concentrations of both aripiprazole and OPC-14857 increased approximately linearly with increasing of doses except for 15/20 mg/day group which were lower than expected for the dosing regimen based on the results from the other groups. The exact reason is unknown since demographic characteristics of this group were similar to that of the other groups; none of the

concomitant medications unique to this group are known to affect the metabolism of aripiprazole; and the metabolic ratios were similar to that seen in the earlier groups (0.35 to 0.4).

Study 138-014 (Vol. 61-62): ***Tolerability, Pharmacokinetics and Pharmacodynamics of Aripiprazole during Oral Administration in Children and Adolescents with Conduct Disorder (Ongoing)***

The primary objective of this study is to determine the multiple dose pharmacokinetics of aripiprazole in children and adolescents with conduct disorder. The secondary objective is to assess the safety profile and pharmacodynamics of aripiprazole in this patient population. This is an open-label, 15-day, multi-center (Phase A) study with an optional 18-month open-label safety extension (Phase B). Children ages of 6 to 12 years (N=12) and adolescents ages of 13 to 17 years (N=11), with a diagnosis of conduct disorder and a score of 2 to 3 on the Rating of Aggression Against People and/or Property (RAAPP), were enrolled.

Dosing Schedule

Body Weight	Initially	Dose (Day 1-14)	Due to tolerance, changed to
BW<25 kg	2 mg/day (N=5)		1 mg/day
25 kg<BW<50 kg	5 mg/day		2 mg/day
50 kg<BW<70 kg	10 mg/day		5 mg/day
>70 kg	15 mg/day		10 mg/day

Pharmacokinetic Results

Table 1. Aripiprazole Pharmacokinetic Parameters

Dose (mg)		N	C_{max}	D_{14}/D_1	AUC	D_{14}/D_1	T_{max}	CL/F	
Children			(ng/ml)		(ng.h/ml)		(h)	(L/h)	(L/h/kg)
1 mg	Day 1	3	9.0 (54)		73 (83)		4.0 (3-8)	--	--
	Day 14	3	22.4 (74)	2.5	480 (a)	6.6	4.0 (0-6)	2.56 (a)	0.11 (a)
2 mg	Day 1	4	16.4 (40)		228 (37)		3.0 (2-8)	--	--
	Day 14	5	48.9 (51)	3.0	825 (62)	3.6	2.0 (1-4)	2.66±1.07	0.07±0.04
5 mg	Day 1	5	51.1 (25)		682 (20)		1.0 (1-4)	--	--
	Day 14	3	142.0 (21)	2.8	2276 (23)	3.3	2.0 (1-3)	2.25±0.58	0.05±0.02
Dose (mg)		N	C_{max}	D_{14}/D_1	AUC	D_{14}/D_1	T_{max}	CL/F	
Adolescents			(ng/ml)		(ng.h/ml)		(h)	(L/h)	(L/h/kg)
2 mg	Day 1	2	14.2 (a)		210 ((a)		2.5 (2-3)	--	--
	Day 14	2	43.8 (a)	3.1	800 (a)		2.0 (2-2)	2.51±(a)	0.05±(a)
5 mg	Day 1	5	23.9 (13)		417 (296)		3.0 (2-8)	--	--
	Day 14	5	73.9 (53)	3.1	1357 (56)	3.3	4.0 (2-6)	4.03±1.71	0.07±0.03
10 mg	Day 1	3	38.5 (50)		566 (31)		2.0 (2-6)	--	--
	Day 14	3	13.8 (22)		2433 (38)	4.3	3.0 (2-24)	4.28±1.40	0.05±0.02
15 mg	Day 1	1	62.2		625		2.0	--	--
	Day 14	1	202.4	3.2	4033	6.4	2.0	3.72	0.03

a-not calculated.

Table 2. OPC-14857 Pharmacokinetic Parameters

Dose (mg) *Children*		N	C_{max} (ng/ml)	D_{14}/D_1	AUC (ng.h/ml)	D_{14}/D_1	T_{max} (h)
1 mg	Day 1	2	0.9 (0.48)		NA		18.0 (12-24)
	Day 14	3	4.1 (58)		60.0 (78)		1.0 (0-6)
2 mg	Day 1	4	1.3 (48)		17.7 (57)		24.0 (12-24)
	Day 14	5	12.1 (27)		249.0 (28)	13.8	6.0 (1-24)
5 mg	Day 1	5	3.7 (37)		54.9 (340		24.0 (24-24)
	Day 14	3	29.4 (40)	7.9	601.3 (45)	10.9	2.0 (1-4)
Adolescents							
2 mg	Day 1	2	0.9 (0.49)		13.1 (NA)		24.0 (24-24)
	Day 14	2	9.6 (13)		192.7 (17)		3.5 (3-4)
5 mg	Day 1	5	2.0 (80)		40.0 (55)		12.0 (2-24)
	Day 14	5	22.1 (26)	11.0	423.3 (34)	10.6	4.0 (0-24)
10 mg	Day 1	3	2.7 (69)		74.2 (30)		24.0 (4-24)
	Day 14	3	35.8 (55)	13.2	725.0 (54)	9.8	1.0 (0-24)
15 mg	Day 1	1	1.5 (NA)		20.4 (NA)		24.0
	Day 14	1	33.4 (NA)		595.1 (NA)		0 (NA)

Table 3. Clearance Comparison

	Children (N=10) (6-12 yrs)	Adolescents (N=11) 13-17 yrs)	Adults (Study 31-93-201) (21-44 yrs)
CL/F (L/h)	2.25-2.66	2.51-4.28	
Mean±SD	2.52±1.05	3.79±1.41	3.48±1.03
Children/Adolescents and Adults -34%			
CL/F (L/h/kg)	0.07	0.06	0.05

Summary

- In children and adolescents who received a constant daily dose through Days 1 to 14 of the study, the C_{max} and AUC values of aripiprazole were generally 2- to 7-fold higher on Day 14 compared to Day 1. This extent of accumulation was similar for children and adolescents, and is reasonably consistent with the observation in adults (3- to 5-fold accumulation).

- Unadjusted for body weight, children had 34% lower clearance compared to adolescents and adults, however, when normalized for body weight, the values for the mean apparent oral clearance were fairly constant.
- OPC-14857 was the predominant circulating metabolite in plasma; at steady state, the AUC values for this metabolite averaged about 27% and 32% of the AUC of the parent drug in children and adolescents, respectively. At the 2 mg and 5 mg doses of aripiprazole, the C_{max} and AUC values of metabolite OPC-14857 were similar in children and adolescents. The metabolite to parent AUC ratios in children and adolescents are similar to those observed in adults.

- Plasma concentrations of metabolite DM-1451 were below the limit of quantitation in all subjects. Plasma concentrations of metabolite DM-1452 in children and adolescents were low, ranging from 0.5 to 6 ng/ml. The AUC values for DM-1452 averaged about 2% of the AUC of the parent compound in children and adolescents.

Metabolites OPC-3373 and DCPP were quantifiable in only some subjects at a few time points.

Study 98-205 (Vol. 63-66): ***A Phase I Single-Dose Evaluation of the Pharmacokinetics of Aripiprazole in Normal and Hepatically –Impaired Subjects***

The purpose of this study was to evaluate the pharmacokinetics of aripiprazole (OPC-14597) in normal subjects and in subjects with varying degrees of hepatic impairment. Twenty-five (25) subjects between the ages of 39 to 71, with normal hepatic function or varying degrees of hepatic impairment participated in this single-dose, open-label study. Genotyping was conducted at the screening and only CYP2D6 extensive metabolizers were included in the study.

Aripiprazole 15 mg tablets (Lot #97K87A015A) was administered orally. Blood samples were collected up to 504 hours post-dose for pharmacokinetic analysis. Plasma protein binding of radiolabeled aripiprazole was done in subject samples using equilibrium dialysis with liquid scintillation counting of the EDTA plasma and dialysate. Creatinine clearance was measured as a determination of renal function, and indocyanine green (ICG) 25 mg was administered intravenously and its clearance was measured to determine hepatic blood flow.

Demographic Characteristics

Characteristics	Age (yrs)	Gender (M/F)	Weight (Kg)	Race White/Black/(Hispanic/Latino)
Normal Subjects (n=6)	52±10	3/3	71.3±14.6	0/0/6
Child-Pugh Class A (n=8)	52±9	4/4	72.5±17.2	5/1/2
Child-Pugh Class B (n=8)	54±8	6/2	81.2±13.3	6/0/2
Child-Pugh Class C (n=3)	51±12	3/0	81.7±14.4	0/0/3

Table 1. Comparison of Pharmacokinetic Parameters of Aripiprazole (15 mg Single-Dose)

Group Parameter	Normal (N=6)	Mild HI (N=8)	Moderate HI (N=8)	Severe HI (N=3)	Ratio Mil/N	Mid/N	S/N
C_{max} (ng.ml)	64.5±21.1	73.9±25.4	46.6±14.0	35.1±7.6			
GeoMean (CV%)	60.6 (32.8)	69.2 (34.4)	44.8 (30.1)	34.5 (21.7)	1.14	0.74	0.57
AUC_∞ (ng.h/ml)	4147±1372	5533±2214	4847±2915	3171±880			
	3923 (33.1)	5150 (40.0)	4204 (60.1)	3088 (27.8)	1.31	1.07	0.79
$t_{1/2}$ (h)	90.9±37.0	176.1±114.5	159.6±79.8	140.1±2.3			
	84.7 (40.7)	152.6 (65.0)	142.8 (50.0)	140.1 (1.7)			
CL/F (ml/h/kg)	55.98±13.10	42.99±13.83	52.11±28.61	61.63±19.19			
	54.64 (23.4)	40.96 (32.2)	44.45 (54.9)	59.32 (31.1)	0.75	0.81	1.09
f_u (%)	0.25±0.02	0.30±0.03	0.29±0.05	0.34±0.04			
	0.25 (25.9)	0.30 (11.1)	0.28 (17.0)	0.33 (12.1)	1.20	1.12	1.32
CL/F_u (L/h/kg)	22.46±5.81	14.13±3.83	19.90±10.23	18.71±7.09			
	21.80 (25.9)	13.67 (27.1)	16.98 (51.4)	17.71 (37.9)	0.63	0.78	0.81
CL_r (ml/h/kg)	0.04±0.04	0.06±0.05	0.07±0.05	0.19±0.08			
	0.02 (104)	0.04 (82.6)	0.06 (63.7)	0.17 (41.1)	2.0	3.0	8.5
T_{max} (h)	2 (1-5)	4.5 (1-8)	4 (2-12)	2 (2-3.1)			

Figure 1. Scatter plot (Individual and Mean±SD) of C_{max} for Aripiprazole in normal subjects and subjects with hepatic impairment

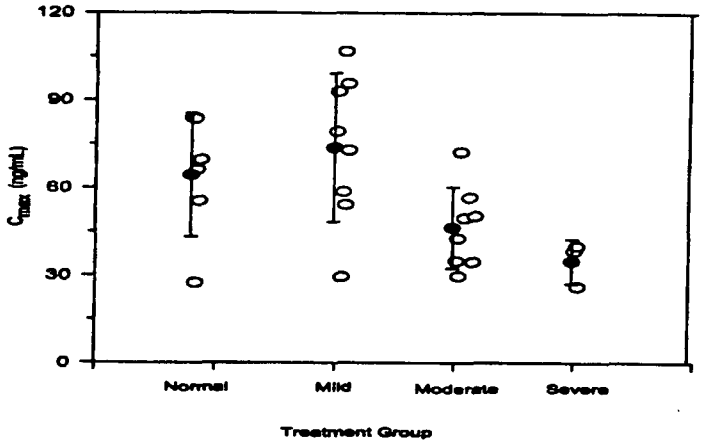


Figure 2. Scatter plot (Individual and Mean±SD) of unbound oral clearance for Aripiprazole in normal subjects and subjects with hepatic impairment

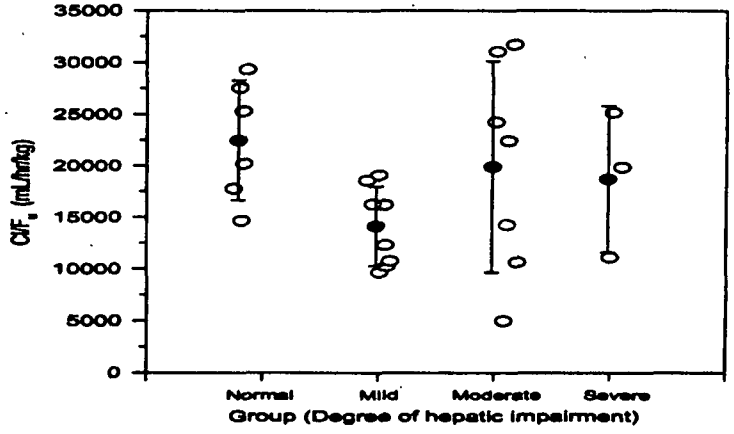


Table 2. Comparison of Pharmacokinetic Parameters of OPC-14857

Group Parameter	Normal (N=6)	Mild HI (N=8)	Moderate HI (N=8)	Severe HI (N=3)	Ratio Mil/N	 Mid/N	 S/N
C_{max} (ng.ml)	10.4±4.4	7.1±3.3	5.3±1.2	5.0±3.7			
GeoMean (CV%)	9.4 (42.1)	6.4 (46.4)	5.2 (22.4)	4.2 (73.7)	0.68	0.55	0.45
AUC_∞ (ng.h/ml)	2456±975	1832±374	1751±598	1986±935			
	2280 (39.7)	1798 (20.4)	1669 (34.1)	1872 (47.1)	0.79	0.73	0.82
$t_{1/2}$ (h)	126.6±92.8	209.3±134.2	153.2±40.1	197.8±96.2			
	107.7 (73.2)	180.3 (64.1)	148.5 (26.2)	185.8 (48.6)			
T_{max} (h)	84 (4-1200	96 (36-120)	96 (48-312)	71 (48-122)			

Figure 3. Scatter plot (Individual and Mean±SD) of C_{max} for OPC-14857 in normal subjects and subjects with hepatic impairment

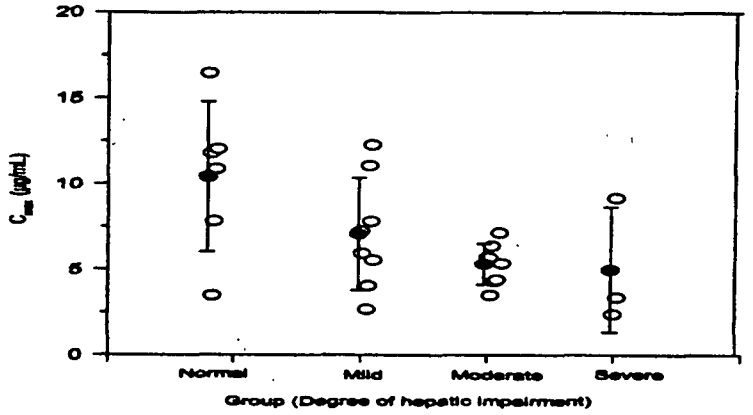


Figure 4. Scatter plot (Individual and Mean±SD) of AUC_∞ for Aripiprazole in normal subjects and subjects with hepatic impairment

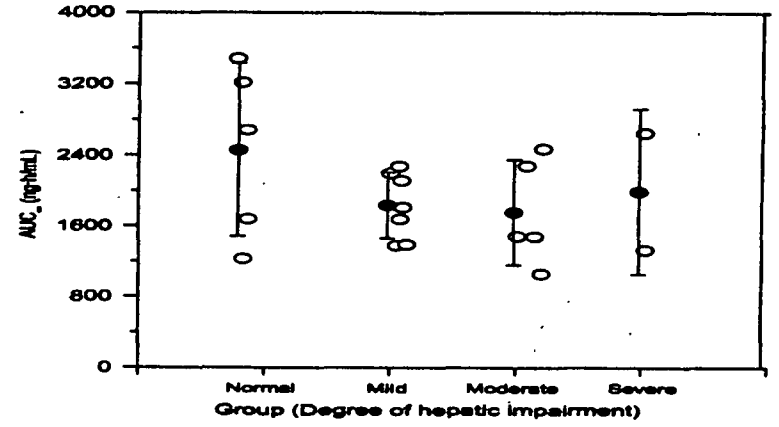


Table 3. Comparison of Pharmacokinetic Parameters of OPC-3373

Group	Normal	Mild HI	Moderate HI	Severe HI	Ratio		
Parameter	(N=6)	(N=8)	(N=8)	(N=3)	Mil/N	Mid/N	S/N
C_{max} (ng.ml)	9.2±3.6	7.7±3.3	5.0±2.8	8.0±3.1			
GeoMean (CV%)	8.8 (38.4)	7.0 (42.4)	4.4 (54.9)	7.7 (38.6)	0.80	0.50	0.88
AUC_t (ng.h/ml)	13.9±7.4	35.9±30.5	18.0±32.2	15.8±8.9			
	12.5 (53.3)	22.9 (85.0)	6.1 (179)	13.8 (56.4)	1.83	0.49	1.10
T_{max} (h)	1 (0.5-10	2 (1-5)	2 (1-5)	1 (1-3)			

Summary

- The C_{max} of aripiprazole and the active metabolite OPC-14857 in severe hepatic impairment subjects was lower (43% and 55%, respectively) than in normal subjects.

- In the previous study, no detectable amounts of aripiprazole were excreted unchanged in urine. Although aripiprazole renal clearance did increase in subjects with severe

hepatic impairment compared to normal subjects, this increase is not clinically relevant since renal clearance is a very minor fraction of the total clearance.

- An increase (36%) in the mean unbound fraction of aripiprazole and a decrease (35%) in mean albumin was observed in subjects with severe hepatic impairment when compared to normal subjects. However, unbound clearance was not significantly altered by hepatic impairment.

- In general, no meaningful differences are apparent in the pharmacokinetics of aripiprazole and its metabolites (OPC-14857 and OPC-3373) between healthy subjects with mild to moderate hepatic impairment.

- Three subjects in hepatically impaired subjects had ECG changes that met the criteria for potentially clinically significant abnormalities. Two (one with mild HI and one with severe HI) of these occurrences were increased QT_c on Day 6 (451 msec and 475 msec, respectively) and one with mild HI was first degree AV block on Day 1.

Discussion

Seven subjects in the hepatically impaired groups were concomitantly taking spironolactone, five of them had terminal elimination half-life of aripiprazole greater than 240 hours. The only other concomitant medications taken by more than 1 subject were vitamins (4 subjects) and furosemide (2 subjects). The possibility of spironolactone assay interference was excluded. A literature search for CYP450 or p-glycoprotein (PGP) inhibition caused by spironolactone yielded no literature on PGP inhibition by spironolactone, and evidence that it inhibits CYP450 11B1 and 2C11, but not 3A4, 2D6, 2C9, or 2C19. Therefore, there does not appear to be any spironolactone-related assay interference or likelihood of enzyme inhibition that could account for the prolonged half-life.

Although all subjects were classified as extensive metabolizer genotype at entry into the study, subjects with hepatic impairment were sub-classified based on whether the subjects had any mutant alleles, since literature suggested that this may affect drugs metabolized by CYP2D6. The terminal elimination half-life was then compared between the two groups and there was no consistent pattern that would link the presence of a mutant allele with a prolonged half-life.

Study 98208 (Vol. 67-68, sVol. 4-7): ***An Open-Label Study of the Pharmacokinetics of Single Oral Dose of Aripiprazole in Normal, Healthy Subjects and Subjects with Severe Renal Impairment***

The primary objective of this study was to determine the single-dose pharmacokinetics of aripiprazole in subjects with severe renal impairment. This was an open-label study in 6 subjects with normal renal function and 6 subjects with severely impaired renal function (CYP2D6 EM genotype). Each subject received a single 15 mg oral dose of aripiprazole (Batch #99C77A015A).