**Demographic Characteristics**

| Characteristics | Age (yrs) | Gender (M/F) | Weight (Kg) | Race White/Black/(Hispanic/Latino) | $CL_{CR}$ (ml/min) |
|---|---|---|---|---|---|
| Normal Subjects (n=7) | 57±9.3 | 3/4 | 107.7±20.0 | 3/3/1 | 118.5±25.1 |
| Renally Impaired (n=6) | 60±14.7 | 3/3 | 104.9±24.3 | 2/3/1 | 25.2±5.1 |

Blood samples were collected within 0.5 hour prior to aripiprazole dosing and, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 168, 216, 264, 312, 360, 408, 456, and 504 hours post-dose for drug and metabolites concentration determination. Additional samples were collected at pre-dose and 6, 216 and 506 hours post-dose for protein binding determination. Urine samples were also collected prior to dosing and from 0-12, 12-24, 24-36, 36-48, 48-72, 72-96 and 96-120 hours post-dose for drug and metabolites analysis.

**Table 1. Summary of Aripiprazole Pharmacokinetic Parameters (15 mg Dose)**

| Parameter ***Renal Function*** | $C_{max}$ (ng/ml) | $AUC_{\infty}$ (ng.h/ml) | CL/F (ml/h/kg) | $t_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|
| Normal (n=6) | 37.6±10.6 | 6094±3589 | 39.3±36.0 | 163.0±55.5 | 5.5 (2-24) |
| Impaired (n=6) | 52.7±20.7 | 4487±1723 | 33.0±12.9 | 160.4±56.5 | 4.0 (2-10) |
| Geometric mean (CV%) | | | | | |
| Normal (n=6) | 36.3 (28.1) | 4942 (58.9) | 29.7 (91.4) | 154.6 (34.0) | |
| Impaired (n=6) | 49.2 (39.3) | 4190 (38.4) | 31.4 (39.0) | 151.4 (35.2) | |
| **RI/Normal** | **1.36** | **0.85** | **1.06** | | |

**Table 2. Summary of Other Aripiprazole Pharmacokinetic Parameters (15 mg Dose)**

| Parameter ***Renal Function*** | $V_z/F$ (L/kg) | $A_{e,}$ (μg) | CLr (ml/h/kg) | $f_u$ (%) | $CL/f_u$ (ml/h/kg) |
|---|---|---|---|---|---|
| Normal (n=6) | 7.2±3.6 | 6.7±4.7 | 0.03±0.01 | 1.54±0.70 | 2486±1480 |
| Impaired (n=6) | 7.0±1.4 | 26.7±2.6 | 0.10±0.04 | 1.46±0.65 | 2417±606 |
| Geometric mean (CV%) | | | | | |
| Normal (n=6) | 6.6 (49.9) | 5.6 (69.6) | 0.03 (37.2) | 1.41 (45.2) | 2106 (59.5) |
| Impaired (n=6) | 6.9 (19.4) | 26.6 (9.7) | 0.10 (35.6) | 1.35 (44.4) | 2333 (25.1) |
| **RI/Normal** | **1.04** | **4.75** | **3.33** | **0.96** | **1.11** |

**Figure 1. Mean plasma aripiprazole concentration-time profiles following a single 15 mg dose of aripiprazole to normal healthy subjects and subjects with severe renal impairment**

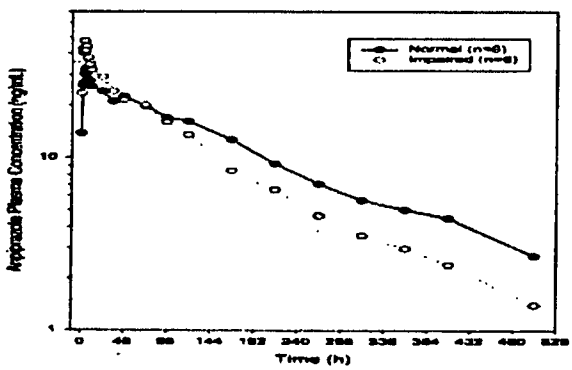


**Table 3. Summary of OPC-14857 Pharmacokinetic Parameters (15 mg Dose)**

| Parameter<br>***Renal Function*** | $C_{max}$<br>(ng/ml) | $AUC_{\infty}$<br>(ng.h/ml) | $T_{max}$<br>(h) | $T_{1/2}$<br>(h) | Ae<br>(μg) |
|---|---|---|---|---|---|
| Normal (n=6) | 4.7±2.3 | 2104±855 | 120 (48-168) | 280.8±88.0 | 14.6±7.8 |
| Impaired (n=6) | 7.5±4.9 | 2236±1035 | 84 (24-120) | 146.1±41.7 | 27.1±5.4 |
| Geometric mean (CV%) | | | | | |
| Normal (n=6) | 4.3 (48.6) | 1930 (40.7) | | 270.2 (31.3) | 13 1 (53.7) |
| Impaired (n=6) | 6.6 (66.3) | 2062 (46.3) | | 140.4 (28.6) | 26.8 (19.8) |
| **RI/Normal** | **1.53** | **1.07** | | **0.52** | **2.04** |

**Figure 2. Mean plasma OPC-14857 concentration-time profiles following a single 15 mg dose of aripiprazole to normal healthy subjects and subjects with severe renal impairment**

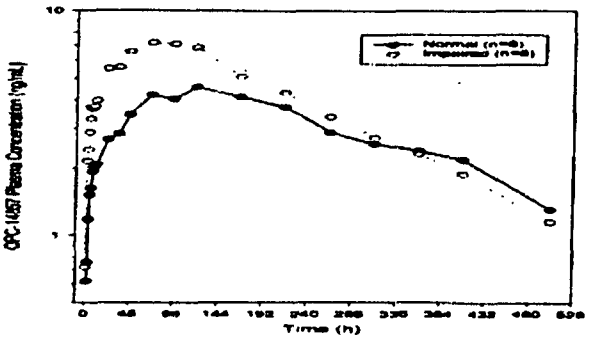


**Table 4. Summary of OPC-3373 Pharmacokinetic Parameters (15 mg Dose)**

| Parameter<br>***Renal Function*** | $C_{max}$<br>(ng/ml) | $AUC_t$<br>(ng.h/ml) | $T_{max}$<br>(h) | Ae<br>(μg) |
|---|---|---|---|---|
| Normal (n=6) | 3.7±1.6 | 11.1±7.1 | 1.5 (1-4) | 1021±212 |
| Impaired (n=6) | 8.8±3.4 | 304.3±221.2 | 3.0 (1-10) | 585±217 |
| Geometric mean (CV%) | | | | |
| Normal (n=6) | 3.4 (43.3) | 8.7 (63.6) | | 1002 (20.7) |
| Impaired (n=6) | 8.2 (38.8) | 223.7 (72.7) | | 555 (37.1) |
| **RI/Normal** | **2.41** | **25.71** | | **0.55** |

**Table 5. Summary of OPC-3952 and DCPP Ae Values (15 mg Dose)**

| | ***OPC-3952*** | | ***DCPP*** | |
|---|---|---|---|---|
| Parameter<br>***Renal Function*** | $A_e$<br>(μg) | GeoMean<br>(%CV) | Ae<br>(μg) | GeoMean<br>(%CV) |
| Normal (n=6) | 177.6±85.0 | 160.3 (47.8) | 16.1±14.8 | 8.8 (91.9) |
| Impaired (n=6) | 117.2±24.9 | 115.5 (21.2) | 0 | |
| **RI/Normal** | | **0.72** | | |

## Summary

- Compared to healthy subjects, subjects with severe renal impairment had higher $C_{max}$ (36% greater) and lower AUC (15% lower) of aripiprazole. However, body weight normalized clearance was similar between these two populations.

- Mean renal clearance of aripiprazole was about 3-fold higher in subjects with severe renal impairment, however, this difference is not considered clinically relevant since urinary clearance is a minor fraction of the overall clearance (0.3%).

- Severe renal impairment did not cause a change in the unbound fraction of aripiprazole, and values for both groups were similar. Consequently, the values for unbound clearance ($CL/f_u$) fraction of drug are reflective of the total clearance (CL/F) values.

- For OPC-14857, the mean $C_{max}$ increased about 53% but mean AUC was unchanged in subjects with severe renal impairment. Mean urinary excretion of OPC-14857 was increased about 2-fold in subjects with severe renal impairment.

- For OPC-3373, plasma concentrations were 26-fold higher (as determined by $AUC_t$) and urinary excretion was 2-fold lower in subjects with severe renal impairment compared to normal healthy controls. However, even the increased concentrations for OPC-3373 seen in the renally impaired subjects were much lower than aripiprazole plasma concentrations (5% of aripiprazole AUC).

- Mean urinary excretion of OPC-3952 was about 28% lower in subjects with severe renal impairment compared to normal healthy controls.

- In normal healthy subjects, the mean urinary excretion of DM-1451 was too low to be quantified. The mean urinary excretion of DCPP was approximately 2.4-fold greater than that of aripiprazole. In subjects with severe renal impairment, only 1 subject had consistently detectable urine concentrations of DM-1451 and DCPP.

**Conclusion**

- Compared to healthy subjects, subjects with severe renal impairment had higher $C_{max}$ (36% greater) and lower AUC (15% lower) of aripiprazole.

- The $C_{max}$ of OPC-14857 increased by 53% and the AUC was unchanged in subjects with severe renal impairment and renal excretion was increased 2-fold.

- The renal excretion of OPC-3373, which is predominantly excreted in urine, decreased by 50% in subjects with severe renal impairment.

- The safety and tolerability profile of aripiprazole observed in this study of subjects with impaired renal function was consistent with what was observed in other clinical pharmacology studies with aripiprazole.

**Study 98-206** (Vol. 69-79): ***A Double-Blind, Placebo-Controlled Study of the Effects of Orally Administered Ketoconazole on Aripiprazole (OPC-14597) Pharmacokinetics in Healthy Adult Male and Female Subjects***

The purpose of this study was to determine whether inhibition of CYP3A4 alters the pharmacokinetic characteristics of aripiprazole in healthy volunteers. This was a double-blind, parallel group, placebo-controlled study in 29 healthy volunteers (mean age 29 yrs, 16 Caucasians, 3 Blacks, 8 Hispanic/Latinos, 1 UK and 1 Asian). The subjects had their CYP3A4 metabolic capacity determined at baseline using an erythromycin breath test (EBT).

**Study Design**

| | Medication | DB Test 2-h post Dose | Blood and Urine Sampling | |
|---|---|---|---|---|
| Baseline | | Yes | | |
| Day 1 | Aripiprazole 15 mg (N=23) or placebo (N=6) | Yes | 312 hours | 72 hours |
| Day 15-28 | Ketoconazole 200 mg/day | Yes on Day 15 | | |
| Day 16 | Aripiprazole 15 mg or placebo | Yes | 312 hours | 72 hours |

Two single doses of aripiprazole or placebo were administered. Ketoconazole was administered for 14 days. $^{14}$C-erythromycin was administered on four occasions for erythromycin breath tests. Aripiprazole 15 mg tablets (Lot #97K87A015A) was used and the study site provided the $^{14}$C-erythromycin.

***Pharmacokinetic Results of Aripiprazole***

**Table 1. Summary of Aripiprazole Pharmacokinetic Parameters (15 mg Dose with and without Ketoconazole 200 mg/day)**

| Parameter | $C_{max}$ (ng/ml) | $AUC_\infty$ (ng.h/ml) | CL/F (ml/h/kg) | $t_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|
| Alone (n=18) | 61.3±17.4 | 3750±1940 | 65±28 | 83±33 | 3.5 (2-12) |
| Comb (n=18) | 85.2±25.4 | 6803±5844 | 40±16 | 100±53 | 5.0 (3-8) |
| Geometric mean (CV%) | | | | | |
| Alone (n=6) | 59.1 (28.4) | 3377 (51.7) | 60 (43.0) | 76 (39.8) | |
| Comb (n=6) | 80.8 (29.8) | 5513 (85.9) | 36 (40.0) | 90 (53.0) | |
| **Comb/Alone** | **1.37** | **1.63** | **0.60** | **1.18** | |

**Table 2. Summary of Other Pharmacokinetic Parameters of Aripiprazole (15 mg Dose with and without Ketoconazole 200 mg/day)**

| Parameter | $V_z/F$ (L/kg) | $A_{e,72h}$ (μg) | CLr (ml/h/kg) | $f_e$ (%) |
|---|---|---|---|---|
| Alone (n=18) | 6.92±2.36 | 4925±4456 | 0.03±0.02 | 0.03±0.03 |
| Comb (n=18) | 4.96±1.72 | 7026±7088 | 0.03±0.03 | 0.05±0.05 |
| **Comb/Alone** | **0.72** | **1.43** | **1.00** | **1.67** |

**Table 3. Summary of OPC-14857 Pharmacokinetic Parameters (15 mg Dose with and without Ketoconazole 200 mg/day)**

| Parameter | $C_{max}$ (ng/ml) | $AUC_{\infty}$ (ng.h/ml) | CL/F (ml/h/kg) | $t_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|
| Alone (n=18) | 7.8±1.9 | 1534±435 | 143±55 | 99±41 | 3.5 (2-12) |
| Comb (n=18) | 11.6±4.6 | 2741±921 | 79±23 | 137±78 | 5.0 (3-8) |
| Geometric mean (CV%) | | | | | |
| Alone (n=6) | 7.6 (24.4) | 1471 (28.2) | 135 (38.5) | 92 (41.4) | |
| Comb (n=6) | 10.9 (20.4) | 2604 (33.6) | 76 (29.1) | 120 (56.9) | |
| **Comb/Alone** | **1.43** | **1.77** | **0.56** | **1.30** | |

**Table 4. Summary of Other Pharmacokinetic Parameters of OPC-14857 (15 mg Dose with and without Ketoconazole 200 mg/day)**

| Parameter | $V_z/F$ (L/kg) | $A_{e,\,72\,h}$ (μg) | CLr (ml/h/kg) | $f_e$ (%) |
|---|---|---|---|---|
| Alone (n=18) | 19±5 | 19045±7554 | 0.57±0.23 | 0.13±0.05 |
| Comb (n=18) | 14.3±6.3 | 25717±11352 | 0.57±0.21 | 0.17±0.08 |
| **Comb/Alone** | **0.75** | **1.35** | **1.00** | **1.31** |

**Figure 1. Mean plasma aripiprazole and OPC-14857 concentration-time profiles following single oral 15 mg aripiprazole doses, given alone and in combination with 200 mg ketoconazole, in healthy subjects**

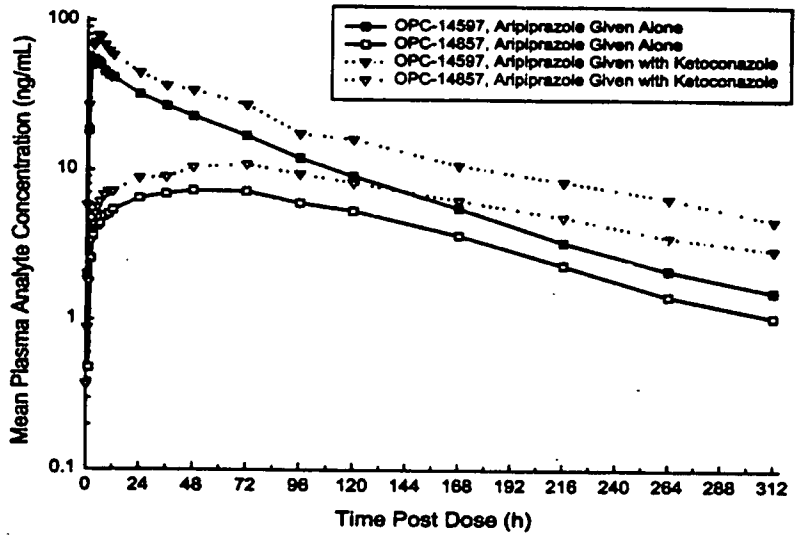



**Table 5. Summary of Pharmacokinetic Parameters of OPC-3373 (15 mg Dose with and without Ketoconazole 200 mg/day)**

| Parameter | $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | CL/F (ml/h/kg) | $t_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|
| Alone (n=18) | 8.2±3.8 | 17±12 | 1846±292 | 3.7±0.2 | 1.0 (1-2) |
| Comb (n=18) | 4.1±1.5 | 37±50 | -- | -- | 86 (4-168) |
| **Comb/Alone** | **0.50** | **2.18** | | | |

**Table 6. Summary of OPC-3373 Pharmacokinetic Parameters (15 mg Dose with and without Ketoconazole 200 mg/day)**

| Parameter | $V_z/F$ (L/kg) | $A_{e,72\,h}$ (ng) | CLr (ml/h/kg) | $f_e$ (%) |
|---|---|---|---|---|
| Alone (n=18) | 9.8±1.1 | 745669±161760 | 177±27 | 8.9±1.9 |
| Comb (n=18) | -- | 316416±149147 | -- | 3.8±1.8 |
| **Comb/Alone** | | **0.42** | | **0.43** |

**Table 7. Summary of Other Metabolites Pharmacokinetic Parameters (15 mg Dose with and without Ketoconazole 200 mg/day)**

| Parameter | DCPP | | DM-1451 | | U-3 | |
|---|---|---|---|---|---|---|
| | Alone (n=1) | Comb (n=7) | Alone (n=11) | Comb (n=10) | Alone (n=18) | Comb (n=6) |
| $C_{max}$ (ng/ml) | 2.5 | -- | 1.0 (ND) | 1.2 (0.06) | -- | -- |
| $T_{max}$ (h) | 3 | -- | 4 (ND) | 8 (6-10) | -- | -- |
| $f_e$ (%) | 0.03 | 0.39±0.23 | 0.01±0.01 | 0.02±0.02 | 10.0±3.3 | 4.7±2.4 |
| $A_{e,72\,h}$ (ug) | 2.5 | 29.9±17.9 | 2.1±1.6 | 3.0±2.6 | 830±274 | 390±203 |
| **Com/Alone** | | **12.16** | | **1.41** | | **0.47** |

## Summary

- When ketoconazole 200 mg was coadministered, mean AUC of aripiprazole and OPC-14857 increased by 63% and 77%, respectively. Their mean $C_{max}$ also increased by 37% and 43%, respectively. For both moieties, apparent clearance was decreased 40% and 44%, respectively.

- OPC-3373 $C_{max}$ was reduced by 50%, and AUC increased 2-fold when aripiprazole was co-administered with ketoconazole.

- Less than 1% of the dose was excreted in urine as either aripiprazole or OPC-14857. The mean amount of each compound excreted in urine increased 35-43% following co-administration of aripiprazole with ketoconazole.

- Excretion of the metabolites in urine, OPC-3373 and U-3, was reduced by 53-58% by co-administration of ketoconazole.

- The DCPP metabolite was detected in the urine of only one subject after administration of aripiprazole alone, but was detected in the urine of seven subjects following administration of aripiprazole in combination with ketoconazole, with a mean $A_{e,72\,h}$ about 10-fold greater.

### *EBT Results*

The $f_e$ EBT results on the four occasions that CYP3A4 activity was assessed are summarized in the following table.

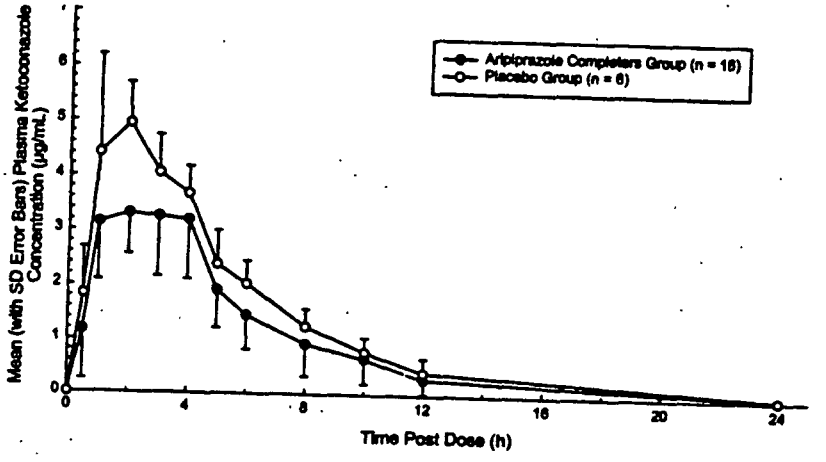
**Table 8. Summary of Fraction of Radioactivity Dose Expired in 1-hour Following Intravenous Bolus $^{14}$C-Erythromycin Doses in Healthy Subjects**

| Group | Baseline | A or P Alone | Ketoc Alone | Combination |
|---|---|---|---|---|
| Aripiprazole (n=18) | 1.96±0.43 | 1.76±0.49 | 0.66±0.27 | 0.51±0.24 |
| Placebo (n=6) | 1.98±0.89 | 1.95±0.88 | 0.67±0.31 | 0.46±0.28 |

The 10% reduction in CYP3A4 activity (as measured by EBT) for aripiprazole given alone was much smaller than its 66% reduction in CYP3A4 activity following administration of a single 200 mg dose of ketoconazole alone. The additional reduction in CYP3A4 activity following co-administration of aripiprazole with ketoconazole was smaller than the decrement observed in the placebo group following the second ketoconazole dose.

***Ketoconazole Exposure***

**Figure 2. Mean (with SD error bars) plasma ketoconazole concentration-time profiles on the second day of 200 mg QD ketoconazole dosing in healthy subjects**




This plot show that both treatment groups in this study attained systemic ketoconazole exposure. Since plasma ketoconazole concentrations were near peak levels at 2-h post dose, administration of the EBT at that time likely provided an assessment of maximal (or near maximal) CYP3A4 inhibition.

**Conclusion**

- Coadministration of ketoconazole with a single 15 mg dose of aripiprazole increased AUC of aripiprazole by 63%, and of its active metabolite OPC-14857 by 77%; the $C_{max}$ was increased by 37% and 43%, respectively.

- Single 15 mg oral doses of aripiprazole decreased the fraction of the radioactive intravenous dose of $^{14}$C-erythromycin expired in 1 hour by 10%, in contrast, ketoconazole decreased this parameter by 66%.

- Administration of a single oral dose of 15 mg of aripiprazole either alone or with 200 mg/day of ketoconazole was safe and tolerated by healthy subjects.

**Comment**

The worst-case scenario that 400 mg clinical dose of ketoconazole was not studied. It is expected to see even higher increase in aripiprazole systemic exposure when both drug coadministered at clinical dose and dosage adjustment should be considered.

**Study 98-207** (Vol. 80-83): ***An Open-Label Study of Aripiprazole (OPC-14597) Pharmacokinetics in Healthy Adults with Poor and Extensive Metabolizer Genotype for Cytochrome P450 2D6, and the Effect of Co-administered Quinidine on Aripiprazole Pharmacokinetics***

The primary objective of this study was to assess the effect of CYP2D6 inhibition (quinidine co-administration) on aripiprazole pharmacokinetics. The secondary objective was to assess the effect of poor and extensive CYP2D6 metabolizer genotype on aripiprazole pharmacokinetics. This was an open-label, parallel group study and dosing schedule is shown below:

**Study Design and Dosing Schedule**

| Group | N | Genotype | Aripiprazole (Day 1) | Quinidine Base (Day 1-13) |
|---|---|---|---|---|
| 1 | 12 | EM | 10 mg (Lot #98B85A010C) | |
| 2 | 12 | EM | 10 mg | 166 mg (Lot #W232), Coadministered on Day 1 |
| 3 | 5 | PM | 10 mg | |

Cardioquin 275 mg contains 166 mg of quinidine base.

**Demographic Characteristics**

| Characteristics | Age (yrs) | Gender (M/F) | Weight (Kg) | Race White/Black/(Hispanic/Latino) |
|---|---|---|---|---|
| Group 1 EM (n=12) | 29±7.5 | 6/6 | 72.1±10.5 | 8/0/4 |
| Group 2 EM (n=12) | 30±8.9 | 6/6 | 74.3±12.7 | 8/2/2 |
| Group 3 PM (n=5) | 32±9.9 | 2/3 | 70.8±18.4 | 4/0/1 |

***Pharmacokinetic Results***

**Table 1. Summary of Aripiprazole Pharmacokinetic Parameters (10 mg Dose)**

| Parameter | $C_{max}$ (ng/ml) | $AUC_{\infty}$ (ng.h/ml) | CL/F (ml/h/kg) | $V_z/F$ (L/kg) | $t_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|
| EM alone (n=12) | 53.5±21.1 | 3221±1389 | 50.0±23.5 | 5.6±1.6 | 85±23 | 4 (2-24) |
| EM Comb (n=12) | 58.3±15.4 | 6654±2126 | 23.8±10.2 | 4.5±2.2 | 141±71 | 4 (2-12) |
| PM alone (n=5) | 49.1±17.6 | 5698±1894 | 31.1±21.4 | 6.8±5.8 | 146±36 | 6 (3-6) |
| Geometric mean (CV%) | | | | | | |
| EM alone (n=12) | 49.8 (39.4) | 2984 (43.1) | 45.6 (47.1) | 5.4 (29.3) | 81.8 (26.5) | |
| EM Comb (n=12) | 56.2 (26.4) | 6319 (32.0) | 22.0 (42.7) | 4.0 (48.8) | 127.3 (50.5) | |
| PM alone (n=5) | 46.3 (35.8) | 5420 (33.2) | 27.0 (68.7) | 5.5 (85.3) | 141.3 (25.0) | |
| **EM Comb/EM** | **1.13** | **2.12** | **0.48** | **0.75** | **1.56** | |
| **PM/EM** | **0.93** | **1.82** | **0.59** | **1.02** | **1.73** | |

**Figure 1. Mean plasma aripiprazole concentration-time profiles following single oral 10 mg aripiprazole doses, given alone or in combination with 166 mg quinidine to healthy subjects of CYP2D6 extensive metabolizer genotypes, and to poor metabolizers**

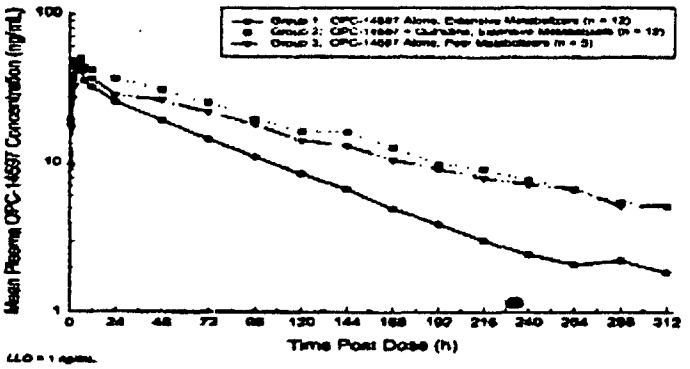
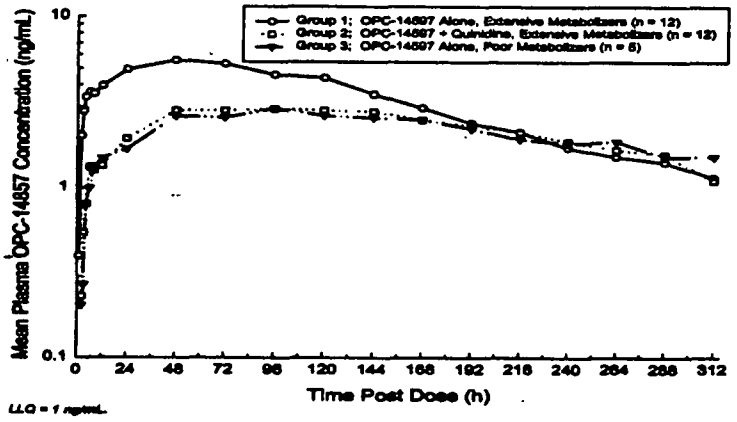



**Table 2. Summary of OPC-14857 and OPC-3373 Pharmacokinetic Parameters (10 mg Dose)**

| | *OPC-14857* | | | *OPC-3373* | | |
|---|---|---|---|---|---|---|
| Parameter | $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | $T_{max}$ (h) | $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | $T_{max}$ (h) |
| EM alone (n=12) | 6.1±1.9 | 1012±229 | 72 (24-144) | 5.1±2.2 | 10.6±9.0 | 4 (2-24) |
| EM Comb (n=12) | 3.2±0.9 | 687±237 | 120 (72-192) | 4.1±1.3 | 6.3±4.8 | 4 (2-12) |
| PM alone (n=5) | 3.2±1.0 | 674±185 | 96 (48-192) | 4.4±0.7 | 9.4±4.4 | 6 (3-6) |
| Geometric mean (CV%) | | | | | | |
| EM alone (n=12) | 5.7 (31.9) | 989 (22.6) | | 4.7 (43.0) | 6.3 (84.7) | 1.1 (1-2) |
| EM Comb (n=12) | 3.1 (28.3) | 651 (34.5) | | 4.0 (31.1) | 4.9 (76.6) | 1 (1-4.1) |
| PM alone (n=5) | 3.1 (31.0) | 649 (27.5) | | 4.3 (16.4) | 8.7 (47.3) | 2 (1-4) |
| **EM Comb/EM** | **0.54** | **0.66** | | **0.84** | **0.77** | |
| **PM/EM** | **0.54** | **0.66** | | **0.91** | **1.38** | |

**Figure 2. Mean plasma OPC-14857 concentration-time profiles following single oral 10 mg aripiprazole doses, given alone or in combination with 166 mg quinidine to healthy subjects of CYP2D6 extensive metabolizer genotypes, and to poor metabolizers**



**Summary**

- In EM genotype subjects, there was a 112% increase in mean aripiprazole AUC when aripiprazole was given with quinidine, compared to when aripiprazole was given alone. There was a corresponding decrease in CL/F (52%) and increase in $t_{1/2}$ (56%). This increase in AUC was not accompanied by a marked difference in mean $C_{max}$ or V/F. These results are consistent with inhibition of aripiprazole metabolism.

- OPC-14857 $C_{max}$ and AUC decreased by 46% and 34%, respectively when aripiprazole was given with quinidine compared to when aripiprazole was given alone, indicating that CYP2D6 has a role in aripiprazole metabolism, i.e., formation of OPC-14857. $T_{max}$ for the parent drug was 4 hours, but was 72 hours for OPC-14857 suggesting that OPC-14857 kinetics are formation rate limited. Consistently, the median $T_{max}$ occurred much later (120 hours) when the CYP2D6 inhibitor, quinidine was co-administered with aripiprazole.

- Plasma OPC-3373 concentrations were low in all subjects, with $C_{max}$ for any subject less than 9 ng/ml [redacted]. Based on assessment of $C_{max}$ and $AUC_t$, co-administration of the CYP2D6 inhibitor quinidine did not affect formation of OPC-3373.

- The mean plasma aripiprazole and OPC-14857 concentrations were similar for PM genotype subjects and for EM subjects coadministered quinidine with aripiprazole. Overall, the other pharmacokinetic parameters for these two groups were also quite similar.

- In both EM groups, orthostatic lightheadedness was the most frequently occurring adverse event. In the EM group receiving aripiprazole alone, headache and lightheadedness was the most frequently occurring AEs. Nausea was the most frequently occurring AE in the Poor Metabolizer group, and the second most frequent AE in the combination group.

- One subject had an inconsistent increase in $QT_c$ that met the criteria for abnormality, which the investigator did not considere it to be abnormal. A few EM subjects had decreased standing blood pressure readings often occurrring at 6 hours post dosing on Day 1 that met the criteria for vital sign abnormalities.

- There is no evidence that CYP2D6 genotype or quinidine co-administration has any impact on the likelihood for vital sign abnormalities following administration of aripiprazole.

**Conclusion**

- Co-administration of the CYP2D6 inhibitor quinidine with aripiprazole resulted in a 2-fold increase in the aripiprazole AUC and no change in its $C_{max}$. The $C_{max}$ and AUC of OPC-14857 decreased with quinidine coadministration (46% and 33%, respectively).

- The mean plasma aripiprazole and OPC-14857 concentrations were similar for PM genotype subjects and for EM subjects coadministered quinidine with aripiprazole. Overall, the other pharmacokinetic parameters for these two groups were also quite similar.

- The administration of single 10 mg doses of aripiprazole with and without 166 mg of quinidine base was well-tolerated in healthy subjects.

**Comment**
The net increase in active moieties exposure in poor metabolizers and in subjects coadministered aripiprazole with quinidine was greater than 50%. Dosage adjustment should be considered for coadministration of aripiprazole with potential CYP2D6 inhibitors, also for patients who are CYP2D6 poor metabolizers.

**Study 00-233** (Vol. 84): ***Population Pharmacokinetic Pharmacodynamic Analysis of Aripiprazole***

**Population PK Analysis**

The objectives of this population PK analysis were (1) to describe the PK of aripiprazole in patients with schizophrenia; (2) to identify predictors of exposure to the drug (demographics, laboratory values, concomitant medications, disease, etc.) and identify sub-populations with altered PK; and (3) to estimate the inter-individual and residual variability of aripiprazole pharmacokinetics. The PK data file for analysis contained 2563 plasma samples of 694 patients from the following 5 studies:

***31-93-202***: Efficacy and Tolerability of Ascending Doses of OPC-14597 Compared to Placebo and to Haloperidol in Acutely Relapsing Hospitalized Schizophrenic Patients (34 patients, 175 concentrations)
***31-94-202***: A Dose Ranging Study of the Efficacy and Tolerability of OPC-14597 in Acutely Relapsing Hospitalized Schizophrenic Patients (180 patients, 1255 concentrations)
***31-97-201***: A Phase III Double-Blind Placebo-Controlled Study of Aripiprazole in the Treatment of Psychosis (204 patients, 631 concentrations)
***31-97-202***: A Phase III Double-Blind Placebo-Controlled Study of Aripiprazole in the Treatment of Psychosis, with Risperidone as Active Control (202 patients, 664 concentrations)
***31-97-203***: An Open-Label Follow-on Study of the Long-Term Safety of Aripiprazole in Patients with Psychosis (515 patients, 1501 concentrations)

***Results of Population PK Analysis***

- The PK of aripiprazole were described by a linear one-compartment model with first order absorption.

- Although clearance was related to lean body weight, and volume of distribution was related to weight and age, these dependencies are unlikely to be clinically important.

- The estimates of the apparent oral clearance in patients were similar to those for normal volunteers.

- The results of the analysis indicated that no dose adjustments are needed based on demographic variables.

- Although the analysis indicated no dosage adjustment for any of the medications co-administered with aripiprazole, the number of patients on the concomitant medications, except benzodiazepines, was too small to be conclusive.

**Population PK/PD Analysis**

The objectives of the population PK/PD analysis were (1) to assess the relationship between PD (as measured by a decrease from baseline in the total PANSS score) versus systemic exposure, duration of treatment and covariates; and (2) to estimate the inter-individual variability of aripiprazole pharmacodynamics. The PK/PD file contributed 2472 total PANSS scores from 582 aripiprazole patients and 1205 scores from 306 placebo patients in 4 studies (Open-label Study 31-97-203 was not used).

***Results of PK/PD Analysis***

- The change from baseline of the total PANSS score in patients taking aripiprazole was described as the sum of change due to placebo and change due to the aripiprazole. Both effects (decrease from baseline) increased with duration of dosing during the study.

- The placebo effect increased with increasing baseline score, and was lower in patients who were administered lorazepam concomitantly.

- The total effect of the drug (placebo and aripiprazole effect) was significantly higher in patients with higher baseline score, and lower in patients with concomitant lorazepam administration.

- The modeling indicated that neither exposure nor dose was found to be correlate well with the efficacy of aripiprazole.

**Population PK/Safety Analysis**

The objective of the population PK/Safety analysis of aripiprazole was to assess the relationship between patients' aripiprazole plasma concentrations and $QT_c$ prolongation. The data from the Studies 31-97-201 and 31-97-202 were used for the PK/Safety analysis. The data included 251, 506 and 616 $QT_c$ observations from respectively 184, 313 and 328 aripiprazole patients in the 2-hour, 12-hour and 48-hour window (the maximum time difference between ECG and blood draw).

***Results of PK/Safety Analysis***

- No relationships could be determined between the change from baseline of $QTC_B$, $QTC_F$ or $QTC_n$ and the corresponding plasma concentrations of aripiprazole.

- There was no prolongation of $QT_c$ in patients on aripiprazole, regardless of the algorithm used to calculate $QT_c$.

- The variability in changes from baseline of $QT_c$ in aripiprazole patients was comparable to that in placebo patients.

Pharmacometrics consult has been requested to verify the information generated from these population PK or PK/PD or PK/Safety analyses that has impact on labeling. See Pharmacometrics review.

**Study 97-205** (Vol. 85-90): ***Influence of Multiple Dose Administration of OPC-14597 on the Metabolism of Dextromethorphan***

The objective of this study was to assess the effect of multiple doses of OPC-14597 (aripiprazole) on the metabolism of dextromethorphan (DM). This was an open label, multiple dose study in 22 healthy volunteers. Dosing schedule is shown below:

**Dose Schedule**

| | Dextromethorphan | (Oral in the morning) | Aripiprazole |
|---|---|---|---|
| Group 1 | Day 0 and Day 15 (30 mg/day) | 30 mg/day on Day 2-15 | |
| Group 2 | Day 0 and Day 17 (30 mg/day) | 10 mg on Day 2, 20 mg on Day 3, 30 mg on Day 4-17 | |

Aripiprazole 10mg Lot #5K75A010, 15 mg Lot #5K75A015

**Demographic Characteristics**

| | | Completers (n=6) | Non-Completers (n=16) |
|---|---|---|---|
| Age (years) | Mean±SD | 26±8 | 28±8 |
| Gender-Male | N (%) | 6 (100%0 | 16 (100%) |
| Ethnic Origin-Caucasian | N (%) | 6 (100%) | 16 (100%) |
| Weight (kg) | Mean±SD | 81±12 | 83±14 |

All 22 enrolled subjects were Caucasian males. Thirteen (59%) of 22 subjects denied ever having used tobacco and 11 (50%) subjects were current alcohol drinkers. Additional 16 subjects were enrolled but did not complete the study. Of these 22 subjects, 13 (59%) discontinued due to AEs and 3 (14%) withdrew consent. There were only 6 (27%) of 22 subjects who completed the study.

**Table 1. Mean Dextromethorphan and Metabolites Urinary Excretion Data (Mean with CV%)**

| | | | $A_{e\,48\,h}$ (mg) | | | |
|---|---|---|---|---|---|---|
| Compound | DM | DRP | MMP | HMP | DM/DRP | DM/MMP |
| DM alone (n=6) | 0.17 (212) | 6.59 (24) | 0.03 (189) | 4.30 (34) | 0.03 (211) | 4.37 (64) |
| DM + A (n=6) | 0.24 (194) | 8.11 (22) | 0.04 (131) | 4.61 (13) | 0.03 (192) | 4.12 (71) |

**Summary**

Although the mean amounts of DM and its metabolites excreted in the urine showed a slight increase when DM was given with aripiprazole, there was a large degree of variability (%CV) in the observed individual subject results, precluding definitive conclusion from being drawn. There was a slight decrease in the mean DM/MMP $A_{e\,48h}$

molar ratio and no change in the mean DM/DRP $A_{e\ 48h}$ molar ratio. The ratio results were also quite variable (CV>64%), and did not consistently increase among the subjects who completed the study.

**Table 2. Summary of Aripiprazole Pharmacokinetic Parameters**

| Parameter | $C^{ss}_{min}$ (ng/ml) | $C^{ss}_{max}$ (ng/ml) | $AUC_\tau$ (ng.h/ml) | CL/F (ml/h/kg) | $T_{max}$ (h) |
|---|---|---|---|---|---|
| Mean±SD | 252±144 | 375±213 | 6998±4205 | 64±22 | 6 (2-8) |
| GeoMean (CV%) | 226 (57) | 338 (57) | 6231 (60) | 60 (34) | |
| Parameter | $t_{1/2}$ (h) | $V_z/F$ (L/kg) | $CL_\tau$ (ml/h/kg) | | |
| Mean±SD | 67±20 | 5.8±1.4 | 0.04±0.02 | | |

**Table 3. Summary of OPC-14857, OPC-3373, DCPP and DM-1451 Pharmacokinetic Parameters**

| Parameter | $C^{ss}_{min}$ (ng/ml) | $C^{ss}_{max}$ (ng/ml) | $AUC_\tau$ (ng.h/ml) | $CL_\tau$ (ml/h/kg) | $T_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|
| ***OPC-14857*** | | | | | | |
| Mean±SD | 107±21 | 135±28 | 2773±553 | 0.26±0.07 | 124±46 | 3 (1-24) |
| GeoMean (CV%) | 105 (20) | 133 (21) | 2723 (20) | 0.26 (26.2) | 120 (37) | |
| ***OPC-3373*** | | | | | | |
| Mean±SD | 2±3 | 19±7 | 140±72 | 214±110 | 80±77 | 2 (1-4) |
| GeoMean (CV%) | | 18 (37) | 121 (52) | 190 (51.3) | 59 (96) | |
| ***DCPP*** | | | | | | |
| Mean±SD | 0 | 7±0.8 | 52±76 | | | |
| GeoMean (CV%) | | 7 (12) | 21 (144) | | | |
| ***DM-1451*** | | | | | | |
| Mean±SD | 0.26±0.53 | 3±1 | 31±31 | 3.96±2.74 | 150 | 6 (2-12) |
| GeoMean (CV%) | | 18 (37) | 21 (98) | 3.22 (69.2) | 150 | |

## Summary

- At steady-state, aripiprazole and its metabolites showed no detectable inhibition of CYP2D6 or CYP3A4, as judged by results using DM as a probe drug.

- Dosing with 30 mg of aripiprazole daily for 14 days was tolerated by normal volunteers, with the majority of AEs being mild to moderate in severity and not unexpected. Most of the AEs resolved spontaneously. There were no severe AEs.

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

- There was no apparent association between plasma aripiprazole or its metabolite concentrations and ability to tolerate the 30 mg per day treatment.

Study **00-231** (Vol. 91-94): ***An Open-Label Study of the Influence of Co-administered Aripiprazole Oral Tablets (OPC-14597) on Dextromethorphan Oral Solution Metabolism via Cytochrome P450 2D6 in Healthy Volunteers***

The primary objective of this study was to determine the effect of co-administered aripiprazole on dextromethorphan metabolism via CYP2D6. This was an open-label, sequential crossover study of dextromethorphan (DM), with multiple doses of aripiprazole. A total of 25 subjects (all CYP2D6 EMs) were enrolled and 17 subjects completed the study. All subjects received a single 10 mg dose of aripiprazole (Lot #98J82A010A) daily for 14 days (Days 4-18) and a single 30 mg dose of DM on Days 1 (control Phase) and Day 18 at 2 hours after aripiprazole dose.

All subjects had blood samples collected for aripiprazole and metabolite analyses at 0.5 hour prior to aripiprazole dosing, then 1, 2, 3, 4, 5, 6, 8, and 12 hours post-aripiprazole dosing (Day 18), and 24, 48, 72, 96, 120, 144, 192, and 240 hours (Days 19-28) post-final aripiprazole dosing.

***Dextromethorphan and Metabolites Urinary Excretion***

**Table 1. Mean Dextromethorphan and Metabolites Urinary Excretion Data (Mean±SD)**

| | $A_{e\ 70\ h}$ *in mg* | | | $f_{e,\ 70\ h}$ *(%)* | |
|---|---|---|---|---|---|
| Compound | DM | DRP | DM/DRP | DM | DRP |
| DM alone (n=16) | 0.083±0.087 | 7.31±1.99 | 0.014±0.02 | 0.36±0.38 | 33.4±9.1 |
| DM + A (n=16) | 0.09±0.102 | 6.63±2.93 | 0.016±0.017 | 0.39±0.44 | 30.2±13.4 |
| Geomean (CV%) | | | | | |
| DM alone | 0.052 (105) | 6.96 (27) | 0.007 (136) | 0.22 (105) | 31.8 (27) |
| DM + A | 0.051 (113) | ND | 0.009 (107) | 0.22 (113) | ND |

All subjects were genotyped to be extensive metabolizers for CYP2D6. However, the DM/DRP $A_{e,\ 70\ h}$ ratio of Subject No. 20 is 3.8 in DM given alone treatment, whereas those for other 16 subjects who completed the study are less than 0.1. A urinary metabolic ratio (DM/DRP) of <0.3 is defined as EM phenotype, and ≥0.3 is defined as PM phenotype. It has been shown that CYP2D6 genotype can only accurately predict phenotype in about 95% of subjects. The remaining 5% discrepancies could be due to the imprecision of the phenotypic test or to unidentified mutations.

| | Genotype | DM/DRP | Phenotype | Aripiprazole Concentration |
|---|---|---|---|---|
| Subject #20 | EM | 3.8 | PM (≥0.3) | 2.5 |
| Other 16 subjects | EM | <0.1 | EM (<0.3) | 1 |

***Aripiprazole Pharmacokinetics***

**Table 2. Summary of Aripiprazole Pharmacokinetic Parameters**

| Parameter | $C^{ss}_{min}$ (ng/ml) | $C^{ss}_{max}$ (ng/ml) | $C^{ss}_{avg}$ (ng/ml) | $AUC_\tau$ (ng.h/ml) | Fluctuation Index (%) |
|---|---|---|---|---|---|
| Mean±SD | 93.3±43.5 | 153.9±57.9 | 118.0±48.8 | 2832±1172 | 54.8±15.4 |
| GeoMean (CV%) | 82.7 (47) | 141.4 (38) | 107.4 (41) | 2577 (41) | 53 (28) |
| Parameter | CL/F (ml/h/kg) | $T_{max}$ (h) | $t_{1/2}$ (L/kg) | $V_z/F$ (ml/h/kg) | Accumulation Index (%) |
| Mean±SD | 61.0±41.4 | 3. 0 (2-12) | 68±20 | 5.73±4.55 | 4.61±1.22 |
| Geomean (CV%) | 53 (68) | | 65 (30) | 4.98 (79) | 4.46 (26) |

**Table 3. Summary of OPC-14857 and OPC-3373 Pharmacokinetic Parameters**

| Parameter | $C^{ss}_{min}$ (ng/ml) | $C^{ss}_{max}$ (ng/ml) | $C^{ss}_{avg}$ (ng/ml) | $AUC_\tau$ (ng.h/ml) | Fluctuation Index (%) |
|---|---|---|---|---|---|
| ***OPC-14857*** | | | | | |
| Mean±SD | 41.4±17.3 | 53.0±19.7 | 45.9±17.8 | 1101±428 | 27.0±11.3 |
| GeoMean (CV%) | 36.2 (42) | 47.2 (37) | 40.8 (39) | 978 (39) | 25.0 (42) |
| ***OPC-3373*** | | | | | |
| Mean±SD | 1.9±1.0 | 9.6±4.9 | 3.1±1.3 | 73.5±32.1 | 391±546 |
| GeoMean (CV%) | ND (54) | 8.2 (51) | 2.4 (44) | 57.1 (44) | 271 (140) |

| Parameter | $T_{max}$ (h) | $t_{1/2}$ (h) | Accumulation Index (%) |
|---|---|---|---|
| ***OPC-14857*** | | | |
| Mean±SD | 3. 0 (1-24) | 87.7±28.1 | 5.79±1.68 |
| Geomean (CV%) | | 83.9 (32) | 5.58 (29) |
| ***OPC-3373*** | | | |
| Mean±SD | 3. 0 (1-3) | ND | ND |

**Figure 1. Steady-state aripiprazole and metabolites concentration-time profiles during a dosing interval (Day 18) following 14 days of daily oral 10 mg aripiprazole doses to CYP2D6 extensive metabolizer healthy subjects**

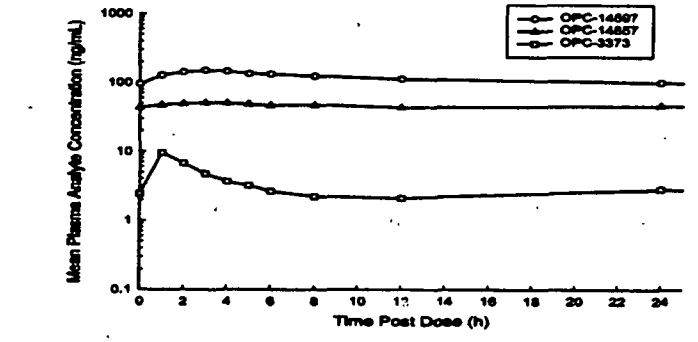



**Figure 2. Mean plasma aripiprazole and metabolites concentration-time profiles following the 14th daily oral 10 mg aripiprazole dose to CYP2D6 extensive metabolizer healthy subjects**

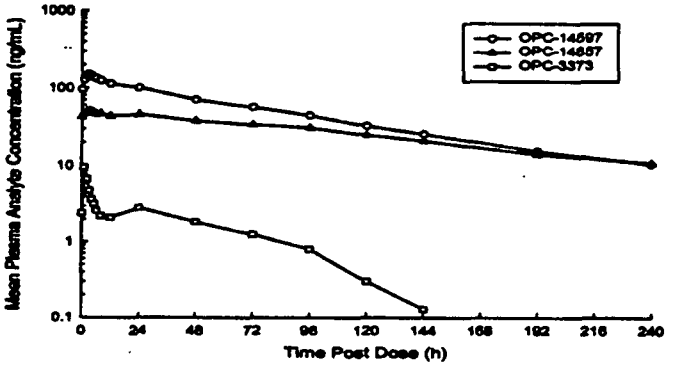


**Table 4. Comparison of Aripiprazole Pharmacokinetic Parameters with Study 31-93-201(10 mg)**

| Parameter | $C^{ss}_{max}$ (ng/ml) | $AUC_\tau$ (ng.h/ml) | CL/F (L/h) | $t_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|
| Current Study | 154 | 2832 | 4.4 | 68 | 3.00 |
| Study 31-93-201 | 162 | 2947 | 3.6 | 53 | 2.8 |

**Summary**

- The mean DM/DRP $A_{e,\,70\,h}$ molar ratios for DM given alone and in combination with aripiprazole were similar (0.014 and 0.016, respectively). The stick plot shows that the changes in this ratio upon aripiprazole co-administration were small for each subject, and no consistent trend for increase or decrease was observed.

- Using dextromethorphan as a probe drug, no inhibition of CYP2D6 was detected following 14 days of daily oral 10 mg aripiprazole dosing.

- The pharmacokinetic profile of aripiprazole in the current study is similar to that of the other study (Study 31-93-201) where aripiprazole was administered at doses of 10 mg once daily for 14 days.

- A total of 151 treatment emergent adverse events occurred during this study. Nine subjects had a total of 25 vital sign abnormalities. Prior to the vital sign abnormalities, one experienced vasovagal reaction, one had orthostatic lightheadedness and nausea, one experienced anxiety, and one with orthostatic lightheadedness and syncope.

**Study 00-226** (Vol. 95-97): ***An Open-Label, Two-Period, Randomized, Crossover Study of the Effect of Increased Gastric pH by Concomitant Famotidine Administration on Aripiprazole Pharmacokinetics***

The primary objective of this study was to assess the effect of famotidine co-administration on single dose aripiprazole pharmacokinetics. This was an open label, two-period, randomized, complete block, crossover study in 16 healthy young male and female subjects. All subjects received a single 15 mg dose of aripiprazole (Lot #97K87A015A) on two occasions separated by at least 21 days, one of the doses was administered concomitantly with a single dose of 40 mg of famotidine (Lot #J5911). A total of 17 subjects (12 males and 5 females; 11 Caucasians and 6 Blacks) enrolled in the study and 16 completed the study.

**Table 1. Summary of Aripiprazole Pharmacokinetic Parameters (15 mg Dose)**

| Parameter | $C_{max}$ (ng/ml) | $AUC_\infty$ (ng.h/ml) | CL/F (ml/h/kg) | $V_z/F$ (L/kg) | $t_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|
| A alone (n=16) | 60.5±15.6 | 3973±1912 | 62.7±30.2 | 5.81±2.49 | 71.2±24.2 | 4 (2-12) |
| A + F (n=12) | 38.1±9.4 | 3363±1434 | 71.1±31.4 | 7.02±2.20 | 74.8±20.9 | 5 (3-72) |
| *Geometric mean (CV%)* | | | | | | |
| A alone (n=16) | 58.7 (26) | 3546 (48) | 56.5 (48) | 5.47 (43) | 67.1 (34) | |
| A+F (n=16) | 36.9 (25) | 3089 (43) | 65.0 (44) | 7.07 (31) | 72.0 (28) | |
| **A+F/A** | **0.63** | **0.87** | **1.15** | **1.29** | **1.07** | |

$T_{lag}$ (h) 0.19±0.25 for A alone and 0.56±0.44 for A+F.

Table 2. Summary of OPC-14857 and OPC-3373 Pharmacokinetic Parameters (10 mg Dose)

| Parameter | *OPC-14857* | | | *OPC-3373* | | |
|---|---|---|---|---|---|---|
| | $C_{max}$ (ng/ml) | $AUC_{\infty}$ (ng.h/ml) | $T_{max}$ (h) | $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | $T_{max}$ (h) |
| A alone (n=16) | 9.2±3.1 | 1715±544 | 48 (24-96) | 7.8±3.0 | 35.4±50.6 | 2 (1-5) |
| A+F (n=16) | 7.2±2.0 | 1437±372 | 72 (12-144) | 3.7±2.4 | 16.9±14.6 | 1 (1-2) |
| *Geometric mean (CV%)* | | | | | | |
| A alone (n=16) | 8.7 (33) | 1635 (32) | | 7.2 (39) | 22.6 (143) | 1.1 (1-2) |
| A+F (n=16) | 6.9 (28) | 1393 (26) | | 3.1 (66) | 11.1 (86) | 1 (1-4.1) |
| **A+F/A** | **0.79** | **0.85** | | **0.43** | **0.49** | |

OPC-14857 $t_{1/2}$(h) 92±33 for A alone and 90±41 for A+F.

**Figure 1. Mean plasma aripiprazole concentration-time profiles following single oral 15 mg aripiprazole doses, given alone and in combination with 40 mg famotidine, in healthy subjects (N=16)**

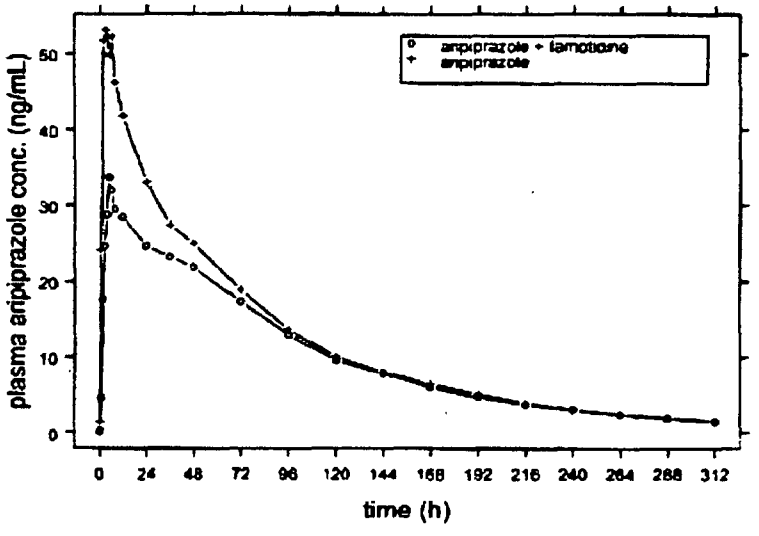
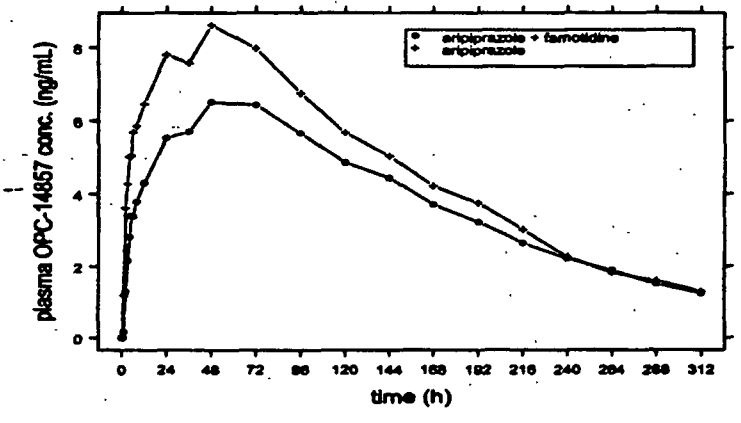



**Figure 2. Mean plasma OPC-14857 concentration-time profiles following single oral 15 mg aripiprazole doses, given alone and in combination with 40 mg famotidine, in healthy subjects (N=16)**



**Summary**

- Aripiprazole mean $C_{max}$ decreased 37% and AUC decreased 13% when aripiprazole was co-administered with famotidine.

- For the active metabolite OPC-14857, mean $C_{max}$ decreased 21% and AUC decreased 15% when aripiprazole was co-administered with famotidine.

- Similar to aripiprazole and its major metabolite, the plasma concentrations of OPC-3373 were lower when aripiprazole was given with famotidine. Other metabolites, 2,3-DCPP and DM-1451 had no plasma levels recorded above the limit of quantitation.

- According to the sponsor, the safety profile of aripiprazole was similar with and without concomitant administration of famotidine to other aripiprazole studies in healthy volunteers.

**Comment**

Famotidine is a competitive inhibitor of histamine $H_2$-receptors and inhibits gastric acid secretion with a subsequent increase in gastric pH. The solubility of aripiprazole is pH-dependent, with 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.

**Study 00-227** (Vol. 98-100): ***A Single Dose, Historic-Control, Pharmacokinetic Study of orally Administered Aripiprazole (OPC-14597) in Healthy Volunteers also Receiving Activated Charcoal***

The objective of this study was to determine the effect of a single oral dose of activated charcoal on aripiprazole pharmacokinetics. A total of 9 healthy male and female subjects received a single dose of oral 15 mg aripiprazole (Lot #98B85A015B), followed 1 hour later by a single 50 g dose of activated charcoal.

**Table 1. Summary of Aripiprazole Pharmacokinetic Parameters (15 mg Dose)**

| Parameter | $C_{max}$ (ng/ml) | $AUC_\infty$ (ng.h/ml) | CL/F (ml/h/kg) | $V_z/F$ (L/kg) | $t_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|
| A+Charcoal (n=9) | 39.2±18.4 | 1994±798 | 131±73 | 14.4±7.8 | 89±53 | 3 (2-7) |
| 31-98-206 (n=18) | 61.3±17.4 | 3750±1940 | 65±28 | 6.9±2.4 | 83±33 | 3.5 (2-12) |
| 31-00-225 (n=10) | 62.6±10.1 | 4335±1333 | 48±19 | 5.2±1.0 | 82±26 | 5 (3-12) |
| *Geometric mean (CV%)* | | | | | | |
| A+Charcoal (n=9) | 35.4 (47) | 1838 (40) | 116 (56) | 12.6 (54) | 76 (60) | |
| 31-98-206 (n=18) | 59.1 (28) | 3377 (52) | 60 (43) | 6.6 (34) | 76 (40) | |
| 31-00-225 (n=10) | 61.9 (16) | 4146 (31) | 45 (39) | 5.2 (180 | 79 (32) | |
| **A+C/Historical** | **0.57-0.60** | **0.44-0.54** | **1.93-2.58** | **1.91-2.42** | | |

**Table 2. Summary of OPC-14857 and OPC-3373 Pharmacokinetic Parameters (10 mg Dose)**

| Parameter | *OPC-14857* $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | $T_{max}$ (h) | *OPC-3373* $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|
| A+Charcoal (n=9) | 4.2±2.4. | 572±309 | 48 (7-144) | 5.0±2.7 | 10.7±7.4 | 1 (1-2) |
| 31-98-206 (n=18) | 7.8±1.9 | 1250±327 | 48 (24-96) | 8.2±3.8 | 16.8±11.9 | 1 (1-2) |
| 31-00-225 (n=10) | 8.1±2.6 | 1437±372 | 72 (24-120) | 5.8±3.8 | 37.5±26.6 | 2 (1-24) |
| *Geometric mean (CV%)* | | | | | | |
| A+Charcoal | 3.5 (58) | 491 (54) | | 4.3 (53) | 7.5 (70) | |
| 31-98-206 | 7.6 (25) | 1204 (26) | | 7.6 (46) | 13.7 (71) | |
| 31-00-225 | 7.7 (32) | 1393 (26) | | 4.9 (66) | 29.8 (71) | |
| **A+C/Historical** | **0.45** | **0.35-0.41** | | **0.57-0.88** | **0.25-0.55** | |

OPC-14857 $t_{1/2}$(h) 98±44 for A+Charcoal and 90±41 and 99±31for Historical studies.

## Summary

- Administration of activated charcoal at 1 hour after aripiprazole dosing reduced plasma concentrations of aripiprazole and its active metabolite OPC-14857 to about one-half of those expected for an aripiprazole dose given alone.

- Administration of aripiprazole 15 mg followed 1 hour later by activated charcoal was safe and well-tolerated by healthy subjects in this study.

- This study suggests that activated charcoal has potential utility as a rescue treatment in cases of accidental or intentional aripiprazole overdose.

**Study 00-232** (Vol. 101-104): ***An Open-Label Study of the Influence of Co-administered Aripiprazole Oral Tablets (OPC-14597) on Omeprazole Oral Capsule Pharmacokinetics in Healthy Volunteers***

The primary objective of this study was to determine the effect of co-administered aripiprazole on the pharmacokinetics of orally administered omeprazole. This was an open-label, sequential-crossover, multiple-dose study. A total of 25 healthy subjects (M/F 20/5; White/Black/(Hispanic/Latino) 15/7/3; age 30±8 yrs and BW 77.2±11.6) were enrolled and 15 subjects completed the study. Subjects received a single 10 mg dose of aripiprazole (Lot #98J82A010A) daily for 15 days (Days 4-17) and received a 20 mg omeprazole dose on Day 1 and Day 18 at 2 hours after the aripiprazole dose.

**Table 1. Summary of Omeprazole and Its metabolite 5'-Hydroxyomeprazole Pharmacokinetic Parameters (20 mg dose given alone and in combination with 10 mg multiple doses of aripiprazole)**

| Parameter | *Omeprazole* $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | $T_{max}$ (h) | *5'-Hydroxyomeprazole* $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|
| O alone (n=15) | 196.1±103.4 | 451.3±444.6 | 2 (1-4.1) | 155.9±26.2 | 452.3±102.3 | 2 (1-4.1) |
| O+A (n=15) | 228.0±145.5 | 496.4±529.6 | 1.9 (1-3) | 167.7±63.6 | 451.1±114.1 | 1.9 (1-3) |
| *Geometric mean (CV%)* | | | | | | |
| O alone (n=15) | 171.8 (53) | 343.4 (98) | | 153.5 (17) | 442.0 (23) | |
| O+A (n=15) | 181.0 (64) | 343.9 (107) | | 158.0 (38) | 438.0 (25) | |
| **O+A/O alone** | **1.05** | **1.00** | | **1.03** | **0.99** | |

**Figure 1. Individual subjects' AUCt and Cmax of omeprazole following single oral 20 mg omeprazole doses, given alone and in combination with multiple doses of aripiprazole 10 mg/day, in healthy subjects**

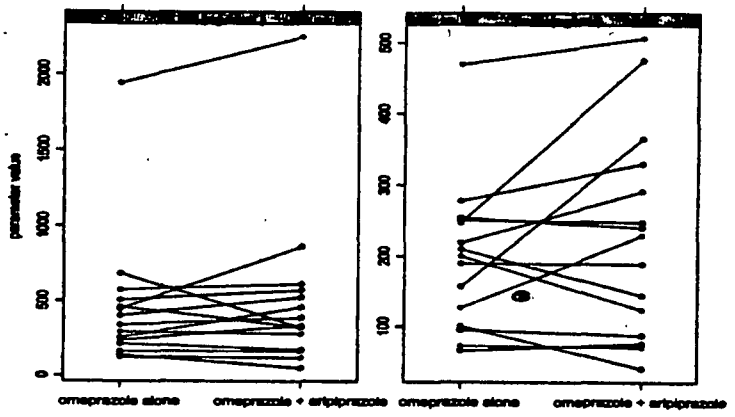


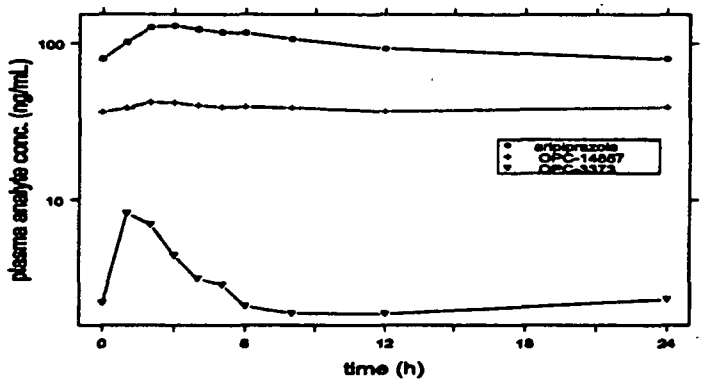

**Table 2. Summary of Aripiprazole and Its Metabolites Pharmacokinetic Parameters (10 mg Dose)**

| Parameter | $C^{ss}_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | CL/F (ml/h/kg) | $V_z/F$ (L/kg) | $t_{1/2}$ (h) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|
| Aripiprazole (n=15) | 136.5±34.4 | 2354±623 | 60.0±19.3 | 4.7±1.0 | 57.6±16.8 | 3 (2-6) |
| OPC-14857 (n=15) | 44.5±15.1 | 933±311 | | | 97±48 | 3 (0-24) |
| OPC-3373 (n=15) | 9.0±4.1 | 63.6±32.4 | | | | 1 (1-2) |

**Table 3. Summary of Aripiprazole and Its Metabolites Pharmacokinetic Parameters (10 mg Dose)**

| Parameter | $C^{ss}_{min}$ (ng/ml) | $C^{16}_{min}$ (ng/ml) | $C^{17}_{min}$ (ng/ml) | $C^{18}_{min}$ (ng/ml) |
|---|---|---|---|---|
| Aripiprazole (n=15) | 75.9±21.3. | 72.2±32.1 | 73.8±24.9 | 79.7±26.3 |
| OPC-14857 (n=15) | 34.6±12.5 | 33.8±17.7 | 33.6±13.5 | 36.6±13.2 |
| OPC-3373 (n=15) | 1.3±0.8 | 2.1±1.7 | 2.0±1.4 | 2.2±1.6 |

**Figure 2. Mean plasma aripiprazole and metabolite concentration-time profiles on Day 18 following multiple doses of aripiprazole 10 mg/day for 15 days, and 20 mg single oral dose of omeprazole, in healthy subjects**



**Summary**

- This study was conducted to assess the possible influence of steady-state aripiprazole and OPC-14857 concentrations on omeprazole metabolism. Omeprazole was selected as a suitable probe drug since CYP2C19 predominates over CYP3A4 in its metabolism.

- Administration of 10 mg QD aripiprazole for 15 days resulted in steady-state plasma concentrations of aripiprazole, that had no effect on the pharmacokinetics of omeprazole, a CYP2C19 substrate.

- According to the machine interpretation of the ECG, Subject 101 had an increased $QT_c$ of 465 msec on Day 8 and AV block on Day 16 that met the criteria for potential clinical significance. At the Sponsor's request, the Investigator re-read the ECG and manually calculated the $QT_c$ value, obtaining a result of 420 msec.

**Study 138-043** (Vol. 105-107): ***Effect of Concomitant Administration of Aripiprazole on the Pharmacokinetics and Pharmacodynamics of Warfarin in Healthy Male Subjects***

The objectives of this study were to demonstrate lack of effect of concomitant aripiprazole administration on $AUC_{inf}$ for S-warfarin (primary), and for R-warfarin (secondary) and to compare the area under the International Normalized Ratio (INR)-time curve ($AUC_{INR}$) between treatments of warfarin alone and warfarin with aripiprazole (secondary).

This was a sequential 2-period open-label study in 12 healthy male Caucasian subjects. Each subject received a single 30 mg dose of warfarin in Period 1, and 10 mg aripiprazole (Batch #98B85A010E) once daily during Days 1-18 and warfarin 30 mg single dose on Day 15 after 2 hours of aripiprazole dosing in Period 2. Plasma samples were collected for warfarin pharmacokinetic analyses (pre-dose and over 144 h after warfarin dosing), aripiprazole pharmacokinetic analyses (pre-dose and over 24 h on Day 14 and Day 15) and pharmacodynamic analyses (0-144 h after warfarin administration).

**Table 1. Summary of Warfarin Pharmacokinetic Parameters (30 mg Dose)**

| Parameter | $C_{max}$ | $AUC_t$ | $AUC_\infty$ | $t_{1/2}$ | $T_{max}$ |
|---|---|---|---|---|---|
| ***S-Warfarin*** | (ng/ml) | (ng.h/ml) | (ng/h/ml) | (h) | (h) |
| Warfarin alone (n=11) | 1668 (18) | 49648 (28) | 53634 (38) | 38.4±15.2 | 2.5 (0.5-4.0) |
| W+A (n=11) | 1722 (12) | 51712 (31) | 55927 (41) | 39.9±13.7 | 2.5 (1.5-4.0) |
| W+A/W | **1.03** | **1.04** | **1.04** | | |
| ***R-Warfarin*** | | | | | |
| Warfarin alone (n=11) | 1649 (17) | 69843 (140 | 78196 (20) | 43.8±11.5 | 2.5 (0.5-6.0) |
| W+A (n=11) | 1735 (10) | 73236 (14) | 83255 (19) | 48.6±11.0 | 2.5 (1.0-4.0) |
| W+A/W | **1.05** | **1.05** | **1.06** | | |

**Table 2. Summary of Aripiprazole and OPC-14857 Pharmacokinetic Parameters (10 mg Dose)**

| Parameter | *Aripiprazole* | | | *OPC-14857* | | |
|---|---|---|---|---|---|---|
| | $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | $C_{min}$ (ng/ml) | $C_{max}$ (ng/ml) | $AUC_t$ (ng.h/ml) | $C_{min}$ (ng/ml) |
| Day 14 (n=11) | 116 (40) | 2055 (48) | 72.6±42.5 | 31.4 (23) | 687 (23) | 27.7±8.6 |
| Day 15 (n=11) | 111 (45) | 1941 (56) | 74.6±42.4 | 31.0 (24) | 653 (23) | 28.8±6.8 |
| Day 16 (n=11) | | | 72.9±53.6 | | | 26.7±6.1 |

Median $T_{max}$ 3-4 h for both Aripiprazole and OPC-14857

**Table 3. Summary of Warfarin Pharmacodynamic Parameters (30 mg Dose)**

| Parameter | $AUC_{INR}$(h) | $INR_{MAX}$ (fraction) | $AUC_{PT}$(s.h) | $PT_{max}$ (s) |
|---|---|---|---|---|
| Warfarin alone (n=11) | 243.8±48.3 | 2.7±0.7 | 2726±562 | 31±8 |
| W+A (n=11) | 215.0±36.6 | 2.3±0.6 | 2401±428 | 26±6 |
| **W+A/W** | **0.88** | **0.85** | **0.88** | **0.84** |
| **90% CI** | **0.84-0.93** | | | |

## Conclusion

- Steady-state concentrations of aripiprazole (10 mg dose) did not affect the pharmacokinetics of S- and R-warfarin or the pharmacodynamics of warfarin ($AUC_{INR}$).
- The steady state $C_{max}$ and AUC values for aripiprazole and metabolite OPC-14857 were similar on Day 14 (aripiprazole alone) and Day 15 (aripiprazole with warfarin).
- Multiple dosing of aripiprazole 10 mg administered alone or with single oral dose of warfarin 30 mg was considered reasonably safe and well-tolerated.

Study 138-022 (Vol. 108): ***Safety, Tolerability and Pharmacokinetics of Aripiprazole and Carbamazepine Coadministration in Patients with Schizophrenia or Schizoaffective Disorder*** (ongoing)

The primary objective is to assess the safety profile of carbamazepine and aripiprazole when coadministered to chronically ill patients with schizophrenia or schizoaffective disorder who require mood stabilizer therapy for the management of symptoms. A secondary objective is to assess the pharmacokinetics of aripiprazole during carbamazepine coadministration. This is an open label, sequential treatment design study with 3 phases:

Phase A – aripiprazole monotherapy (30 mg QD) and assessment of aripiprazole pharmacokinetics
Phase B – carbamazepine is added to aripiprazole and its dose is titrated to a therapeutic range (8-12 mg/l), 200 mg/day for 3 days, then 200 mg BID
Phase C – assessment of aripiprazole pharmacokinetics in the presence of therapeutic concentrations of carbamazepine and study discharge procedures.

The study is ongoing. A total of 8 patients are planned to complete the study. Data from 3 patients are reported here.

**Table 1. Summary of Aripiprazole and Its Major metabolite OPC-14857 Pharmacokinetic Parameters following Daily Dose of Aripiprazole Alone or in Combination with Carbamazepine in Patients with Schizophrenia or Schizoaffective Disorder**

| Phase | Day | $C_{max}$ (ng/ml) | $C_{min}$ (ng/ml) | $AUC_\tau$ (ng.h/ml) | $CL_T/F$ (ml/h) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|
| *Aripiprazole* | | | | | | |
| A alone | 14 | 557±221 | 413±219 | 10417±4742 | 3249±1231 | 3 (2, 3) |
| | 15 | | 368±198 | | | |
| Comb | 1 | 233±99 | 115±77 | 4092±2043 | 8953±5072 | 4 (3, 4) |
| | 2 | | 137±87 | | | |
| **Ratio C-Day 1/A-Day14** | | **0.42** | **0.28** | **0.39** | **2.76** | |
| *OPC-14587* | | | | | | |
| A alone | 14 | 136±30 | 127±29 | 2947±657 | NA | 8 (1, 24) |
| | 15 | | 125±41) | | | |
| Comb | 1 | 53±10 | 40±14 | 1100±306 | NA | 8 (6, 12) |
| | 2 | | 41±33 | | | |
| **Ratio C-Day 1/A-Day14** | | **0.39** | **0.31** | **0.37** | NA | |

## Interim Conclusion

- Coadministration of carbamazepine with aripiprazole resulted in more than 50% decrease in $C_{max}$, $C_{min}$ and AUC values of both aripiprazole and its major metabolite OPC-14857.

- Carbamazepine plasma concentrations were determined by a local clinical laboratory using standard methodology for therapeutic carbamazepine monitoring.

- Because only 3 subjects completed the study as of the interim database lock date, there are no safety conclusions at this point.

**Study 138-021** (Vol. 109): ***Safety, Tolerability and Pharmacokinetics of Aripiprazole and Lithium Coadministration in Patients with Schizophrenia or Schizoaffective Disorder***

The primary objective of this study was to assess the safety profile of lithium and aripiprazole when administered to patients. A secondary objective was to assess the pharmacokinetics of aripiprazole during lithium coadministration. This was an open label, sequential treatment design study in chronically institutionalized patients with schizophrenia or schizoaffective disorder who required lithium for the management of symptoms. The study design is described below:

| | |
|---|---|
| Baseline: | Assessment of EEG, PANSS, MMSE, EPS |
| Days 1-36: | Aripiprazole 30 mg QD (Lot #98B85A015D) |
| Day 13: | Baseline EEG |
| Day 14: | Blood sampling for aripiprazole PK |
| Days 15-36: | Lithium starting at 900 mg, titrated to therapeutic concentration (1.0-1.4 mEq/L) monitor concentration every 4 days |
| Day 36: | Blood sampling for aripiprazole PK and assessment of efficacy and safety |

A total of 12 subjects (20-47 years old; BW 90.3±21.8; M/F 11/1; race White/Black/(Hispanic/Latino, 7/3/2) were enrolled in the study. Of these, 5 discontinued early (2 withdrew consent; 1 discontinued due to a serious AE, 1 due to treatment failure/lack of efficacy and 1 for other reasons unrelated to AEs). Seven subjects completed the study as designed.

**Table 1. Summary of Aripiprazole and Its Metabolite OPC-14857 Pharmacokinetic Parameters (Comparison of Aripiprazole 30 mg/day Alone and Taken with Lithium) (N=7)**

| Parameter | $C_{max}$ | $AUC_t$ | CL/F | | $C_{min}$ | $T_{max}$ |
|---|---|---|---|---|---|---|
| ***Aripiprazole*** | (ng/ml) | (ng.h/ml) | (ml/min) | (ml/min/kg) | (ng/ml) | (h) |
| A alone-Day 14 | 364 (23) | 6113 (34) | 85.1±24.8 | 0.97±0.44 | 212±83 | 2 (2-24) |
| A + L –Day 36 | 432 (28) | 7041 (18) | 72.1±14.1 | 0.80±0.21 | 231±72 | 2 (1-12) |
| Ratio Comb/A | **1.19** | **1.15** | | | | |
| ***OPC-14857*** | | | | | | |
| A alone-Day 14 | 115 (34) | 2360 (36) | | | 108±33 | 24 (0-24) |
| A + L –Day 36 | 136 (25) | 2534 (17) | | | 115±29 | 2 (0-24) |
| Ratio Comb/A | **1.18** | **1.07** | | | | |

According to the sponsor, there is no suggestion that treatment with aripiprazole increased EPS. None of the subjects had EEG findings suggestive of epileptiform activity, encephalopathy or other pathological EEG rhythms. There were no clinically relevant ECG abnormalities during the study. There is no suggestion that treatment with aripiprazole or the combination of aripiprazole and lithium affected PANSS or MMSE scores.

**Summary**

- The coadministration of aripiprazole 30 mg daily and therapeutic doses of lithium was safe and well tolerated.
- The coadministration of aripiprazole 30 mg daily and therapeutic doses of lithium did not produce any clinical relevant electroencephalographic changes.
- Coadministration of lithium with aripiprazole resulted in less than 20% increase in exposure of aripiprazole and its active metabolite, OPC-14857.

**Study 138-023** (Vol. 110): ***Safety, Tolerability and Pharmacokinetics of Aripiprazole and Divalproex Sodium Coadministration in Patients with Schizophrenia or Schizoaffective Disorder***

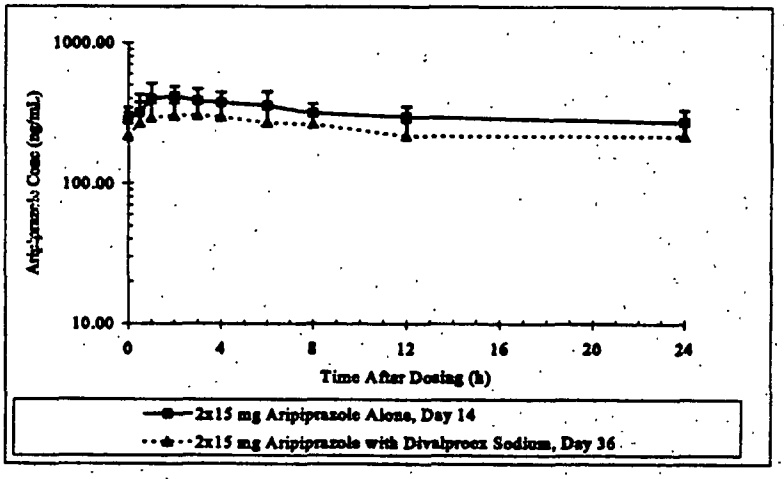
The primary objective of this study was to assess profile of divalproex sodium and aripiprazole when coadministered to chronically institutionalized subjects with a diagnosis of schizophrenia or schizoaffective disorder who required valproate for the management of symptoms. A secondary objective was to assess the pharmacokinetics of aripiprazole during divalproex sodium coadministration. This was an open label, sequential treatment design study. A total of 10 male patients were enrolled in the study (33±6 year old, BW 85.7±10.0 kg, White/Black/(Hispanic/Latino) 2/6/2). Of these, 4

discontinued early, 2 due to withdrawal of consent and 2 due to AEs (i.e., inguinal hernia, hostile behavior). Six (6) subjects completed the study as designed. Each subject who completed the study was administered 30 mg/day (as 2x15 mg, Batch #98B85A015D) aripiprazole monotherapy on Days 1 to 14 and aripiprazole 30 mg/day with concomitant divalproex sodium (titrated upward until plasma concentration of 50-125 mg/L was achieved) on Days 15 to 36.

**Table 1. Summary of Aripiprazole and Its Metabolite OPC-14857 Pharmacokinetic Parameters (Comparison of Aripiprazole 30 mg/day Alone and Taken with Divalproex Sodium) (N=6)**

| Parameter | $C_{max}$ | $AUC_\tau$ | CL/F | $C_{min}$ | $T_{max}$ |
|---|---|---|---|---|---|
| ***Aripiprazole*** | (ng/ml) | (ng.h/ml) | (ml/min/kg) | (ng/ml) | (h) |
| A alone-Day 14 | 427 (23) | 7474 (19) | 0.82±0.18 | 281±66 | 2 (1-2) |
| A + V–Day 36 | 316 (27) | 5677 (25) | 1.08±0.25 | 219±97 | 4 (2-24) |
| Ratio Comb/A | **0.74** | **0.76** | **1.32** | **0.78** | |
| ***OPC-14857*** | | | | | |
| A alone-Day 14 | 109 (19) | 2202 (24) | | 98±16 | 2 (0.5-2) |
| A +V –Day 36 | 102 (30) | 2021 (32) | | 87±33 | 3.5 (0.5-24) |
| Ratio Comb/A | **0.93** | **0.92** | | | |

**Figure 1. Mean (SD) plasma concentration-time profiles of aripiprazole in patients following daily oral administration of 2x15 mg aripiprazole alone and with divalproex sodium (N=6)**




Between Days 15 and 36, serum valproate levels were monitored to confirm that concentrations were within 50-125 mg/L were achieved. Inspection of the individual plasma valproate concentrations reveals that all subjects achieved apparent steady-state valproate concentrations by Day 36 of the study with the minimum target of 50 mg/L.

## Conclusion

- According to the sponsor, the coadministration of aripiprazole and valproate did not produce any clinical relevant electroencephalographic changes in any subjects, and the combination therapy was safe and well tolerated.

- Coadministration of divalproex sodium decreased the AUC, $C_{max}$ and $C_{min}$ of aripiprazole by 24%, 26%, and 22%, respectively; it increased CL/F by 32%. These changes in pharmacokinetics of aripiprazole are not considered clinically significant.

**Comment**
Valproate is a broad-spectrum inhibitor of UGT enzymes, epoxide hydrolase, and CYP2C9 enzymes. It was shown that coadministration of valproate increased plasma concentration and AUC of lamotrigine, lorazepam, and carbamazepine-10, -11-epoxide. Valproate does not inhibit cyclosporine or oral contraceptives, suggesting a lack of inhibition of CYP3A-metabolized drugs. There is no data suggesting that valproate is an inhibitor of CYP2D6 enzyme or an inducer of CYP3A4 and/or CYP2D6. Therefore, the slight increase in the oral clearance of aripiprazole in the presence of divalproex sodium is not likely due to induction of the metabolism of aripiprazole, whose major metabolic pathway are mediated by CYP3A4 and CYP2D6.

As valproate and aripiprazole share the same plasma protein binding site II, valproate is likely to act as a protein binding displacer when coadministered with aripiprazole. The decrease in the steady-state $C_{min}$ and AUC values of aripiprazole after coadministration of valproate, observed in the present study, is consistent with this hypothesis.

## Human Pharmacodynamics (PD) Study Reports

**Study 94-201** (Vol. 111-113): ***Interaction of OPC-14597 (30 mg/day) with Brain $D_2$ Receptors: A Positron Emission Tomography (PET) Scan Study in Healthy Young Male Volunteers***

The objective of this study was to determine the degree of brain $D_2$ receptor occupancy induced by aripiprazole given at daily doses of up to 30 mg for 14 days. This is an open label study. A total of 17 young male healthy subjects (Caucasians/Blacks/Asian 12/4/1) received oral aripiprazole at one of five doses: 10 mg/day on Day 1, 20 mg/day on Day 2, then 30 mg/day on Day 3-14, or 10, 2, 1, or 0.5 mg/day on Days 1-14. Subjects received intravenous $^{11}$C-raclopride, a selective dopamine $D_2$ receptor antagonist, and underwent PET scanning for determination of dopamine $D_2$ receptor occupancy at baseline and Day 14. Trough plasma concentrations were measured every day throughout the study, from Day 1 to Day 13. On Day 14, samples were drawn 15 min before the start of the PET scan, and every 30 min during the PET scan. Additional samples were collected at 24-h intervals on Days 15-20. PET scan was performed at baseline and on Day 14.

**Table 1. Summary of Aripiprazole Pharmacokinetic parameters**

| Dose (mg/day) | N | BW (kg) | $C_{max, Day 14}$ (ng/ml) | $AUC_{0-24 h}$ (ng.h/ml) | $T_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 0.5 | 2 | 159 | 10 | 156 | 5 | 121 |
| 1 | 3 | 198 | 12 | 283 | 6 | 115 |
| 2 | 2 | 162 | 36 | 689 | 5 | 46 |
| 10 | 2 | 174 | 112 | 2205 | 7 | 36 |
| 30 | 4 | 181 | 506 | 10721 | 4 | 78 |

The selective $D_2$ receptor antagonist $^{11}$C-raclopride was infused during two PET scanning procedures (Baseline and Day 14) to determine $D_2$ receptor occupancy with aripiprazole. Two quantitative procedures, the [redacted] and the 2-Compartment method, were then used to estimate $D_2$ receptor occupancy. Table 2 summaries the brain $D_2$ receptor occupancy in the caudate and putamen by aripiprazole.

**Table 2. Dopamine $D_2$ Receptor Occupancy**

| Dose (mg/day) | N | Caudate | | Putamen | |
|---|---|---|---|---|---|
| | | Farde (14 Days) | 2-Compartment | Farde (14 Days) | 2-Compartment |
| 0.5 | 3 | 30.3±9.7 | 39.4±7.1 | 33.7±10.5 | 42.4±4.7 |
| 1 | 3 | 49.2±8.8 | 47.5±10.6 | 57.2±5.6 | 54.8±7.6 |
| 2 | 3 | 74.3±2.4 | 69.5±4.3 | 71.5±9.8 | 71.6±7.6 |
| 10 | 2 | 85.4 | 88.6 | 85.4 | 85.8 |
| 30 | 4 | 92.3±0.5 | 92.2±3.1 | 86.4±6.9 | 93.6±1.8 |

The two methods applied to estimate dopamine $D_2$ receptor occupancy (i.e., the [redacted] and two-Compartment methods) yielded similar results. The $D_2$ receptor occupancy [redacted]) was 81-95% in both caudate and putamen for the 30 mg/day dose group and decreased to 23%-46% for the 0.5 mg/day dose group. $D_2$ receptor occupancy was greater than 60% for doses of 2 mg/day or higher.

**Summary**

- The pharmacokinetics of aripiprazole in this study are consistent with dose proportionality.
- Aripiprazole enters the brain and binds to human $D_2$ receptors in a dose-related manner that approaches saturation at the 10 mg/day dose.
- Aripiprazole appeared to be safe and weli tolerated.

**Study 00-239** (Vol. 114-118): ***A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Sequential Crossover Study of Potential Pharmacodynamic Interactions between Orally Co-administered Aripiprazole (OPC-14597) and Ethanol in Healthy Volunteers***

The primary objective of this study was to assess the potential for pharmacodynamic interactions between orally co-administered aripiprazole and ethanol. The secondary objective was to determine the effect of orally co-administered ethanol on the pharmacokinetics of aripiprazole. This study was a double-blind, placebo-controlled, parallel group, multiple-dose, sequential crossover design as illustrated below:

Day 1: a single dose of a placebo tablet at 8:00 AM (2 hours after breakfast)
Days 2-15: 10 mg/day aripiprazole (Group 1) or placebo (Group 2) at 8:00 AM
Day 15: 10 mg aripiprazole or placebo taken with a 0.8 g/kg ethanol dose at 8:00 AM
PD assessment: prior to dosing and at 1, 2, 3, 4, 5, 6, and 8 hours after the dose on Days 1and 15
Day 1-Day 15: subjects were confined to the Phase I facility and returned 9 times over 12 days (to Day 27) for PK sampling and safety assessment.

**Demographic Characteristics, by Group (All subjects were extensive metabolizers)**

| Group | N | M/F | Age (years) | Weight (kg) | Race (White/Black/ Asian Pacific Island/(Hispanic/Latino) |
|---|---|---|---|---|---|
| Placebo | 13 | 10/3 | 28±8 | 73.7±11.8 | 9/2/1/1 |
| Aripiprazole 10 mg | 13 | 12/1 | 26±6 | 75.7±10.8 | 12/1/0/0 |

### *Pharmacodynamics Evaluation*

Pharmacodynamic evaluation included changes from baseline of Digit Symbol Substitution Test (DSST), Pursuit Rotor Movement (PRM) and Simple Reaction Time (SRT) using the following parameters: $I_{max}$-peak intensity of observed change in effect from baseline, $t_{max,I}$-time to peak intensity of observed change in effect from baseline, and AUEC-area under the change in effect from baseline-time curve.

**Table 1. Summary of Blood Ethanol Concentrations**

| Time after the Dose | 0.5 h | 1 h | 2 h |
|---|---|---|---|
| | Blood Ethanol Concentration (mg/dl) | | |
| Placebo Group (N=10) | 42±20 | 95±22 | 101±29 |
| Aripiprazole group (N=10) | 32±14 | 83±22 | 95±9 |

**Table 2. Summary of Changes in DSST, PRM and SRT Scores from Baseline following a Single Oral 0.8 g/kg Ethanol Dose Coadministered with Either Aripiprazole or Placebo**

| Parameter | $I_{max}$ (%) | $t_{max,I}$ (h) | AUEC (%.h) |
|---|---|---|---|
| | ***Change in Digit Symbol Substitution Test (DSST) Score*** | | |
| Placebo+Ethanol (n=10) | 9±10, 12 (-16 to 18) | 5.08 (3.08 to 8.08) | 26±29, 28 (-32 to 57) |
| Arip + Ethanol (n=10) | -7±12, -12 (-28 to 13) | 4.08 (1.08 to 8.08) | -29±36, -17 (-114 to 10) |
| | ***Change in Simple Reaction Time (SRT)*** | | |
| Placebo+Ethanol (n=10) | 75±72, 67 (-46 to 223) | 2.08 (1.08 to 8.08) | 176±221, 215 (-219 to 588) |
| Arip + Ethanol (n=10) | 80±48, 77 (23to 182) | 2.08 (2.08 to 8.08) | 303±189, 325 (57 to 540) |
| | ***Change in Pursuit Rotor Movement (PSM) Score*** | | |
| Placebo+Ethanol (n=10) | -20.3±9.9, -15.6 (-36.3 to –10.7) | 2.8 (1.4 to 5.2) | -42.9±40, -29.1 (-114 to –4.1) |
| Arip + Ethanol (n=10) | -20.6±10.2, -16.3 (-40.3 to –8.2) | 3.3 (1.2 to 5.4) | -48.1±35, -37.5 (-100 to –6.3) |

Mean±SD, Median (Range)

## Summary

- Blood ethanol concentrations were similar between the subjects co-administered ethanol with placebo and those given ethanol with aripiprazole. Hence, it is reasonable to attribute similar degrees of impairment in the pharmacodynamic measures to ethanol for the two treatment groups.

- On Day 15, prior to ethanol administration, there was no apparent difference in mean DSST scores between the placebo and aripiprazole groups. After ethanol dosing on Day 15, the aripiprazole group had lower mean DSST scores than at baseline, whereas the placebo group had higher mean DSST scores. Owing to the unexpected increase in DSST performance after ethanol intake in the placebo group, it is difficult to interpret the between-group differences.

- There was no apparent difference in mean SRT, PRM scores on Day 15 of dosing, prior to ethanol administration, between the placebo and aripiprazole groups. In both groups, ethanol prolonged mean SRT and PRM (Day 15) compared to baseline (Day 1). As indicated by the similarities in mean change in PRM score from baseline (ΔPRM)-time shape, there were no significant differences in $I_{max}$, $t_{max,l}$, and AUEC between the aripiprazole and placebo treatment groups.

- The mean change in SRT score from baseline (ΔSRT)-time profile for the aripiprazole group did not return to predose level over the 8 h measurement period, whereas the profile for the placebo group did. Despite this difference in profile shape, there were no significant differences in $I_{max}$, $t_{max,l}$, and AUEC for ΔSRT between the aripiprazole and placebo treatment groups.

- Overall, the results indicate that aripiprazole co-administration did not potentiate ethanol's impairment of SRT and PRM.

**Conclusion**

- There was no significant difference between aripiprazole co-administration with ethanol and placebo co-administration with ethanol for either gross motor skills or stimulus response.

- It is not possible to determine if co-administration of aripiprazole with ethanol had a meaningful impact on cognitive function.

***Pharmacokinetics of Aripiprazole***

**Table 3. Summary of Aripiprazole Pharmacokinetic Parameters**

| Parameter | $C^{ss}_{min}$ (ng/ml) | $C^{ss}_{max}$ (ng/ml) | $C^{ss}_{av}$ (ng/ml) | $AUC_\tau$ (ng.h/ml) | CL/F (ml/h/kg) |
|---|---|---|---|---|---|
| A alone | 110±25 | 171±36 | 133±25 | 3185±600 | 43.2±12.6 |
| A+Ethanol | 109±24 | 173±28 | 133±27 | 3202±646 | 43.3±13.7 |
| Parameter | $T_{max}$ (h) | $t_{1/2}$ (h) | $V_z/F$ (L/kg) | | |
| A alone | 3 (2-6) | ND | ND | | |
| A+Ethanol | 4.5 (1-6) | 62±13 | 3.7±0.8 | | |

**Table 4. Summary of OPC-14857 Pharmacokinetic Parameters**

| Parameter | $C^{ss}_{min}$ (ng/ml) | $C^{ss}_{max}$ (ng/ml) | $C^{ss}_{av}$ (ng/ml) | $AUC_\tau$ (ng.h/ml) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| A alone | 44.9±10.8 | 55.8±12.3 | 48.1±11.0 | 1155±264 | ND |
| A+Ethanol | 41.6±12.5 | 55.3±13.6 | 47.6±12.7 | 1143±305 | 82.6±23.7 |

$T_{max}$ (h) 2 (0-8) for A alone and 14.5 (0-24) for A plus ethanol.

**Table 5. Summary of OPC-3373 Pharmacokinetic Parameters**

| Parameter | $C^{ss}_{min}$ (ng/ml) | $C^{ss}_{max}$ (ng/ml) | $C^{ss}_{av}$ (ng/ml) | $AUC_\tau$ (ng.h/ml) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| A alone | 1.5±1.1 | 6.9±2.2 | 3.2±1.1 | 77.6±25.7 | ND |
| A+Ethanol | 1.2±0.8 | 4.3±1.6 | 2.4±0.8 | 57.1±18.2 | 53.5±12.0 |

$T_{max}$ (h) 2 (0-8) for A alone and 14.5 (0-24) for A plus ethanol.

## Summary

- When aripiprazole was given with ethanol, the mean aripiprazole and its major metabolite OPC-14857 PK parameters were similar to those following administration of aripiprazole alone. These results are consistent with a lack of effect of ethanol on aripiprazole absorption or its primary metabolic pathway.

- When aripiprazole was given with ethanol, the minor, inactive metabolite OPC-3373 minimum and maximum concentrations were decreased by 22% and 40%, respectively, compared to those for aripiprazole given alone. As a result, a 27% decrease in OPC-3373 $AUC_t$ was also observed when aripiprazole given with ethanol. The decreased plasma concentrations of OPC-3373 could be due to partial inhibition of a minor metabolic pathway, or due to increased urinary excretion of OPC-3373.

Study 138030 (Vol. 119): ***The safety and Tolerability of Aripiprazole in the Long-Term Treatment of Schizophrenia and Schizoaffective Disorder: An Open-Label, Multi-Center Flexible Dose Trial***

This study had no pharmacokinetic or pharmacodynamic endpoints. Only safety data were generated from this study.

***Total 35 Studies***

## In Vitro Absorption and Metabolism Studies

### Absorption

***Evaluation of Permeability of Aripiprazole through Caco-2 Cells*** (Vol. 1.30, Pharm-Tox Vol. 18)

The objectives of this study were to determine the in vitro permeability of aripiprazole across the Caco-2 cell monolayer and to predict the extent of absorption in humans after oral administration.

Caco-2 cells are derived from a human colon carcinoma and undergo spontaneous enterocytic differentiation in cell culture and resemble small intestinal epithelial cells. When they grow to confluency on a semi-permeable membrane, the cell polarity and tight junctions are well established. Pc values calculated by the rate of passage of compounds through the Caco-2 cell monolayer can be related to the extent of in vivo absorption in man.

Permeability studies were conducted with the monolayers cultured between 14 and 21 days in culture, and the cell passage numbers were between 20 and 40. The transport medium was modified Hank's balanced salt solution (MHBS) containing either 10 mM HEPES (N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid) or 25 mM MES (2-N-morpholinoethanesulfonic acid) depending on the intended pH, (e.g., pH 5.5, 6.5 or 7.4 for apical and pH 7.4 for basolateral). Each monolayer was washed twice with MHBS. The permeability studies were initiated by adding an appropriate volume of MHBS containing test compounds (20 mM aripiprazole and metoprolol) to either the apical (apical to basolateral transport) or basolateral (basolateral to apical transport) side of the monolayer. Aliquots of 0.2 ml and 1.1 ml was placed in the apical and basolateral sides, respectively. The monolayer was placed on an orbital shaker (50 cycles/min) and incubated for 4 hours at 37°C. Samples were taken from both the apical and basolateral compartment at the end of the 4-hour period.

Permeability coefficient (Pc) was calculated using the following equation:
$Pc=dA/(dt).S.C_0)$
where dA/dt is the flux of test compound across the monolayer (nmol/sec), S is the surface area of the cell monolayer (0.33 $cm^2$), and $C_0$ is the initial concentration (μM) in the donor compartment. Pc values are expressed as nmol/sec.

**Table 1. 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 significant nonspecific binding to Caco-2 cell device (poor recovery<5%).

The apical to basolateral permeability of aripiprazole at an apical pH of 5.5 was comparable to mannitol, but it was higher (2-fold) than mannitol at pH 6.5. The recovery of aripiprazole in each experiment at an apical pH of 5.5 and 6.5 was more than 90%. The permeability at an apical pH of 7.4 could not be determined because aripiprazole had a very low solubility in the Caco-2 buffer (<5 μM) and non-specific binding was also significant at this pH.
Correlation between the extent of absorption in humans vs. permeability across Caco-2 cell monolayer with known drugs is shown in Table 2.

**Table 2. Correlation between the Extent of Absorption in Humans vs. Permeability Across Caco-2 Cell Monolayer (Apical pH 6.5, Basolateral pH 7.4)**

| Compound | absorbed (%) | Pc (nm/sec) | Compound | absorbed (%) | Pc (nm/sec) | Compound | absorbed (%) | Pc (nm/sec) |
|---|---|---|---|---|---|---|---|---|
| Inulin | 5 | 10 | Terbutaline | 73 | 29 | Sulfisoxazole | 100 | 245 |
| BMS-189664 | 10 | 20 | Ketoconazole | 76 | 95 | Sulfamethoxazol | 100 | 263 |
| Sulfasalazine | 13 | 22 | Guanabenz | 79 | 111 | Antipyrine | 100 | 288 |
| Mannitol | 15 | 32 | BvAraU | 82 | 41 | Naproxen | 100 | 401 |
| Pravastatin | 34 | 33 | Propranolol | 90 | 111 | BMS-193884 | 100 | 443 |
| Nadolol | 35 | 17 | Hydralazine | 90 | 141 | Salicylic Acid | 100 | 440 |
| Acebutalol | 40 | 48 | Desipramine | 95 | 81 | Caffeine | 100 | 331 |
| Ranitidine | 50 | 24 | Metoprolol | 95 | 137 | Ibuprofen | 100 | 395 |
| Atenolol | 50 | 25 | Cimetidine | 95 | 49 | Dexamethasone | 100 | 120 |
| Timolol | 72 | 47 | Acetaminophen | 95 | 199 | BMS-180291 | 100 | 215 |

Aripiprazole is a base with a pKa around 14. 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. Therefore, the permeability of aripiprazole at an apical pH of 6.5 (47 nm/sec) is consistent with moderate absorption. Clinical data, however, suggested that aripiprazole is well-absorbed in humans (>85%).

**Conclusion**
The permeability of aripiprazole at an apical pH of 6.5 suggests that aripiprazole may have moderate absorption in humans after oral administration. However, clinical data suggest that absorption in humans exceeds 85%.

**Metabolic Studies**
Vol.1.32 (Pharm-Tox Vol. 20):
***A Study of the Absorption, Distribution, Metabolism and Excretion following Oral Administration of $^{14}$C-OPC-14597 in Healthy Volunteers (Study 31-96-201)*** (BMS Document Control number 920011356 1.0)

***The Pharmacokinetics and Metabolism of Dual Label [$^{14}$C]-Aripiprazole in healthy Male Subjects (Study CN138-028)*** (930000373 1.0)

Vol.1.33 (Pharm-Tox Vol. 21):
***Biotransformation of Dual Label [$^{14}$C]-Aripiprazole in Humans after Oral Administration*** (930000409 4.0)

***Report-011139: Investigation and Determination of OPC-14597 Metabolites in Human Plasma*** (920001395 1.1)

***Report-008556: Identification of OPC-14597 Metabolites in Humans and Rats (2)*** (920001376 1.1)

***Assessment of the Biliary Excretion of DM-1454, CM-1458 and DM-1460 during Multiple Dose Administration of Aripiprazole in Healthy Subjects (Study CN138-061)*** (930000381 1.0)

***Comparative profiles of Selected Conjugated Metabolites in Bile and Plasma of Mice, Rats, Monkeys, and Humans after Daily Oral Administration of Aripiprazole*** (930000451 1.0)

**Vol.1.35** (Pharm-Tox Vol. 23):
***Determination of the Metabolite Formation Pathway of BMS-337044 from BMS-337039***

This study was undertaken to determine the metabolic formation pathway of a previously identified active metabolite, BMS 337044 (OPC-14857), from BMS-337039 (aripiprazole). BMS-337044 could be formed either by hydroxylation of aripiprazole

followed by dehydration or by direct dehydrogenation. Aripiprazole and the hydroxy metabolite, BMS-337045, were incubated separately with human liver microsomes. Metabolic profiles and the concentrations of BMS-337044 in liver microsomal incubations were determined by [redacted]. Metabolites of aripiprazole were identified by [redacted] and comparison of their [redacted] were made.

Aripiprazole was metabolized in human liver microsomes to form six (6) metabolites, including BMS-337044, BMS-337045, DCPP, BMS-337047, BMS-38412 and BMS-337040. BMS-337045 was not metabolized in human liver microsomes to BMS-337044.

**Conclusion**

- These results indicated that BMS-337044 (OPC-14857) was formed by direct [redacted] of aripiprazole, rather than by [redacted] of BMS-337045 (hydroxylated metabolite).

**Report-011228 (Study #013318):** ***In Vitro Metabolism of OPC-14597 by Liver Microsomes from Humans and Animals***

The *in vitro* metabolism of OPC-14597 (aripiprazole) was investigated using human and animal liver microsomes to compare the human and animal metabolic patterns of the compound. For aripiprazole at 20 μM, the metabolites produced in humans, in order of descending concentrations, were DM-1452, DM-1451, and OPC-14857, indicating a metabolic pattern similar to that seen in male cynomolgus monkeys and in male mice. For aripiprazole at 200 μM, the metabolic pattern in male cynomolgus monkeys and in male mice was similar to that in humans.

**Table 1. Metabolic Activity from Aripiprazole to DM1451, DM-1452 and OPC-14857 by Human and Animal Liver Microsomes**

| | *OPC-14857* | | *DM-1451* | | *DM-1452* | |
|---|---|---|---|---|---|---|
| Microsomes | 20 (μM) | 200 | 20 (μM) | 200 | 20 (μM) | 200 |
| Human | 38.6±1.0 | 275±85.7 | 46.0±2.2 | 422±134 | 65.2±4.9 | 523±111 |
| Male cynomolgus monkey | 63.5±1.1 | 242±45.0 | 125±2.0 | 357±79 | 90.5±1.5 | 500±43 |
| Male beagle dog | 117±0.4 | 169±8.5 | 84.9±2.9 | 176±11 | 105±2 | 237±12 |
| Male mouse | 45.4±0.9 | 278±45.7 | 109±4.7 | 590±81 | 76.1±2.9 | 572±29 |
| Male rat | 5.38±0.26 | 26.9±2.5 | 155±8.7 | 127±11.4 | 10.5±0.5 | 49.1±0.9 |
| Female rat | 1.53±0.08 | -- | 57.8±3.6 | -- | 2.74±0.10 | -- |

The metabolism of aripiprazole was presumed to be primarily related to both isoforms CYP2D6 and CYP3A4, with little relationship to other isoforms. DM-1451, DM-1452, and OPC-14857 were produced through metabolism by CYP2D6 and CYP3A4 expressed in human microsomes, indicating Km values of 16-28 μM for CYP2D6 and 298-757 μM for CYP3A4. Thus, the concentrations of aripiprazole (substrate) in this study were set at 20 and 200 μM, which were similar to the Km values for CYP2D6 and CYP3A4.

**Report-013109 (Study #015537):** ***Identification of OPC-14597 Metabolite Produced by Human Liver Microsomes in Vitro***

It had been reported that the metabolite DM-1457 [7-(3-hydroxypropoxy)-3,4-dihydro-2(1H)-quinoline], which was named as SFO-14010 in the previous report, was produced by in vitro reaction of OPC-14597 (aripiprazole) using liver microsomes from human and animals. However, data for the identification of the metabolite DM-1457 was not enough in the previous study. In the present study, OPC-14597 (aripiprazole) was metabolized by human liver microsomes, and the ultraviolet spectrum and mass spectrum of the produced metabolite was measured. As these spectrum agreed with those of authentic DM-1457, the metabolite was identified as DM-1457 (cleaved primary alcohol moiety).

**Report-010707 (Study #011347):** ***Identification of OPC-14597 Metabolites in Humans and Rats (3)***

Two OPC-14597 (aripiprazole) metabolites newly detected in rats in vivo and human P450 in vitro were identified by in vitro reaction using rat liver S9 fraction and recombinant CYP2D6. One metabolite was identified as DM-1452, which was produced by hydroxylation at the 4$^{th}$ position of the 3,4-dihydro-2(1H)quinolinone structure of OPC-14597. The other metabolite was identified as OPC-14857, which is a quinolinone structure with double bonds at the 3$^{rd}$ and 4$^{th}$ positions produced by oxidation at the 3$^{rd}$ and 4$^{th}$ positions of the 3,4-dihydro-2(1H)quinolinone structure of OPC-14597. In addition, a sulfate conjugate of DM-1451 was prepared by in vitro reaction with a rat liver cytosol, since organic synthesis of sulfate conjugates is quite difficult.

***Comparative Biotransformation of [$^{14}$C] Aripiprazole in Human, Monkey, Rat and Mouse Hepatocytes***

The present study was undertaken to determine comparative in vitro biotransformation of 14CBMS-337039 (aripiprazole) in human, monkey, rat and mouse hepatocytes. Dual radiolabeled [$^{14}$C]BMS-337039 was incubated at concentrations of 20 and 100 μM with cryopreserved human, monkey, rat, and mouse hepatocytes. BMS-337039 and its metabolites in the incubation media were semi-quantified by ——— analysis after 2 and 4 hour of incubation. The identities of the radioactive metabolites were determined based on comparison of their — retention times to those of synthetic metabolite standards. The enzymatic activities in hepatocytes were assessed in control incubations in which the metabolism of 7-hydroxycoumarin and 7-ethoxycoumarin was shown to be moderate to extensive.

In human hepatocytes, BMS-337039 underwent slight to moderate phase I biotransformation reactions to form monohydroxylated metabolites BMS-337040 (DM-1451, aromatic) and BMS-337045 (DM-1452, aliphatic), dehydrogenated metabolite BMS-337044 (OPC-14857), and N-dealkylated metabolites DCPP and BMS-337047 (OPC-3373), i.e., cleaved moieties. These phase I metabolites were also observed in

monkey, rat and mouse hepatocytes. In human and monkey hepatocytes, the monohydroxylated metabolite BMS-337040 further underwent phase II biotransformation reactions to form a glucuronide conjugate, BMS-337041 (DM-1454), and a sulfate conjugate, BMS-337042 (DM-1458). Whereas, monkey hepatocytes formed mainly the sulfate conjugate, human hepatocytes formed the glucuronide and the sulfate conjugates to about the same extent. In rat and mouse hepatocytes, the glucuronide conjugate, but not the sulfate, was detected.

**Report-013611 (Study #015506):** ***In Vitro Metabolism of OPC-14597 Using Human and Rabbit Liver Microsomes – The Check of the Production of DM-1456 from OPC-14597***

DM-1456 has newly been identified as one of metabolites of OPC-14597 (aripiprazole) in New Zealand White female rabbit plasma following a single oral administration of aripiprazole at 100 to 300 mg/kg dose in the PK study by ——— analysis. In this study, whether DM-1456 is produced or not in the in vitro metabolic reaction of aripiprazole was investigated using human and female rabbit liver microsomes.

Though DM-1456 was not detected in the in vitro metabolic reaction at a aripiprazole substrate concentration of 100 μM both in human liver microsomes and female rabbit liver microsomes, DCPP, DM-1451, DM-1452, OPC-14857 and OPC-3373 were detected, where formations were inhibited by SKF-525A, inhibitor of cytochrome P450.

These results show that the metabolic pathways from OPC-14597 (aripiprazole) to DCPP, DM-1451, DM-1452, OPC-14857 and OPC-3373 except DM-1456 may be mediated by cytochrome P450.

**Report-010498 (Study #010913):** ***In Vitro Metabolism of OPC-14597 by Microsomes from Human Lymphoblastoid Cell Line Transformed with Human Cytochrome P450 cDNAs***

This study was conducted to investigate the in vitro metabolism of OPC-14597 (aripiprazole) by microsomes from human lymphoblastoid cell line transformed with human cytochrome P450 cDNAs. The results showed that DM-1451, DM-1452, and OPC-14857 were produced through metabolism by the CYP2D6 isoform and that DM-1451, DM-1452, OPC-14857, and DCPP were produced through metabolism by the CYP3A4 isoform. OPC-14597 (aripiprazole) was not metabolized by any other isoform (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1). Therefore, the metabolism of OPC-14597 was presumed to be related primarily to the CYP2D6 and CYP3A4 isoforms and to show little relationship to any other isoforms.

***Enzymatic Reaction***

A 0.5-ml reaction mixture consisting of 50 uM OPC-14597 (combined with 1% of 5 nM OPC-14597 in DMSO), 0.05 mM EDTA, 100 mM Na.K.phosphate buffer (pH 7.4), 2 mM NADH, DADPH-generating system (1 mM NADP, 5 mM $MgCl_2$, 5 mM G-6-P, and 1 U/ml G-6-PDH),

and 1 mg/ml microsomal protein was incubated at 37°C. The reaction mixture containing no microsomes was incubated at 37C for 5 minutes and then combined with the microsomes to start reaction. At 60 minutes, the reaction mixture was centrifuged. After centrifugation, 200 ul of the supernatant was used for [redacted] analysis, and the metabolites produced were measured. Reaction was performed using 2 samples per P450 isoform.

Vol.1.36 (Pharm-Tox Vol. 24):

**Report-010945 (Study #012746): *In Vitro Metabolism of OPC-14597 and Inhibition by OPC-14597 of Dextromethorphan Metabolism by Recombinant Human CYP2D6 and CYP3A4***

The metabolism of OPC-14597 (aripiprazole) by recombinant human CYP2D6 and Cyp3A4 and also the inhibition by OPC-14597 of the metabolism of dextromethorphan by recombinant human CYP2D6 and CYP3A4 were investigated. The results are shown in Table 1:

**Table 1. Enzyme Kinetic parameters**

| Parameter | Production of DM-1451 | DM-1452 | OPC-14857 |
|---|---|---|---|
| | ***CYP2D6*** | | |
| $K_m$ (μM) | 15.7 | 27.9 | 26.2 |
| $V_{max}$ (nmol/nmol P450/min) | 0.42 | 3.92 | 2.81 |
| $V_{max}/K_m$ (ml/μmol P450/min) | 27.0 | 141 | 107 |
| | ***CYP3A4*** | | |
| $K_m$ (μM) | 514 | 757 | 298 |
| $V_{max}$ (nmol/nmol P450/min) | 12.5 | 19.6 | 6.21 |
| $V_{max}/K_m$ (ml/μmol P450/min) | 23.4 | 25.9 | 20.8 |

- The inhibition constant ($K_I$ value) of aripiprazole in dextromethorphan O-demethylation activity by CYP2D6 was 4.38 μM, and the $K_I$ value in dextromethorphan N-demethylation activity by CYP3A4 was 276 μM (a Dixon plot).

**Report-011575 (Study #012786): *Cytochrome P450 Isoforms Responsible for the OPC-14597 Metabolism by Human Liver Microsomes***

This study was conducted to investigate the *in vitro* metabolism of OPC-14957 (aripiprazole) by microsomes from human livers.

- In vitro metabolism of OPC-14597 by the microsomes from human lymphoblastoid cell line transformed with human cytochrome P450 cDNA was investigated, and the results showed that DM-1451, DM-1452, and OPC-14857 were produced through metabolism by the CYP2D6 and CYP3A4 isoforms, and the parameters for the drug-metabolism enzyme activities calculated from the Lineweaver-Burk Plot indicated Km of 16-28 μM (CYP2D6) and 298-757 μM (CYP3A4). (previous study)

- With 15 different human liver microsomes, a good correlation between the metabolic activities of OPC-14597 and of substrates of CYP2D6, CYP3A4, and CYP3A4/5

were observed (r=0.476-0.837 for CYP2D6, r=0.530-0.788 for CYP3A4 and r=0.679-0.934 for CYP3A/4/5).

- In the immunoinhibition study, anti-CYP2D6 antibodies and anti-CYP3A4 antibodies inhibited the metabolic activities of OPC-14597 by 30 to 60% and 60 to 80%, respectively, at the highest concentration (5 mg IgG/mg protein), whereas other anti-CYP antibodies did not show any inhibition. Anti-CYP2D6 and CYP3A4 antibodies inhibited the metabolic activities of OPC-14597.

- In the inhibition study, ketoconazole, a potent inhibitor of CYP3A4, inhibited the metabolic activities of OPC-14597 by approximately 30 to 90% at concentrations of 0.1 to 1 μM. Quinidine, a potent inhibitor of CYP2D6, slightly inhibited the metabolic activities of OPC-14597 by 10 to 30% at concentrations of 1 to 10 μM. Furafylline, sulfaphenazole, tranylcypromine, and diethyldithiocarbamate, inhibitors of CYP1A2, CYP2C9, CYP2C19, and CYP2E1, respectively had little or no OPC-14597 metabolism. Because the inhibitory effect of these inhibitors at high concentrations was considered to be less specific, slight inhibitions caused by 100 μM of these inhibitors were not considered to be significant. Based on these results, the metabolism of OPC-14597 was presumed to be primary related to the CYP2D6 and CYP3A4 isoforms in the human liver microsomes.

- In the inhibition study of CYP2D6-mediated dextromethorphan O-demethylation by OPC-14597, the $K_I$ value calculated by Dixon plot was 15.0 μM. There were some perils of replying on the Dixon plot for the determination of $K_I$ because the Dixon plot had some vague vulnerability to small changes of data. The $K_I$ calculated by the competitive model, which would be considered steady to such deviations, was 6.24 μM.

- Both SKF-525A and cimetidine, inhibitors of cytochrome P450, and anti-NADPH P450 reductase antibody inhibited the DCPP (a metabolite of OPC-14597) formation activity, which suggested that the metabolic pathway from OPC-14597 to DCPP was mediated by cytochrome P450.

**Report-013604 (Study #015578)**: ***In Vitro Metabolism of OPC-14857, a Major Metabolite of OPC-14597 by Microsomes from Human B-Lymphoblastoid Cell Line Transformed with Human Cytochrome P450 cDNAs***

This study was conducted to investigate the *in vitro* metabolism of OPC-14857, a major metabolite of aripiprazole (OPC-14597) in human, by microsomes from human B-lymphoblastoid cell line transformed with human cytochrome P450 cDNAs. The results are as follows:

- 1-(2,3-Dichlorophenyl) piperazine (DCPP) was produced through metabolism by CYP1A1, and CYP3A4.

- Two unknown metabolites, namely UK-1 and UK-2, were detected for the first time in this study. As for UK-1, it was produced through metabolism by CYP2D6 and CYP3A4, and its chemical structure was proposed as hydroxylated-OPC-14857. As for UK-2, it was produced through metabolism by CYP3A4, and its chemical structure was proposed as dehydro-DM-1457.

- OPC-14857 was not metabolized by any other isoforms (CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9-Arg, CYP2C9-cys, CYP2C19, CYP2E1, and CYP4A11).

- Considering the fact that CYP1A1 is expressed at only very low levels in human liver, and the production rate of DCPP by CYP1A1 was low, the metabolism of OPC-14857 was presumed to be primarily related to CYP2D6 and CYP3A4 similar to that of OPC-14597, yielding the aromatic hydroxylated compound (DM-1459).

**Report-011801 (Study #013922):** ***Inhibition of OPC-14597 on Dextromethorphan O-Demethylation Activities of CYP2D6 in Human Liver Microsomes (II)***

In the previous inhibition study of CYP2D6-mediated dextromethorphan O-demethylation by OPC-14597 in human liver microsomes, the $K_i$ estimated by Dixon plot was 15.0 μM and by the competitive model was 6.24 μM. But in the same investigation at the [redacted] the $K_i$ estimated by Dixon plot was 0.18 μM and by the competitive model was 0.68 μM. Although the difference between both the laboratories in the $K_i$ estimated by Dixon plot may have been largely due to the vagueness of the 'classical' Dixon plot, the difference in the $K_i$ estimated using the competitive model with WinNonlin was still about 9 times. So the sponsor examined again using two different microsomal preparations to estimate the $K_i$ values. The results are shown in the following table:

**Table 1. The Inhibition Constant (Ki) of CYP2D6-mediated Dextromethorphan O-demethylation by OPC-14597 (Aripiprazole)**

| Microsomes Source | $K_i$ (by Dixon Plot) | $K_i$ (by Competitive Model) | Dextromethorphan Concentration |
|---|---|---|---|
| [redacted] | 8.00 μM | 6.32 μM | 10, 25, 50 μM |
| | 3.54 μM | 4.40 μM | 5, 10, 20 μM |

OPC-14597 concentrations 0, 5, 10, 20, 50 μM for Georgetown's microsomes and 0, 1, 5, 10, 20, 50 μM for the other.

**Summary**

Although the sponsor could not clarify the cause of the difference in the $K_i$ between both the laboratories, they decided to adopt two $K_i$ values (6.32 and 4.40 μM using two different human liver microsomes obtained from the [redacted] respectively) for CYP2D6 of OPC-14597 estimated by WinNolin in the competitive inhibition model.

*A Study to Assess the Potential for Inhibition of Human Cytochrome P450 by BMS-337039 (OPC-14597, Aripiprazole) and BMS-337044 (OPC-14857)*

The objective of this study was to determine the in vitro inhibitory activity of aripiprazole and OPC-14857 on human cytochrome P450. The capacity of aripiprazole and OPC-14857 to inhibit cDNA-derived cytochrome P450 enzymes in microsomes prepared from baculovirus-infected insect cells was measured using either 3-cyano-7-ethoxycoumarin (CYP1A2 and CYP2C19), 7-methoxy-4-trifluoromethylcoumarin (CYP2C9) or 3-[2-(N, N-diethyl-N-methylamino) ethyl]-7-methoxy-4-methylcoumarin (CYP2D6) as substrates. CYP3A4 was tested with multiple substrates; 7-benzyloxy-4-trifluoromethylcoumarin (BFC) and resorufin benzyl ether (BR).

**Table 1. Summary of IC50 Values (μM; mean of five determinations)**

| Test Substance | CYP1A2 | CYP2C9 | CYP2C19 | CYP2D6 | CYP3A4 | |
|---|---|---|---|---|---|---|
| | | | | | BFC | BR |
| Aripiprazole | >66 | 10 | 2.6 | 2.4 | 25 | NC* |
| OPC-14857 | >50 | 17 | 3.6 | 4.8 | 9.1 | NC* |

*IC50 value was not calculated because of activation by the test substance.

**Summary**

- These in vitro results suggest that aripiprazole and OPC-14857 have the slight potential to alter the metabolic clearance of drugs that are highly metabolized by CYP2C9, CYP2C19, CYP2D6 and CYP3A4 substrates.

- The compounds are unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP1A2.

- Inhibition differences among various substrates of CYP3A4 are not uncommon and are consistent with the unusual inhibition kinetics sometimes observed with this enzyme.

*A Study to Assess the Potential for Inhibition of Human Cytochrome P450 by BMS-337039 and BMS-337044 Utilizing Human Liver Microsomes and Marker Substrates*

The objective of this study was to determine the in vitro inhibitory activity of aripiprazole and OPC-14857 on human cytochrome P450 CYP2C9, CYP2C19, CYP2D6 and CYP3A4 isoforms in human liver microsomes (HLM).

Table 1. Summary of IC50 Values (μm, mean of two determined)

| Isoform | CYP2C9 | CYP2C19 | CYP2D6 | CYP3A4 |
|---|---|---|---|---|
| Marker Substrate | Diclofenac | Mephenytoin | Dextromethorphan | Midazolam |
| Aripiprazole | >66[1] | 54 | 13 | >66[1] |
| OPC-14857 | >50[1] | ND[2] | 17 | >50[1] |

[1]Activation of marker substrate metabolism by the test substance was observed. [2]IC50 value was not determined because of assay interference by the test substance.

**Summary**

- Both aripiprazole and OPC-14857 were weak inhibitors of CYP2D6 with average $IC_{50}$ values of 13 and 17 μM, respectively.

- Aripiprazole was a weak inhibitor of CYP2C19 ($IC_{50}$ 54 μM), while an $IC_{50}$ value with CYP2C19 could not be determined for OPC-14857 because of assay interference by the test substance.

- No inhibition was observed for both compounds with CYP2C9 and CYP3A4 up to the highest concentration tested. However, activation of the marker substrate's metabolism by the test substances was observed.

- The inhibition results observed are less potent than with previously reported IC50 values when utilizing cDNA CYP enzyme system. It is not uncommon that less potent inhibition is observed in HLM (compared to cDNA) when testing a CYP isoform for inhibition by a test substance that may be metabolized in the HLM incubations.

## Protein Binding Studies

Vol.1.30 (Pharm-Tox Vol. 18):

***In Vitro Determination of Protein Binding of BMS-337039 in Mouse, Rat, Rabbit, Monkey, Dog and Human Sera and of BMS-337044 in Human Serum***

The protein binding of BMS-337039 (aripiprazole, OPC-14597, OPC-31) in mouse, rat, rabbit, monkey, dog and human sera and its active metabolite, BMS-337044 (OPC-14857), in human serum were determined in vitro. Serum protein binding was determined by equilibrium dialysis for 6 h at 4 concentrations (500, 1000, 2500, and 5000 ng/ml), in triplicate. At the end of the experiment, portions of serum and buffer for protein binding were analyzed for BMS-337039 or BMS-337044 by a method that had lower limits of quantitation (LLQ) of in buffer for both compounds. The results are summarized in the following table:

**Table 1. Summary of Serum Protein Binding Data for BMS-337039 (Aripiprazole) and its Active Metabolite, BMS-337044 (OPC-14857)**

| | BMS-337039 | | | | | | BMS-337044 |
|---|---|---|---|---|---|---|---|
| | Mouse | Rat | Rabbit | Monkey | Dog | Human | Human |
| C (ng/ml) | | | *Protein Binding (%) (N=3)* | | | | |
| 500 | a | a | 99.7[b] | 99.5±0.07 | a | a | 99.7[b] |
| 1000 | 99.8[c] | 99.8±0.04 | 99.8[d] | 99.5±0.07 | e | a | 99.8[b] |
| 2500 | 99.8±0.04 | 99.7±0.06 | 99.7±0.04 | 99.4±0.01 | 99.7±0.02 | 99.9±0.01 | 99.9±0.01 |
| 5000 | 99.7±0.05 | 99.5±0.05 | 99.7±0.03 | 99.2±0.05 | 99.7±0.06 | 99.7±0.24 | 99.8±0.03 |

a Buffer concentration for the triplicates were below LLQ of 2 ng/ml. b N=1 c N=2 d N=2 One serum replicate was mis-injected. E Protein binding was not determined at this concentration due to insufficient amount of control dog serum.

**Summary**

- BMS-337039 was extensively bound to mouse, rat, rabbit, dog, monkey, and human sera and BMS-337044 was extensively bound to human serum.

- Monkey had the largest percent free drug (0.5-0.8%) and human serum had the smallest percent of free drug (0.1-0.3%) in comparison to the mouse, rat, rabbit, and dog sera who had similar percent of free drug (0.2-0.5%).

- The extent of serum protein binding was independent of concentration over a 10-fold range (500-5000 ng/ml).

- In conclusion, BMS-337039 and BMS-337044 are extensively bound to serum protein.

### *[$^{14}$C]OPC-14597 Human Plasma Protein Binding Method Validation Equilibrium Dialysis*

*In vitro* protein binding assessment of OPC-14597 to human plasma proteins was evaluated by both [illegible] However, due to the high extent of non-specific binding of OPC-14597 to the [illegible] (~30% binding with pre-conditioning), [illegible] was exclusively employed for binding assessments. Each binding investigation was performed using [14C]OPC-14597 standard in K3EDTA human plasma under controlled temperature (37±2°C) and pH 7.4±0.2). Dialysis was accomplished using a [illegible] 12-14K MWCO). A modified Krebs-Ringer phoshate buffer (KRP), pH 7.4, was used as the dialysate and the cell rotation was set at 20 rpm. The resulting samples (dialyzed and non-dialyzed) were assayed by [illegible]

**Report-010398**: ***Determination of Human, Rat and Dog Serum Protein Binding of 14C-OPC-14597 Using a [illegible] Assay***

The in vitro binding of [$^{14}$C]OPC-14597 to serum proteins was measured by the [illegible] and [illegible] methods in previous studies. However, it was difficult to measure the protein binding by those conventional methods due to the marked adsorption of the drug to the membrane and the apparatus wall. Therefore, the present study was conducted to measure the binding of [14C] OPC-14597 to human, rat, and dog serum proteins by a new recently reported method (in which the free drug which is not bound to serum proteins is adsorbed into [illegible]

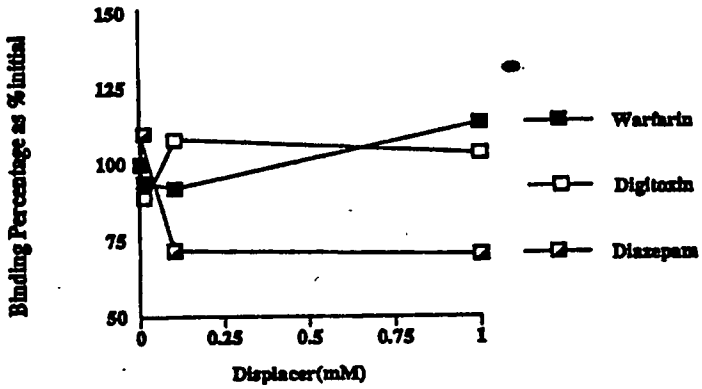
**Table 1.** ***In Vitro*** **Protein Binding of [$^{14}$C]OPC-14597 in Serum of Human, Dog and Rat by [illegible] (n=4)**

| OPC-14597 (ng/ml) | Human | Dog | Rat |
|---|---|---|---|
| 20 | 96.8±6.1 | 101.8±8.2 | 90.1±3.5 |
| 100 | 88.6±2.2 | 88.2±1.4 | 96.1±6.0 |
| 1000 | 92.7±1.5 | 91.4±0.6 | 92.9±2.3 |

**Table 2. In *Vitro* Protein Binding of [$^{14}$C]OPC-14597 in Human Serum Protein Fraction by (n=3)**

| OPC-14597 (ng/ml) | HAS (4%) | γ-GB (1.4%) | AGP (0.1%) |
|---|---|---|---|
| 20 | 86.4±2.9 | 30.2±7.0 | 81.9±29.1 |
| 100 | 96.2±3.6 | 20.0±5.0 | 70.3±8.6 |
| 1000 | 89.1±7.6 | 27.2±11.0 | 61.5±1.7 |

**Figure 1. Displacement of Drugs (Warfarin, Diazepam, and Digitoxin) from human serum albumin by [14C]-OPC-14597**




## Summary

- The serum protein binding of OPC-14597 in a concentration range of 20-1000 ng/ml in humans, rats and dogs determined by _____ was higher than 88% in all three species.

- OPC-14597 showed strong binding to human serum albumin, and that binding was presumed to be at the diazepam site (Site II).

**Report-012757: *In Vitro Protein Binding of OPC-14597 Metabolites, OPC-3373, DCPP, OPC-14857 and DM-1452 in Human Serum (920001406 1.0)***

The *in vitro* protein binding rates of OPC-14597 metabolites, OPC-3373, DCPP (1-(2,3-Dichlorophenyl) piperazine hydrochloride), OPC-14857 and DM-1452 in human serum were investigated. The _____ used for OPC-3373 and _____ method was used for OPC-14857 and DM1452 protein binding determination.

**Table 1. In Vitro Protein Binding of [14C]-OPC-14597 and Its metabolites (OPC-3373, DCPP, OPC-14857 and DM-1452) to Human Serum (N=4)**

| C (ng/ml) | [$^{14}$C]-OPC-14597* | OPC-3373 | DCPP | OPC-14857 | DM-1452 |
|---|---|---|---|---|---|
| 20 | 96.8±6.1 | -- | -- | -- | -- |
| 100 | 88.6±2.2 | 90.2±0.4 | -- | 98.3±1.4 | -- |
| 250 | -- | 90.5±0.2 | -- | 98.0±2.9 | 91.1±4.7 |
| 500 | -- | 90.1±0.1 | 99.4±0.1 | 94.3±4.1 | 88.8±4.9 |
| 1000 | 92.7±1.5 | 90.1±0.1 | 99.2±0.1 | 94.1±3.3 | 88.3±4.6 |
| 2500 | -- | -- | 99.1±0.1 | -- | -- |
| 5000 | -- | -- | 99.0±0.0 | -- | -- |

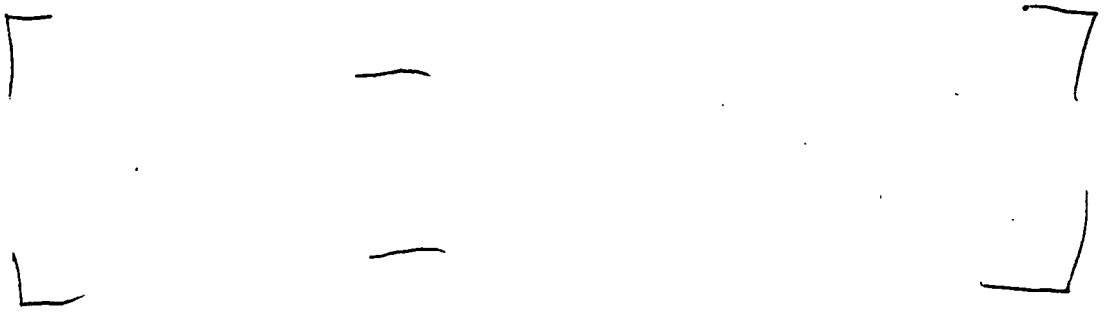
* Previous study results.

## Summary

OPC-3373, DCPP, OPC-14857 and DM-1452 showed protein binding of 90.1-90.5%, 99.0-99.4%, 94.1-98.3% and 88.3-91.1% at concentrations of 100-1000, 500-5000, 100-1000 and 250-1000 ng/ml in human serum, respectively.

## Report-013277: *The Blood-Plasma Partition Ratio of OPC-14597 in Rat, Mouse, Rabbit and Human*

The blood-plasma partition ratio ($R_B$) of OPC-14597 in rat, mouse and human was investigated in in vitro using [14C]-OPC-14597. The procedure is described below:



$R_B=C_B/CP$ $C_B$: the blood concentration (dpm), CP: the plasma concentration (dpm)

**Table 1. The Blood-Plasma Partition Ratio ($R_B$) of OPC-14597 in Fasting and Non-fasting Rat, Fasting Mouse, Rabbit and Human (n=3)**

| OPC-14597 Blood (ng/ml) | Fasting Rat | Non-fasting Rat | Fasting Mouse | Fasting Rabbit | Fasting Human |
|---|---|---|---|---|---|
| | | | ***RB of OPC-14597*** | | |
| 20 | 0.93±0.07 | 0.86±0.05 | 0.79±0.01 | 0.82±0.01 | 0.63±0.04 |
| 200 | 0.89±0.04 | 0.89±0.01 | 0.81±0.04 | 0.78±0.10 | 0.59±0.00 |
| 2000 | 0.90±0.02 | 0.88±0.02 | 0.82±0.01 | 0.85±0.07 | 0.60±0.01 |

## Summary

- The RB of [14C]-OPC14597 in rat, mouse and human was 0.86-0.93, 0.79-0.82 and 0.59-0.63 at concentrations of 20 to 2000 ng/ml in blood, respectively.