CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Abilify® Aripiprazole
PRIMARY REVIEWER: Andre Jackson
NDA: 21436/S-017
TYPE: NDA
FORMULATION: Tablet
STRENGTH: 10 20 and 30 mg
APPLICANT: BMS/Otsuka
Submission Dates: March 23, 2007, 2005

INDICATIONS: Schizophrenia (b) (4) in pediatric populations
Generic Name: Aripiprazole

INTRODUCTION

Abilify™ (aripiprazole, OPC-14597, BMS-337039) is approved in the United States of America (US) for the treatment in adults of acute schizophrenia (November 2002), maintenance of stability in schizophrenia (August 2003), treatment of acute manic and mixed episodes associated bipolar disorder (September 2004), and for the maintenance of efficacy in bipolar I disorder (March 2005).

The mechanism of action of aripiprazole differs from that of currently marketed typical and atypical antipsychotics. It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonism/antagonism at dopamine D_2 and serotonin 5-HT_{1A} receptors, and antagonism at serotonin 5-HT_2 receptors.

STUDY RATIONALE

In a previous study conducted in children and adolescents with conduct disorder, doses up to 15 mg QD were well tolerated. However, a maximum tolerated dose (MTD) in the pediatric population was not determined since it was not a defined objective of the protocol. The purpose of this study was to evaluate the safety and tolerability of doses greater than 15 mg and up to 30 mg in the pediatric population. Doses in excess of 30 mg were not studied due to limitations based upon the no-effect doses established in nonclinical toxicity studies in the most sensitive species.
Establishing an MTD in the pediatric population was desirable (b) (4)

OBJECTIVES

This study assessed the safety, tolerability, and PK of repeated doses of aripiprazole following oral administration to children and adolescent patients preferentially with a primary schizophrenia spectrum diagnosis or bipolar spectrum disorder.

TOLERABILITY

Dose toleration was defined as follows: during the course of the study the subject does

not experience any untoward events or potentially clinically significant changes from baseline in laboratory values, vital signs, ECG tracings, or EPS ratings, that are assessed as possibly related to the drug, and would warrant adjustment or discontinuation of the study drug. A dose level was judged to have been tolerated if 4 out of 6 (67%) of the subjects in a cohort with that maximum dose tolerated the dose.

METHODS

This study was conducted at the following centers:

Site 001
Robert Findling, MD
Director, Child and Adolescent Psychiatry
University Hospitals of Cleveland
Division of Child and Adolescent Psychiatry
11100 Euclid Avenue
Cleveland, OH 44106-5080

Site 002
Ralph Kauffman, MD
Marion Merrell Dow/Missouri Chair in Medical Research
Professor of Pediatrics and Pharmacology
Children's Mercy Hospital
2401 Gillham Road
Kansas City, MO 64108

Site 003
Floyd R. Sallee, MD, PhD
Director, Division of Child Psychiatry
Professor of Psychiatry and Pediatrics
University of Cincinnati College of Medicine
425 Oak Street
Sallee Study Group / Carriage House
Cincinnati, OH 45219

Table1.-Demographic Characteristics

Parameter	Statistic	ARIP 20 mg (N = 8)	ARIP 25 mg (N = 7)	ARIP 30 mg (N = 6)	Total (N = 21)
Age (years)	Mean (SD)	12.4 (2.5)	13.3 (1.8)	10.8 (1.2)	12.2 (2.1)
	Range	10 - 17	11 - 16	10 - 13	10 - 17
Weight (kg)	Mean (SD)	59.50 (18.99)	71.43 (20.68)	50.22 (21.71)	60.82 (21.13)
	Range	36.4 - 83.0	45.1 - 100.0	31.3 - 89.9	31.3 - 100.0
Height (cm)	Mean (SD)	154.0 (9.5)	166.1 (9.2)	147 (12.0)	156.1 (12.4)
	Range	142 - 173	157 -180	134 - 167	134 - 180
BMI	Mean (SD)	24.8 (7.1)	25.8 (7.0)	22.8 (7.2)	24.6 (6.8)
	Range	16.2 - 34.8	16.8 - 33.1	15.5 - 32.2	15.5 - 34.8
Gender	n (%)				
Male		4 (50%)	4 (57%)	6 (100%)	14 (67%)
Female		4 (50%)	3 (43%)	0 (0%)	7 (33%)
Race	n (%)				
Caucasian		6 (75%)	4 (57%)	6 (100%)	16 (76%)
Black or African American		1 (13%)	3 (43%)	0 (0%)	4 (19%)
Other		1 (13%)	0 (0%)	0 (0%)	1 (5%)
Ethnicity	n (%)				
Hispanic/Latino		0 (0%)	2 (29%)	0 (0%)	2 (10%)
Not Hispanic/Latino		8 (100%)	5 (71%)	6 (100%)	19 (90%)

Overall Design and Plan of the Study

This was a multicenter, open-label, sequential cohort, dose-escalation study of multiple doses of aripiprazole ranging from 2 mg to 30 mg. Up to 24 subjects could have participated. Children and adolescent subjects preferentially with a primary schizophrenia diagnosis or bipolar spectrum disorder were eligible to participate in this study. Three cohorts of 6 subjects each were to be administered aripiprazole for up to 12 days (depending upon the maximum dose for the cohort) using a forced titration scheme to achieve one of the following dose levels: 20 mg, 25 mg, and 30 mg. Following the dose-escalation phase, subjects entered the fixed-dose phase and received the maximum dose for that cohort for 14 days.

The dosing schedule for each cohort is outlined in Table 2

Table 2. Dosing Schedule for Dose-escalation and fixed-dose phases.

Cohort	Dose-escalation Phase	Fixed-dose Phase
20 mg Cohort (n = 6)	2 mg × 2 days, 5 mg × 2 days, 10 mg × 2 days, 15 mg × 2 days	20 mg × 14 days
25 mg Cohort (n = 6)	2 mg × 2 days, 5 mg × 2 days, 10 mg × 2 days, 15 mg × 2 days, 20 mg × 2 days	25 mg × 14 days
30 mg Cohort (n = 6)	2 mg × 2 days, 5 mg × 2 days, 10 mg × 2 days, 15 mg × 2 days, 20 mg × 2 days, 25 mg × 2 days	30 mg × 14 days

Pharmacokinetic/Pharmacodynamic Assessments

Blood was collected for the determination of aripiprazole plasma concentrations. Samples (4 mL) were taken on Days 14 and 15 of the fixed-dose phase at predose and at the following postdose hours: 1, 2, 3, 4, 6, 8, 10, and 24 hours. Specific information regarding sample handling and processing is provided in an appendix to the study protocol

Pharmacokinetics

For each subject, the aripiprazole and dehydro-aripiprazole plasma concentration-time data were analyzed using a noncompartmental method. Actual blood sample times were used for PK calculations. Missing time zero values were imputed using the 24-hour postdose value as the dosing interval was 24 hours. Values for $C_{ss,max}$ and t_{max} were taken directly from the observed data. Values of AUC_T were estimated using the linear trapezoidal rule to the actual time of the 24-hour sample. Values of CL_{ss}/F for aripiprazole were determined using standard methods

(b) (4)

(b) (4)

Results

Table 3. Tolerability Results During the Dose-Escalation Phase, as Assessed by Majority Vote of Principal Investigators

1 Page(s) has been Withheld in Full as b5 immediately following this page

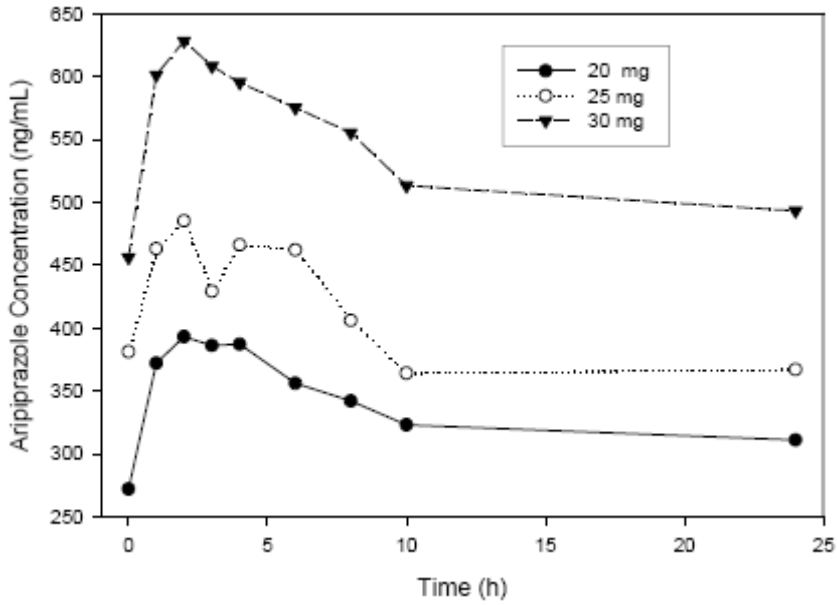

Figure 1. Mean Aripiprazole Plasma Concentrations Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

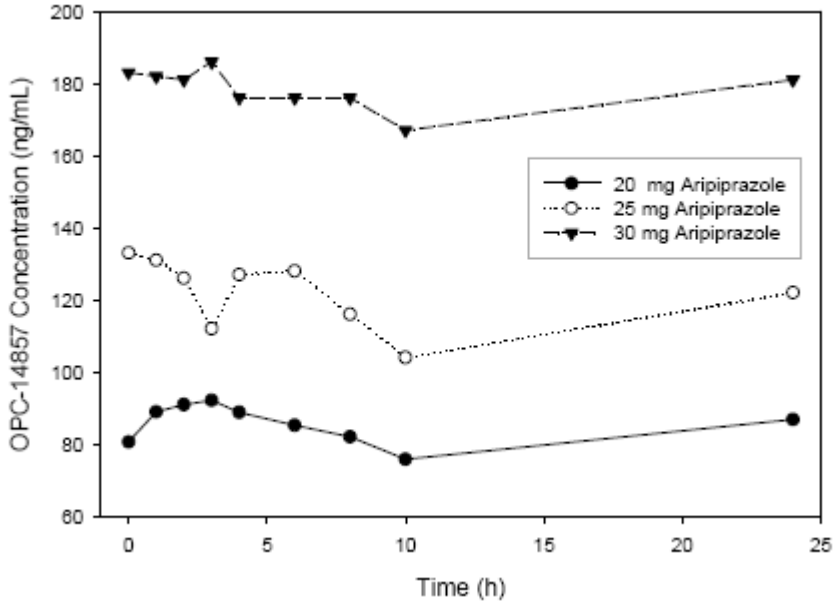

Figure 2. Mean Dehydro-aripiprazole Plasma Concentrations Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

Table 4. Mean (SD) Plasma Pharmacokinetic Parameters for Aripiprazole Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

Parameter	ARIP 20 mg (N = 6)	ARIP 25 mg (N = 5)	ARIP 30 mg (N = 6)
$C_{ss,max}$ (ng/mL)	435 (137)	529 (341)	653 (213)
t_{max} (h)[a]	2.00 (1.00-24.08)	2.05 (1.00-4.02)	2.00 (1.00- 8.00)
AUC_{τ} (ng·h/mL)	8031 (3745)	9488 (7001)	12770 (5444)
CL_{ss}/F (mL/h/kg)	51.7 (22.0)	50.4 (25.9)	58.8 (27.7)

[a]Values are median (minimum - maximum).

Table 5. Mean (SD) Plasma Pharmacokinetic Parameters for Dehydro-aripiprazole Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

Parameter	ARIP 20 mg (N = 6)	ARIP 25 mg (N = 5)	ARIP 30 mg (N = 6)
$C_{ss,max}$ (ng/mL)	99.7 (38.3)	141 (51.0)	202 (63.6)
t_{max} (h)[a]	2.51 (1.00-24.08)	4.02 (1.00-24.03)	2.00 (0- 8.00)
AUC_τ (ng·h/mL)	1995 (711)	2801 (1190)	4208 (1287)
AUC_τ[b] ratio	0.248	0.295	0.330

[a]Values are median (minimum - maximum).

[b]Ratio of mean dehydro-aripiprazole AUC_τ to aripiprazole AUC_τ

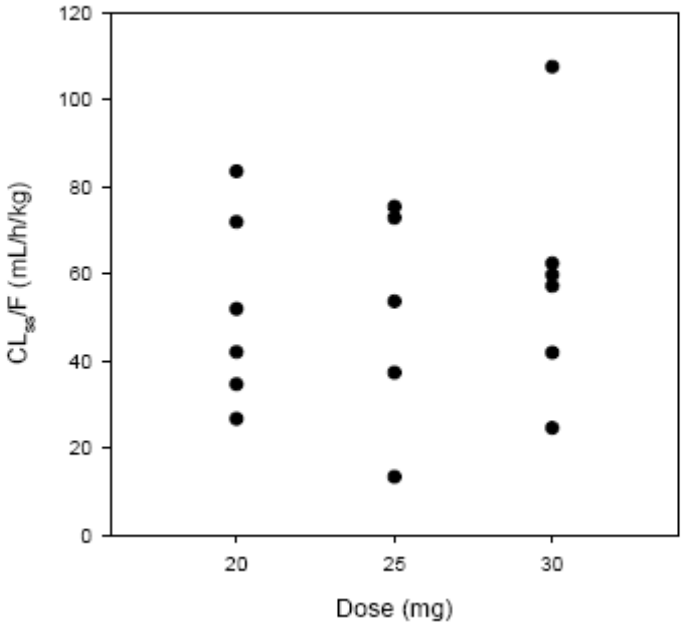

Figure 3 Values of CLss/F Versus Dose Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

CONCLUSIONS

1.There appears to be trend of decreased clearance with dose but it is difficult to verify with 24 subjects although the firm states that the drug appears to be linear. AUC and Cmax appear to be linear although the firm did not do a log analysis of the dose data so linearity appears likely but not definitively determined.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

FDA LABEL-Comments

The firm's proposed label only contained changes to the label by adding pediatric information which is supported by recent pediatric studies. The other portions of the label related to Drug-drug interactions and Clinical Pharmacology are identical to the currently approved label

Andre Jackson_____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 21-436/S017, HFD-860(Mehta, Baweja, Jackson)

C:\Data\REVIEWS\NDA\ABILFY_NDA21436S017_OTSUKA\Pharmkinet\STUDY238\ARIPREV.doc

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andre Jackson
8/22/2007 02:10:24 PM
BIOPHARMACEUTICS

Raman Baweja
8/22/2007 02:55:39 PM
BIOPHARMACEUTICS