Clinical Pharmacology Review

PRODUCT (Generic Name):	Asenapine
PRODUCT (Brand Name):	Saphris
DOSAGE FORM:	Sublingual Tablet
DOSAGE STRENGTHS:	2.5 mg, 5 mg, 10 mg
NDA:	22117
SUBMISSION DATE:	September 12, 2014
SPONSOR:	Forest Labs
REVIEWER	Andre Jackson, Li Zhang, Kevin Krudys, Hao Zhu

Table of Contents

1.0 EXECUTIVE SUMMARY

Forest Laboratories has submitted this (b) (4) supplement for asenapine following a Written Request issued on September 9, 2009, and amended on December 16, 2009. In the Written Request, the sponsor is asked to obtain information on asenapine for pediatric schizophrenia in adolescents ages 13-17 and for pediatric mania

and mixed episodes in bipolar disorder 1 in children and adolescents ages 10-17. To fulfil the Written Request, the sponsor conducted 2 pharmacokinetic studies and 4 clinical trials. In the current submission, the sponsor is requesting a pediatric exclusivity determination. In addition, the sponsor is seeking approval of asenapine for acute treatment of mania and mixed episodes in pediatric bipolar I patients 10-17 years of age.

The sponsor conducted two pediatric pharmacokinetic studies. Study PA7501022 was conducted in adolescents alone (also submitted to the original NDA). Study P06522 was conducted in children and adolescents (10-17 years of age) with schizophrenia or bipolar I disorder. OCP determined that pediatric pharmacokinetic studies have fulfilled the requirement under the Written Request for pediatric pharmacokinetic assessment.

The submitted pharmacokinetic data suggested the exposure in pediatric patients 10-17 years of age is similar to that in adults. The exposure data appear to support the proposed pediatric doses in bipolar I disorder. In addition, exposure-response analysis results supported the use of asenapine in pediatric patients aged 10-17 years with bipolar I disorder. In addition, the proposed pediatric dose for bipolar disorder is acceptable.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the submission and finds the submitted information acceptable, provided an agreement on the label can be obtained from the sponsor. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Recommendations and Comments
Overall	☒ Yes ☐ No ☐ NA	PWR requirements are met.
Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	Adequate information from the pivotal trials to support the approval of pediatric bipolar I disorder.
Proposed dose for general population	☒ Yes ☐ No ☐ NA	Doses of 2.5 mg, 5.0 mg or 10.0 mg BID for Mania and Mixed Episodes in Pediatric Bipolar(10-17 yrs). (b) (4)
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with the sponsor.

1.2 Post-Marketing Studies

No post-marketing studies are requested.

2.0 Question Based Review

2.1 What are the approved adult doses and the proposed pediatric doses?

The approved doses in adult patients and the proposed doses in pediatric patients are listed in Table 1.

Table 1: Approved Doses in Adults and Proposed Pediatric Doses

Treatment	Group	Doses
Schizophrenia	Adult	5mg-10 mg bid
Bipolar	Adult	5mg-10 mg bid
	Pediatric	2.5mg-10mg bid

2.2 Were the exposure for adolescents and adults comparable for Asenapine?

Yes. The exposure for adolescents and adults are comparable. At the dose of 5 mg, the adolescent steady state exposure obtained from study A7501022 (Table 2) was similar to that in adults obtained from a TQT study (Table 3).

Table 2: Adolescent PK Parameters Obtained from Study A7501022

Asenapine Dose	1 mg		3 mg		5 mg		10 mg	
N (n)	8 (7)		8 (5)		8 (8)		8 (8)	
	Median (Range)							
tmax, hr	0.705	(0.25-1.5)	0.890	(0.0-1.5)	1.04	(0.0-2.8)	1.28	(0.0-3.0)
	Arithmetic Mean (%CV)							
Cmax, ng/mL	1.03	(49.6)	2.64	(55.6)	3.54	(47.9)	2.77	(81.8)
Cmin, ng/mL	0.253	(53.8)	0.793	(49.8)	1.02	(41.9)	0.901	(55.8)
AUC(0-τ), hr*ng/mL	6.56	(60.8)	15.8	(49.5)	22.9	(47.5)	19.7	(54.0)
t½, hr	29.3	(40.9)	25.6	(24.6)	32.3	(37.5)	22.6	(21.7)
CL/F, mL/min	3210	(43.5)	4530	(83.5)	6810	(138)	10300	(42.8)
Vd/F, L	7750	(64.4)	12100	(90.0)	14700	(79.5)	19700	(47.3)

N = Number of subjects.
n = Number of subjects where t½ and Vd/F were determined.
Parameters are defined in Table 3.

Table 3: Adult PK Parameters Obtained from a Thorough QT Study

Treatment Group = Asenapine 5/10 mg						
	Day = 1, Dose = 5		Day = 10, Dose = 5		Day = 16, Dose = 10	
	N = 35		N = 28		N = 25	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	2.61 (50.2)	28	4.23 (45.3)	25	6.56 (50.9)
tmax, hr	34	1.92 (51.5)	28	1.79 (46.9)	25	2.01 (46.0)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	35	15.4 (49.1)		NA		NA
$AUC_{(0\text{-}T)}$, ng*hr/mL		NA	28	26.6 (38.4)	25	43.4 (53.1)
t½, hr		NA		NA	20	24.1 (41.3)
Treatment Group = Asenapine 15/20 mg						

2.3 Was the exposure to asenapine in children 10-11 years of age comparable to adults?

Yes. The exposure in children 10-11 years of age is similar to that in adults. At the dose of 5 mg, the Cmax and AUC values are 3.48 ng/ml and 23.6 hr*ng/mL, respectively (Table 4). The observed values are similar to those observed in adults (Table 3) and adolescents (Table 2).

Table 4: Arithmetic Mean (SD) of the Pharmacokinetic Parameters of Asenapine Following Multiple Dose Administration of 2.5, 5, or 10 mg Asenapine BID in a Pediatric Population 10-11 Years of Age

Dose (mg)	Cohort	N	Cmax (ng/mL)	dN Cmax (ng/mL/mg)	Tmax† (hr)	AUC0-12 (hr*ng/mL)	dN AUC0-12 (hr*ng/mL /mg)	t½ (hr)	CL/F (L/hr)	wN CL (L/hr/kg)	Vz/F (L)	wN Vz (L/kg)
2.5	1	6	1.84 (1.17)	0.738 (0.467)	1.0 (0.5-2.0)	11.4 (6.10)	4.56 (2.44)	22.0 (6.12)	264 (107)	5.64 (2.49)	8320 (4370)	173 (74.4)
5	2	6	3.48 (0.629)	0.696 (0.126)	1.8 (1.5-3.0)	23.6 (4.02)	4.71 (0.803)	18.5 (3.11)	218 (38.6)	4.79 (1.08)	5940 (2020)	131 (49.5)
10	3a-d	15*	7.76 (3.79)	0.776 (0.379)	1.0 (0.5-3.0)	44.2 (19.8)	4.42 (1.98)	20.1 (8.96)	293 (197)	5.52 (2.84)	10100 (12900)	171 (162)
10	3a	4	9.24 (5.17)	0.924 (0.517)	1.5 (0.5-1.5)	55.2 (20.9)	5.52 (2.09)	15.9 (2.34)	205 (88.4)	6.05 (3.04)	4590 (1650)	133 (51.2)
10	3b	4	6.75 (0.701)	0.675 (0.0701)	1.0 (1.0-1.0)	41.3 (9.59)	4.13 (0.959)	16.5 (3.38)	253 (64.9)	4.49 (1.41)	6160 (2560)	107 (39.3)
10	3c	3	6.98 (6.46)	0.698 (0.646)	0.5 (0.5-3.0)	36.5 (36.7)	3.65 (3.67)	24.3 (14.9)	512 (391)	8.00 (4.54)	23300 (27100)	336 (329)
10	3d	4	7.87 (2.68)	0.787 (0.268)	1.0 (0.5-1.5)	41.8 (12.6)	4.18 (1.26)	24.6 (11.1)	256 (73.0)	4.46 (1.46)	9520 (6100)	149 (103)

† = Median (minimum-maximum); * = Arithmetic mean results for all subjects in Cohort 3, not stratified by age;
dN = dose-normalized, wN = body weight normalized, SD = standard deviation, hr = hours, BID = twice daily ;
Cohort 1: 2.5 mg BID (10-11 years); Cohort 2: 5 mg BID (10-11 years); Cohort 3a: 10 mg BID (10-11 years);
Cohort 3b: 10 mg BID (12-13 years); Cohort 3c: 10 mg BID (14-15 years); Cohort 3d: 10 mg BID (16-17 years)

2.4 Does the E-R relationship support evidence of effectiveness in bipolar patients?

Yes. The exposure-response relationship demonstrates a reduction of YMRS total score with an increase in asenapine concentration.

For the monotherapy of adults and pediatric patients aged 10-17 years with bipolar I disorder, the proposed dose administration is listed in Table 5.

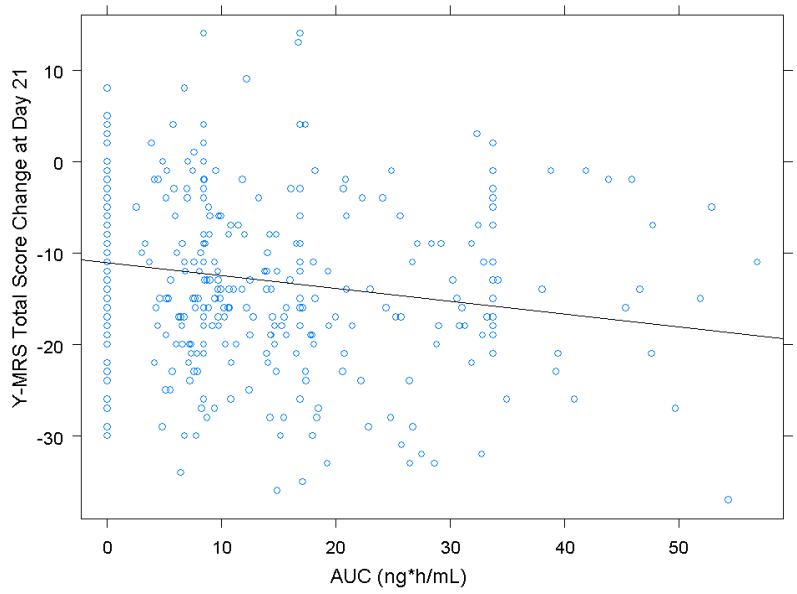
Table 5 Dose administration for patients with bipolar I disorder

Bipolar	Starting Dose	Recommended Dose	Maximum Dose
Adult	10mg BID	5-10mg BID	10mg BID
Peds	2.5mg BID	2.5-10mg BID	10mg BID

In the original NDA (2009), 2 positive trials supported flexible dosing in the range of 5-10 mg BID (10% patients received the dose reduced from 10 mg to 5 mg) in the adult bipolar population. The pediatric Phase 3 trial (P06107) studied fixed doses of 2.5 mg, 5 mg and 10 mg.

The efficacy of Asenapine was established at doses of 2.5 mg, 5 mg and 10 mg. We merged Asenapine treatment groups 2.5mg, 5mg and 10mg data. There was a significant YMRS Total Score reduction with higher Asenapine exposure compared with placebo (P= 0.003, Figure 1). But there was no significant YMRS reduction between Asenapine treatment groups (P= 0.6675).

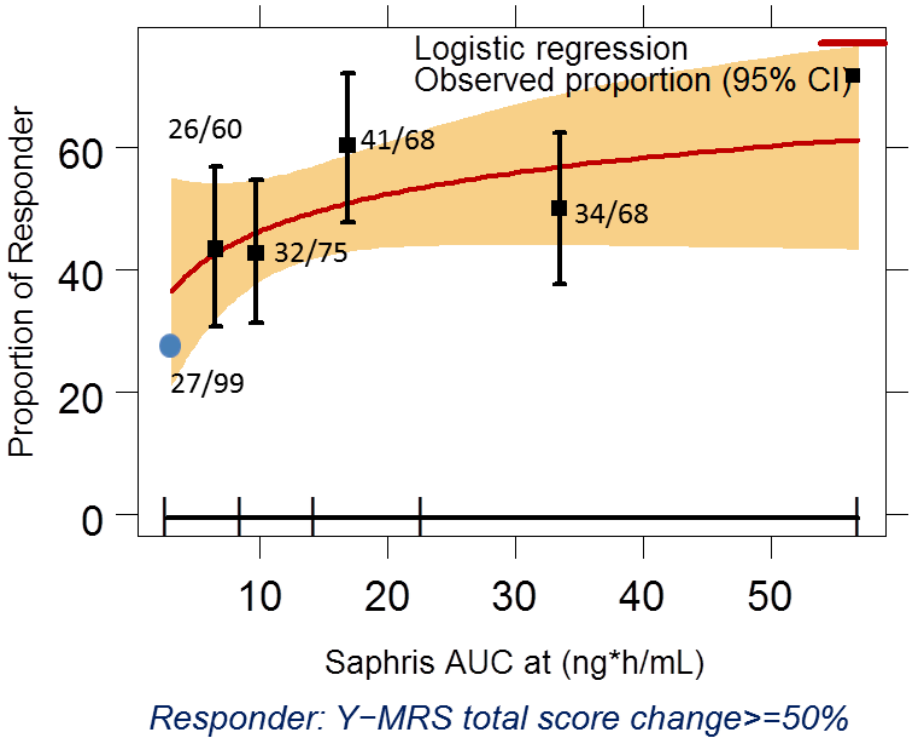
Figure 1 Significant YMRS reduction with higher Asenapine exposure compared with placebo



Source: Reviewer's analysis

In Phase 3 trial P06107, clinical response was defined as YMRS total score change at Day 21 >= 50%. The proportion of responders treated with Asenapine was higher than patients with placebo (50% vs 27%). In addition, there was a trend of increasing response rate with the increase of AUC in Asenapine treated bipolar patients but reached plateau (Figure 3).

Figure 2. Trend of increase of responder rate with the increase of AUC in Asenapine treated patients



(b) (4)

In original NDA (2009), in adult schizophrenia population, there was no suggestion of added benefit with a 10 mg twice daily dose, but there was a clear increase in certain adverse reactions. The pediatric Phase 3 trial (P05896) studied fixed doses of 2.5 mg and 5 mg.

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2.6 Are the pediatric data adequate to support PWR requested sample size?

Yes. The pediatric program includes 561 pediatric subjects with PK samples aged 10-17 years from 2 Phase 1 studies (A7501022 and P06522) and 2 Phase 3 trials (P05896 and P06107). In addition, Phase 3 trial P06107 examined the efficacy and safety of 3-week fixed-dose asenapine treatment in pediatric with bipolar disorder. Therefore, the pediatric data are adequate to support the PWR requested sample size.

2.7 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the active moiety, asenapine, desmethyl-asenapine , and asenapine-11-O-sulfate were appropriately measured in biological fluids.

2.8 What bioanalytical methods are used to assess concentrations of asenapine, desmethyl-asenapine, and asenapine-11-O-sulfate and is the validation complete and acceptable?

Liquid chromatography coupled to mass spectrometry (LC-MS) using electrospray ionization in multi reaction monitoring (MRM) mode. The analytical method was adequately validated and acceptable. The following is a tabular summary of the validation of the bioanalytical method.

Information Requested	Data
Bioanalytical report location	**\\cdsesub1\evsprod\nda022117\0171\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\a7501022-00rnxs\00rnxs.pdf**
Analytes	Asenapine, desmethyl-asenapine , and asenapine-11-O-sulfate
Method description	Liquid chromatography coupled to mass spectrometry (LC-MS) using electrospray ionization in multi reaction monitoring (MRM) mode
QC concentrations	0.075ng/ml, 1.5 ng/ml and 15 ng/ml
Analytes	asenapine and its metabolites Org 30526 (desmethyl-asenapine) and Org 214025 (asenapine-11-O-sulfate)
Internal standard	Asenapine and its internal standard (Org 5222-10), Org 30526 and its internal standard(Org 5649) and Org 214025 and its internal standard (Org 8444)
Linearity	0.025 to 20.0 ng asenapine per mL human plasma 0.050 to 20.0 ng Org 30526 per mL human plasma 0.050 to 20.0 ng Org 214025 per mL human plasma
Lol Quantitation	0.025 ng asenapine/mL 0.05 ng Org 30526/mL 0.05 ng Org 214025/mL
Recovery	59% Org 214025
QC intra run precision	Lower than or equal to 15%,
QC intra run accuracy	Between (and including the limits) -15 and 15%,
QC inter run precision	Lower than or equal to 15%,
QC inter run accuracy	Between (and including the limits) -15 and 15%,
Bench Top stability	24 h
Long Term stability	5 months

3.0 APPENDIX

3.1 INDIVIDUAL CLIN PHARM STUDIES

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

☐ Single Ascending Dose Study ☐ Multiple Ascending Dose Study

Report #:P06522	**Study Period:** 03-Aug-2010 to 02-Aug-2011
NDA 22117	**Link:** \\cdsesub1\evsprod\nda022117\0171\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\p06522\06522.pdf

Title	A SEQUENTIAL GROUPS, OPEN LABEL, RISING MULTIPLE DOSE STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF SUBLINGUAL ASENAPINE IN A PEDIATRIC POPULATION WITH SCHIZOPHRENIA OR BIPOLAR I DISORDER
Objectives:	**Primary Objective:** To assess the pharmacokinetics of multiple rising doses of sublingual asenapine in a pediatric population with schizophrenia or bipolar I disorder. **Secondary Objective:** To assess the safety and tolerability of multiple rising doses of sublingual asenapine in a pediatric population with schizophrenia or bipolar I disorder.
Rationale	(b) (4) [redacted] **Bipolar I Disorder** The majority of patients with bipolar I disorder had a childhood onset of the disease: about 29% at

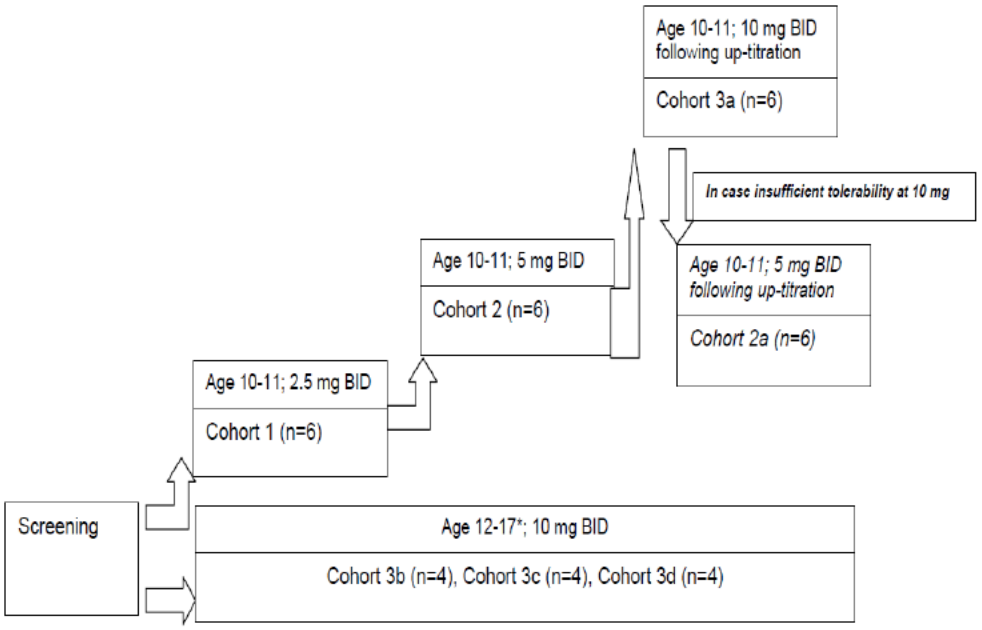
	childhood and 38% at adolescence. Bipolar disorder below the age of 10 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in 10-17 year olds is thought to be relatively common and phenomenological, similar to bipolar disorder seen in adults. Individuals with a childhood onset of bipolar I disorder experience a more chronic, severe, and recurrent course of the disease. Thus, psychotic treatment for these young patients is warranted; however, sound scientific proof of the efficacy and safety of currently available antipsychotics and asenapine, in particular in this pediatric population, is lacking. Therefore, it will be investigated whether asenapine can contribute to satisfy the substantial unmet medical need in the treatment of bipolar I disorder in children and adolescents.

Study Design: Screening was performed within 28 days prior to baseline to see if subjects met all inclusion criteria and none of the exclusion criteria. The diagnosis of schizophrenia or bipolar I disorder, current episode manic or mixed episode, was confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL).

Treatment with current antipsychotic(s) was interrupted prior to baseline (washout period from Day -5 to Day -1) according to a drug-specific washout scheme. Treatment with strong inhibitors or inducers of CYP1A2 and/or CYP2D6 (e.g., fluvoxamine, citalopram, fluoxetine, paroxetine, omeprazole, and rifampicin) and beta-blockers was discontinued as well, applying a washout period of 5 half-lives or 7 days, whichever was longer, and was replaced by non-interacting alternative medication (i.e., medication not interacting with asenapine PK).

Sublingual asenapine was given BID from Days 1 - 6 (Cohorts 1 and 2), Days 1 – 7 (Cohorts 3b, 3c, and 3d), or Days 1 - 11 (Cohort 3a). A final single dose was administered on Day 7 (Cohorts 1 and 2), Day 8 (Cohorts 3b, 3c, and 3d), or Day 12 (Cohort 3a). Safety and tolerability were evaluated throughout the study. Frequent blood sampling for PK evaluation was done during a period of 48 hours after the final dose of asenapine in each cohort. In addition, PK samples were taken for steady-state evaluation at pre-specified times in each cohort. After the last PK sample and follow-up was performed, subjects were re-stabilized onto their own treatment following the instructions of the PI. A continuation of treatment with asenapine was not allowed.

Figure 1. Study Design



*Stratified according to age (6 subjects 10-11, 4 subjects 12-13, 4 subjects 14-15, 4 subjects 16-17 years of age). Gender stratification was such that at a maximum of 4 subjects of 1 gender (Cohort 1, Cohort 2, *Cohort 2a,* Cohort 3a) or 2 subjects of 1 gender (Cohorts 3b, 3c, 3d) was allowed.

Figure 2. Dose (mg) and Timing of Sublingual Asenapine by Cohort

Cohort	Age Group*	Time	Study Day											
			1	2	3	4	5	6	7	8	9	10	11	12
1	10-11 years	AM	2.5	2.5	2.5	2.5	2.5	2.5	2.5	-	-	-	-	-
		PM	2.5	2.5	2.5	2.5	2.5	2.5	-	-	-	-	-	-
2	10-11 years	AM	5	5	5	5	5	5	5	-	-	-	-	-
		PM	5	5	5	5	5	5	-	-	-	-	-	-
3a	10-11 years	AM	2.5	2.5	2.5	2.5	5	5	5	10	10	10	10	10
		PM	2.5	2.5	2.5	5	5	5	10	10	10	10	10	-
3b	12-13 years	AM	5	10	10	10	10	10	10	10	-	-	-	-
		PM	5	10	10	10	10	10	10	-	-	-	-	-
3c	14-15 years	AM	5	10	10	10	10	10	10	10	-	-	-	-
		PM	5	10	10	10	10	10	10	-	-	-	-	-
3d	16-17 years	AM	5	10	10	10	10	10	10	10	-	-	-	-
		PM	5	10	10	10	10	10	10	-	-	-	-	-

Administration	☐ Fast ☑ Fed

Interfering Substances Excluded	
Sampling Times	PK: Blood samples for PK evaluation will be collected pre morning dose on Day 1, 6 and 7. In addition on Day 8 at pre-morning dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 36 and 48h thereafter. A maximum of 15 samples (6 mL of blood per sample) may be taken over a period of 10 days. PD:NA
PK Parameters	AUC0-12 Area under the concentration-time curve during a 12-hour dosing interval Cmax Maximum concentration of drug Tmax Time to reach Cmax t½ Apparent terminal half-life CL/F Apparent total body clearance Vz/F Apparent volume of distribution (calculated for asenapine only) In addition, dose-normalized AUC0-12 and Cmax and weight-normalized Vz/F and CL/F were calculated.
PD Endpoint(s)	NA
PD Parameters	NA
Safety Measures	No clear trend relating total dose to the overall incidence or type of TEAE was observed; however, the incidence and severity of AEs was higher in the older treatment groups (10 mg asenapine, 14-15 and 16-17 year cohorts). Importantly, in subjects aged 10-11 years, the incidence and severity of AEs was greatly improved by gradual up-titration of asenapine, with a decrease in overall incidence of AEs from 50% in Cohort 1 and 67% in Cohort 2 to 17% in Cohort 3a.
Statistical Analysis	

Analytical Method

Method Type	GC/MS	Matrix	Plasma
Analytes	Asenapine Desmethyl asenapine		

Validation	▪ Method validated prior to use	☑ Yes ☐ No

	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Notes:

Results

Study Population

Table 1 Subject Disposition

	Cohort 1 (10-11 yrs)	**Cohort 2** (10-11 yrs)	**Cohort 3a** (10-11 yrs)	**Cohort 3b** (12-13 yrs)	**Cohort 3c** (14-15 yrs)	**Cohort 3d** (16-17 yrs)
Randomized	6	6	6	4	4	4
Female	2	3	2	2	2	2
Male	4	3	4	2	2	2
Mean Age (SD) (yrs)	10.8 (0.4)	10.5 (0.8)	10.3 (0.5)	12.5 (0.6)	14.5 (0.6)	16.5 (0.6)
Completed	6	6	4	4	3	4
Discontinued *	0	0	2	0	1	0
*Subjects 12304 and 12305 (Cohort 3a) and 12316 (Cohort 3c) withdrew consent for the study. SD = standard deviation, yrs = years						

Table 2. Summary of demographics

	2.5 mg Asenapine n=6	5 mg Asenapine n=6	10 mg Asenapine n=18	Total n=30
Sex (n,%)				
Female	2 (33)	3 (50)	8 (44)	13 (43)
Male	4 (67)	3 (50)	10 (56)	17 (57)
Race (n,%)				
White	1 (17)	0	3 (17)	4 (13)
Non-White	5 (83)	6 (100)	15 (83)	26 (87)
Black or African American	5 (83)	6 (100)	15 (83)	26 (87)
Ethnicity (n,%)				
Hispanic or Latino	0	0	3 (17)	3 (10)
Not Hispanic or Latino	6 (100)	6 (100)	15 (83)	27 (90)

Results-See Appendix

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

What is the maximum tolerated dose? 10 mg

What is the basis for considering this dose to be the maximum tolerated dose? Children aged 10-11 years appear to be more sensitive to initial asenapine treatment, which can be prevented by a low initial dose followed by a short up-titration schedule.

Comments

1. At 10 mg BID, Cmax was somewhat higher (~30%) in the 10-11 year old age group compared to the other groups. Although the mean peak concentration in the 14-15 year old age group (N=3) appears lower and delayed, the mean Cmax and Tmax parameters are similar to those of the 12-13 and 16-17 year old age groups (N=4 each).

   In a pediatric population with schizophrenia or bipolar I disorder aged 10-17 years, asenapine PK showed rapid absorption (Tmax ~1 hour) and an apparent terminal half-life of ~20 hours. At 10 mg BID, exposure to asenapine was similar across the age groups from 10-17 years, but maximum asenapine concentrations in 10-11 year old subjects were somewhat higher (~30%) compared to the other age groups.

   • Asenapine administered in doses of 2.5 mg, 5 mg, or 10 mg BID was generally safe and well tolerated in

pediatric subjects (ages 10-17 years) in this study.

APPENDIX

Table 3. Arithmetic Mean (SD) of the Pharmacokinetic Parameters of Asenapine Following Multiple Dose Administration of 2.5, 5, or 10 mg Asenapine BID in a Pediatric Population

Dose (mg)	Cohort	N	Cmax (ng/mL)	dN Cmax (ng/mL/mg)	Tmax† (hr)	AUC0-12 (hr*ng/mL)	dN AUC0-12 (hr*ng/mL /mg)	t½ (hr)	CL/F (L/hr)	wN CL (L/hr/kg)	Vz/F (L)	wN Vz (L/kg)
2.5	1	6	1.84 (1.17)	0.738 (0.467)	1.0 (0.5-2.0)	11.4 (6.10)	4.56 (2.44)	22.0 (6.12)	264 (107)	5.64 (2.49)	8320 (4370)	173 (74.4)
5	2	6	3.48 (0.629)	0.696 (0.126)	1.8 (1.5-3.0)	23.6 (4.02)	4.71 (0.803)	18.5 (3.11)	218 (38.6)	4.79 (1.08)	5940 (2020)	131 (49.5)
10	3a-d	15*	7.76 (3.79)	0.776 (0.379)	1.0 (0.5-3.0)	44.2 (19.8)	4.42 (1.98)	20.1 (8.96)	293 (197)	5.52 (2.84)	10100 (12900)	171 (162)
10	3a	4	9.24 (5.17)	0.924 (0.517)	1.5 (0.5-1.5)	55.2 (20.9)	5.52 (2.09)	15.9 (2.34)	205 (88.4)	6.05 (3.04)	4590 (1650)	133 (51.2)
10	3b	4	6.75 (0.701)	0.675 (0.0701)	1.0 (1.0-1.0)	41.3 (9.59)	4.13 (0.959)	16.5 (3.38)	253 (64.9)	4.49 (1.41)	6160 (2560)	107 (39.3)
10	3c	3	6.98 (6.46)	0.698 (0.646)	0.5 (0.5-3.0)	36.5 (36.7)	3.65 (3.67)	24.3 (14.9)	512 (391)	8.00 (4.54)	23300 (27100)	336 (329)
10	3d	4	7.87 (2.68)	0.787 (0.268)	1.0 (0.5-1.5)	41.8 (12.6)	4.18 (1.26)	24.6 (11.1)	256 (73.0)	4.46 (1.46)	9520 (6100)	149 (103)

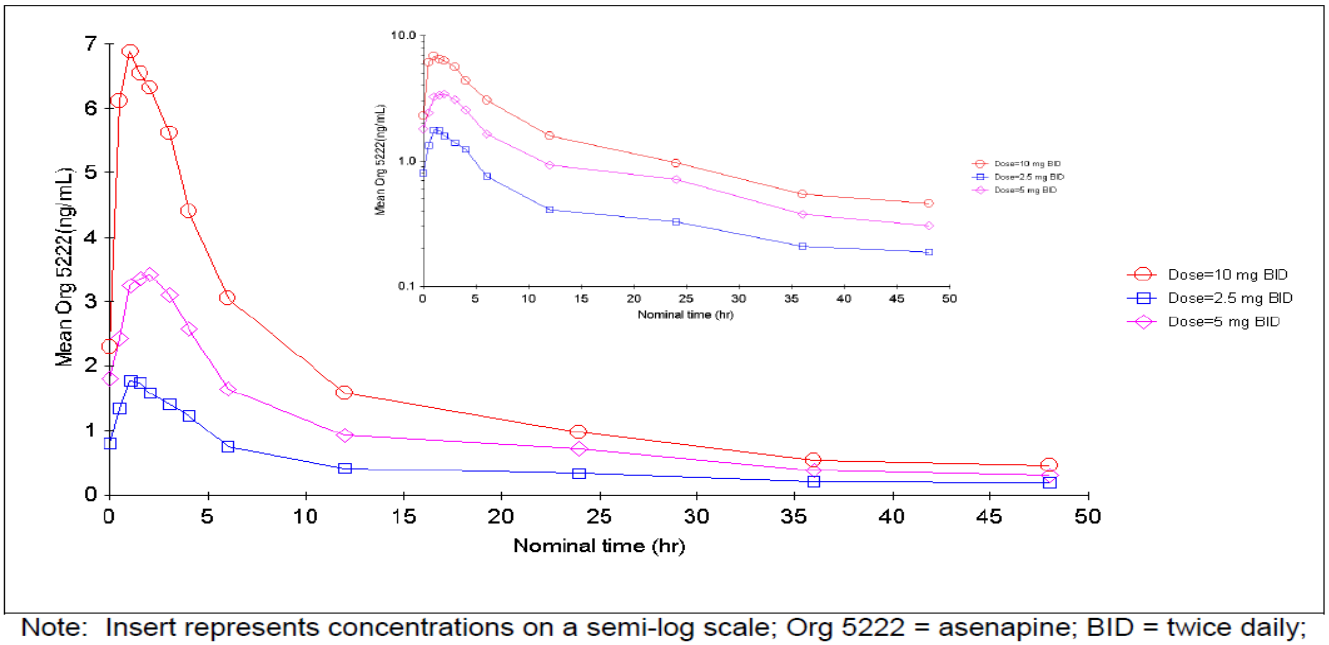
† = Median (minimum-maximum); * = Arithmetic mean results for all subjects in Cohort 3, not stratified by age;
dN = dose-normalized, wN = body weight normalized, SD = standard deviation, hr = hours, BID = twice daily ;
Cohort 1: 2.5 mg BID (10-11 years); Cohort 2: 5 mg BID (10-11 years); Cohort 3a: 10 mg BID (10-11 years);
Cohort 3b: 10 mg BID (12-13 years); Cohort 3c: 10 mg BID (14-15 years); Cohort 3d: 10 mg BID (16-17 years)

Table 4. Arithmetic Mean (SD) of the Pharmacokinetic Parameters of N-desmethylasenapine Following Multiple Dose Administration of 2.5, 5, or 10 mg Asenapine BID in a Pediatric Population

Dose (mg)	Cohort	N	Cmax (ng/mL)	dN Cmax (ng/mL/mg)	Tmax†, ‡ (hr)	AUC0-12 (hr*ng/mL)	dN AUC0-12 (hr*ng/mL /mg)	t½ (hr)	CL/F (L/hr)	wN CL (L/hr/kg)	Vz/F (L)	wN Vz (L/kg)
2.5	1	6	0.648 (0.224)	0.259 (0.0895)	4.0 (4.0-6.0)	6.49 (2.17)	2.60 (0.870)	14.6 (2.82)	421 (130)	8.77 (2.64)	8910 (3450)	187 (80.1)
5	2	6	1.55 (0.673)	0.310 (0.135)	5.0 (3.0-6.0)	15.2 (6.67)	3.04 (1.33)	13.9 (2.97)	424 (287)	9.11 (6.07)	8000 (4030)	173 (87.2)
10	3a-d	15*	3.87 (2.60)	0.387 (0.260)	3.0 (0.0-6.0)	36.5 (23.8)	3.65 (2.38)	14.7 (1.98)	413 (319)	7.31 (4.03	8780 (6280)	156 (87.6)
10	3a	4	6.79 (2.60)	0.679 (0.260)	3.0 (3.0-6.0)	62.9 (24.2)	6.29 (2.42)	12.6 (0.902)	179 (71.7)	5.14 (2.09)	3190 (1080)	91.2 (28.9)
10	3b	4	2.65 (0.907)	0.265 (0.0907)	3.5 (2.0-4.0)	26.3 (9.08)	2.63 (0.908)	16.3 (1.70)	417 (141)	7.24 (2.15)	9710 (2950)	171 (50.7)
10	3c	3	3.45 (3.18)	0.345 (0.318)	2.0 (0.0-4.0)	33.1 (29.9)	3.31 (2.99)	14.2 (1.17)	649 (675)	9.64 (7.74)	12600 (12200)	189 (137)
10	3d	4	2.50 (1.15)	0.250 (0.115)	4.0 (0.0-6.0)	22.9 (7.16)	2.29 (0.716)	15.5 (1.70)	465 (117)	7.82 (3.83)	10600 (3630)	181 (110)

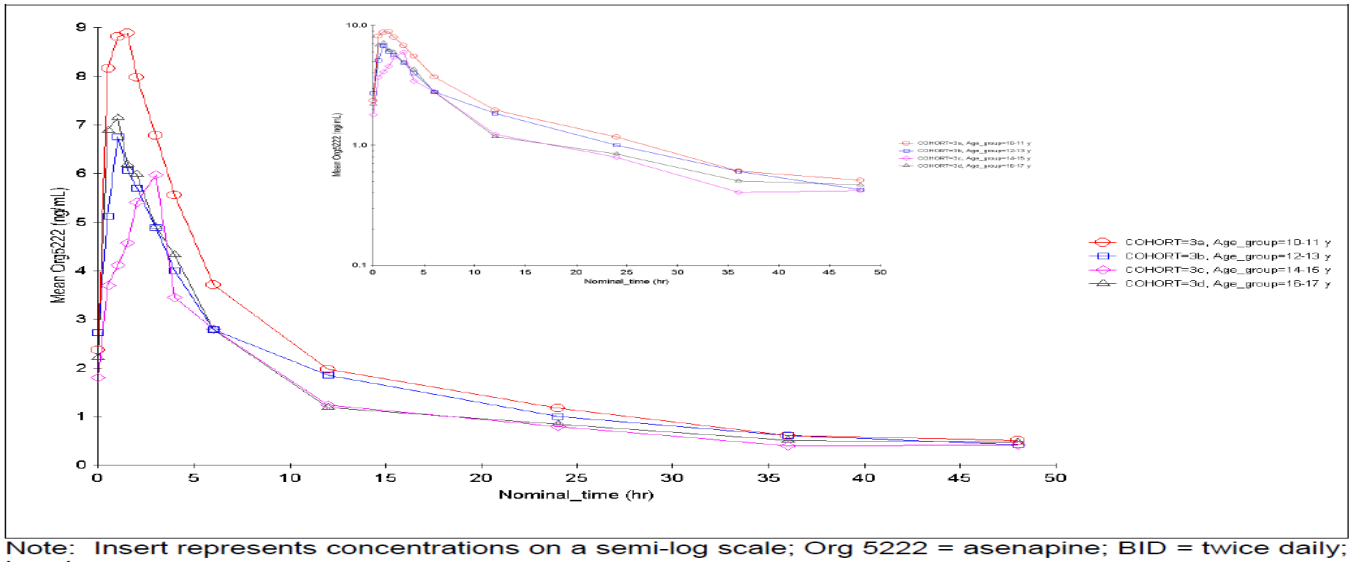
† = Median (minimum-maximum); * = Arithmetic mean results for all subjects in Cohort 3, not stratified by age
‡ = Subjects 11312 (Cohort 3c) and 11318 (Cohort 3d) exhibit peak maximum concentration of N-desmethylasenapine at t=0 hr
dN = dose-normalized, wN = body weight normalized, SD = standard deviation, hr = hours, BID = twice daily
Cohort 1: 2.5 mg BID (10-11 years); Cohort 2: 5 mg BID (10-11 years); Cohort 3a: 10 mg BID (10-11 years); Cohort 3b: 10 mg BID (12-13 years); Cohort 3c: 10 mg BID (14-15 years); Cohort 3d: 10 mg BID (16-17 years)

Figure 1. Arithmetic Mean Asenapine Plasma Concentration-Time Profiles Following Final Dose Administration of 2.5 mg (10-11 years), 5 mg (10-11 years), or 10 mg (10-17 years) Asenapine BID



Note: Insert represents concentrations on a semi-log scale; Org 5222 = asenapine; BID = twice daily; hr = hours

Figure 2. Arithmetic Mean Asenapine Concentration-Time Profiles Following Final Dose Administration of 10 mg Asenapine BID By Age Group



Note: Insert represents concentrations on a semi-log scale; Org 5222 = asenapine; BID = twice daily; hr = hours

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

☐ Single Ascending Dose Study ☐ Multiple Ascending Dose Study

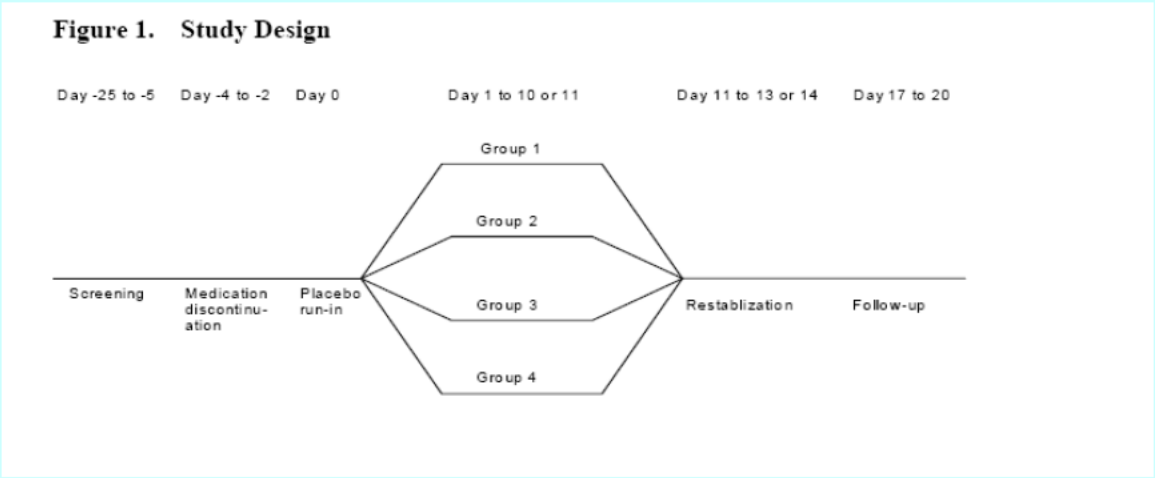
Report #: A7501022	**Study Period:** First Subject Visit: 12 October 2005 Last Subject Visit: 28 March 2006
NDA 22117	**Link:** \\Cdsesub1\EVSPROD\NDA022117\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\a7501022
Title	A Placebo-Controlled, Double-Blind, Randomized, Parallel Group, Multiple-Dose Study With Asenapine in Adolescent Subjects With A Psychotic Disorder to Evaluate Safety, Tolerability, and Pharmacokinetic Parameters

Objectives	The objectives of this study were to evaluate the safety of multiple dose sublingual (SL) administration of asenapine in adolescent subjects, and to evaluate the pharmacokinetics (PK) of multiple dose SL administration of asenapine in adolescent subjects at doses up to 10 mg twice daily (BID).

Study Design:

This study was a placebo-controlled, subject- and investigator-blind, randomized, parallel-group, multiple-dose study in adolescent subjects with a diagnosis of schizophrenia. A total of 40 adolescent subjects were to be enrolled in 4 groups, with 10 subjects randomized per group (8 active, 2 placebo). The trial consisted of a screening period of approximately 3 weeks (Days -25 to -5), background medication tapering and discontinuation period up to 3 days (Days -4 to -2), a placebo run-in (Day 0), treatment period (Days 1-10 or 11), a post-treatment re-stabilization period (Days 11-13 or 14), and a follow-up visit (Days 17-20).

Figure 1. Study design



Beginning on Days 1 through 10 (Groups 1, 2, and 3) and 11 (Group 4), the following dosing regimen was used (Table 1):

Group 1: 1 mg asenapine (8 subjects) or matching placebo (2 subjects) for 10 days.

Group 2: 3 mg asenapine (8 subjects) or matching placebo (2 subjects) for 10 days.

Group 3: 5 mg asenapine (8 subjects) or matching placebo (2 subjects) for 10 days.

Group 4: 5 mg asenapine (8 subjects) or matching placebo (2 subjects) on Day 1,

followed by 10 mg (8 subjects) or matching placebo (2 subjects) for 10 days (the 10-mg

multiple-dose group was titrated 1 day with 5 mg).

Only the morning dose was administered on the last day of dosing. All doses were given q12h.

Table 1. Treatment Schedule

	Day												
Group[a]	0	1	2	3	4	5	6	7	8	9	10	11[b]	12[c]
1	PBO	1 mg	1	1	1	1	1	1	1	1	1		
2	PBO	3 mg[d]	3	3	3	3	3	3	3	3	3		
3	PBO	5 mg	5	5	5	5	5	5	5	5	5		
4	PBO	5 mg	10	10	10	10	10	10	10	10	10	10	

PBO = Placebo.
[a] Eight subjects in each group received asenapine and 2 received matching placebo.
[b] Subjects in Groups 1, 2, and 3 will restart background medication on Day 11.
[c] Subjects in Group 4 will restart background medication on Day 12.
[d] The 3 mg asenapine dose consists of 2 tablets (1 tablet of 1 mg and 1 tablet of 2 mg)

Sampling Times	PK: Blood specimens for PK analyses of asenapine and des-methyl asenapine were drawn prior to the morning dose on Days 8 and 9 (Groups 1, 2, and 3) and Days 9 and 10 (Group 4). Additional samples were drawn at pre-dose and at 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours post-dose on Days 10 (Groups 1, 2, and 3) and 11 (Group 4). Samples were analyzed using validated analytical methods. PD:NA
PK Parameters	

Parameter	Definition	Method of Determination
Cmax	Maximum plasma concentration during the dosing interval	Observed
tmax	Time for Cmax	Observed
Cmin	Minimum plasma concentration during the dosing interval	Observed
AUC(0-τ)	Area under plasma concentration-time profile from time zero to τ, the dosing interval (12 hours)	Linear trapezoidal method
λz	Terminal rate constant	Absolute value of slope of linear regression of natural logarithm (ln) of concentration on time during the terminal phase of concentration-time profile
t½	Terminal half-life	ln(2)/λz
CL/F[a]	Oral clearance	Dose/AUC(0-∞)
Vd/F[a]	Volume of distribution	(CL/F)/λz

[a] Asenapine only

PK Analysis	
PD Endpoint(s)	NA
PD Parameters	NA

Safety Measures	All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) were recorded on the AE page(s) of the CRF. For all AEs, the investigator pursued and obtained information adequate both to determine the outcome of the AE and to assess whether it met the criteria for classification as a SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information was obtained by the investigator to determine the causality of the AE. The investigator assessed causality and indicated that assessment on the CRF. AEs were reportable from the time that the subject provided informed consent, which was obtained prior to the subject's participation in the clinical trial, i.e., prior to undergoing any trial-related procedure and/or receiving investigational product.
Statistical Analysis	

Analytical Method

Method Type	LC\ Mass Spectrometric \ Mass Spectrometric Detectionxxx	Matrix	Plasma
Analytes	Asenapine and Desmethyl-asenapine		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No

- Accuracy and precision of the quality control samples acceptable ☑ Yes ☐ No
- Overall performance acceptable ☑ Yes ☐ No

Results: See Appendix

Demographics

Subject Characteristic	Total Population (N=40)	Percentage or Statistic
Sex		
Male	23	57.5
Female	17	42.5
Race		
Caucasian	13	32.5
Black	27	67.5
Asian	0	0.0
Other	0	0.0
Age at Day 1 (Years)		
Mean		14.8
Standard Deviation		1.7
Median		14.6
Min-Max		12-18
Screening Weight (kg)		
Mean		65.0
Standard Deviation		17.2
Median		65
Min-Max		39.1-104.5

Forty subjects were enrolled and 38 completed this study. Subject 10021991 was withdrawn on Day 2 because of an AE (exacerbation of schizophrenia) and Subject 10021007 withdrew consent on Day 11.

There was one major protocol violation was that an extra dose was given on Day 10 at one of the study sites.

Diagnosis and Main Criteria for Inclusion: Subjects were males and/or females between 12 and 17 years of age who were in good physical health and had a documented history of schizophrenia, bipolar disorder, autism, conduct disorder, oppositional defiant disorder, or any condition for which the chronic use of antipsychotic medication (ie, risperidone, olanzapine, haloperidol) was warranted and/or administered. At least 4 subjects per group must have been between 12 and 15 years of age.

Study Treatment: Placebo or asenapine at doses of 1, 3, 5, or 10 mg q12h was administered orally by the SL route. Dose escalation to the next treatment group proceeded provided none of the following occurred in subjects receiving asenapine: 1) any drug-related SAEs, 2) drug-related clinically significant ECG abnormalities (such as arrhythmias) or

effects on vital signs, 3) drug-related clinically significant laboratory abnormalities, or 4) other findings that, at the discretion of the clinical investigator, indicated that dose escalation should not proceed. Review of the above safety assessments and PK data and agreement between the sponsor and investigator that the dose was well tolerated allowed for progression to the next dose group. At least 7 calendar days were allotted for the collaborative evaluation of the above safety assessments between the conduct of subsequent dose groups.

Concomitant use of medications that induce or inhibit CYP1A2 and CYP3A4, such as fluvoxamine, omeprazole, rifampin, ketoconazole, and erythromycin, was avoided.

Background antipsychotic medication was temporarily withheld during the active treatment period. The investigator evaluated each subject's background antipsychotic medication regimen to determine the appropriateness of its discontinuation in order to participate in the study.

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

What is the maximum tolerated dose? 10 mg

What is the basis for considering this dose to be the maximum tolerated dose?

Dose escalation to the next treatment group proceeded provided none of the following occurred in subjects receiving asenapine: 1) any drug-related SAEs, 2) drug-related clinically significant ECG abnormalities (such as arrhythmias) or effects on vital signs, 3) drug-related clinically significant laboratory abnormalities, or 4) other findings that, at the discretion of the clinical investigator, indicated that dose escalation should not proceed. These conditions were met up to the 10 mg dose.

Comments

1.OCP agrees that the data presented shows comparable exposure between adolescents and adults up to 5 mg for Cmax and Tmax but the half-life of 32 h in adolescents is longer than the reported 24h for adults.

2. OCP agrees with the firm's statement, " The Sponsor does acknowledge that there are elements that need to be assessed further in the planned PK and tolerability study (P06522). These elements include the PK and tolerability in the younger age group of 10-11 years and the PK and tolerability of the 10 mg BID dose level in the broader group of pediatric patients aged 10-17 years. However, these elements are of particular importance for the program in bipolar disorder, because of the lower age range and likely use of the higher (10 mg) dose which is the recommended starting dose for adults." The 10 mg dose needs further investigation.

3.These results confirm that asenapine exposure in the adolescent population increases with increasing dose; however, the increase is not dose proportional. These observations are consistent with what has been observed in the clinical pharmacology studies involving adult subjects. Following 10 mg q12h administration, the mean Cmax and AUC(0-τ) parameter values were less than what was observed for the 5-mg dose.

4. OCP agrees that there should be similarity in pharmacokinetics and tolerability between different diagnostic indications.

5.OCP agrees with the firm that there should be limited effects of maturation on asenapine pharmacokinetics

6. OCP agrees that the assessment of pediatric pharmacokinetics can be done across pooled analysis from multiple studies.

7. The AE data needs to be reviewed by the Medical Officer.

Conclusions

These results indicate that:

Asenapine exposure (Cmax and AUC0-τ) tended to increase with increasing dose from 1 mg BID up to and including 5 mg q12h; however, the increase was less than proportional to dose. Lower asenapine exposure observed in the 10-mg dose group in this study can be attributed to subjects swallowing a larger portion of the dose based on metabolite ratios (Table 4 the desmethyl/asenapine ratio at 10 mg is larger than at the other doses).

Steady state was attained within 8 days of q12h dosing based on morning pre-dose plasma asenapine concentrations.

Asenapine exposure in the adolescent population appears similar to that observed in adults. Multiple doses of asenapine are safe and well tolerated in adolescent subjects with schizophrenia.

APPENDIX

Figure 2. Mean Asenapine Plasma Concentration-Time Profiles Following q12h Administration of Sublingual Asenapine

Tablet Doses to Adolescent Subjects With A Psychotic Disorder, Study A7501022

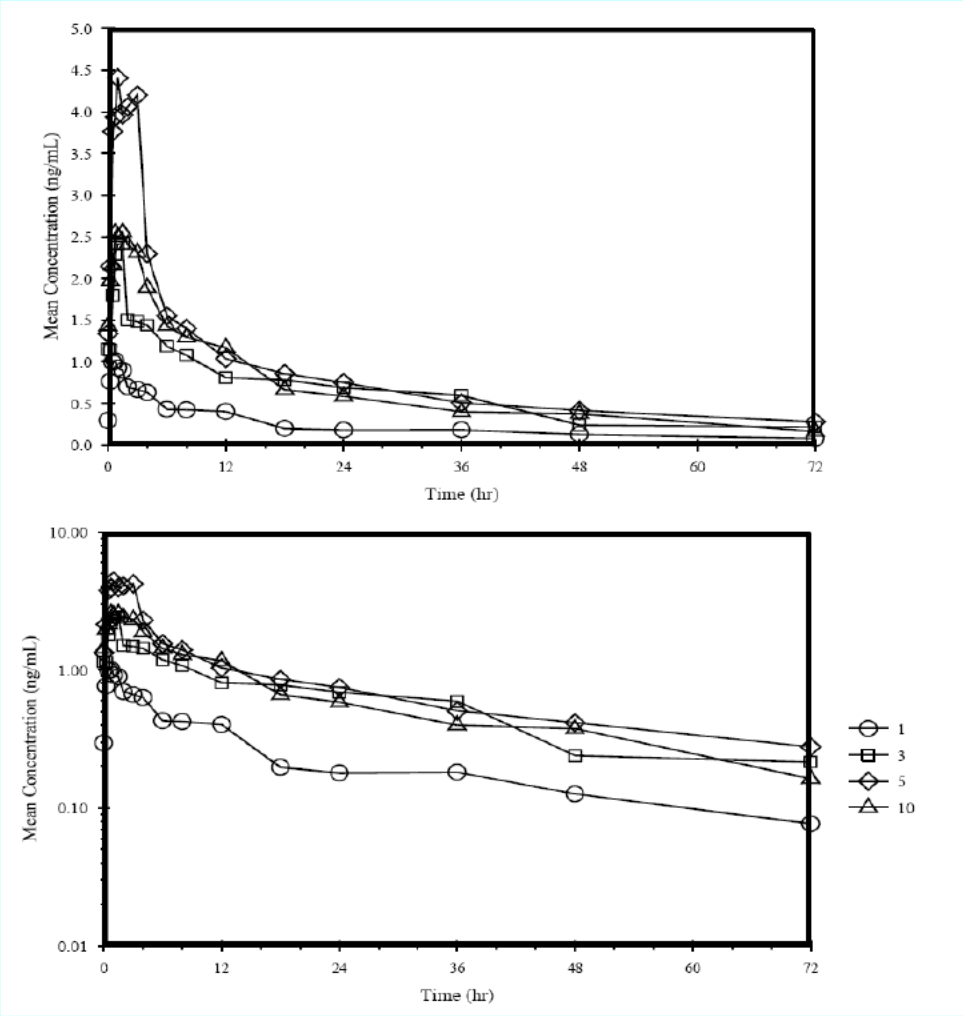
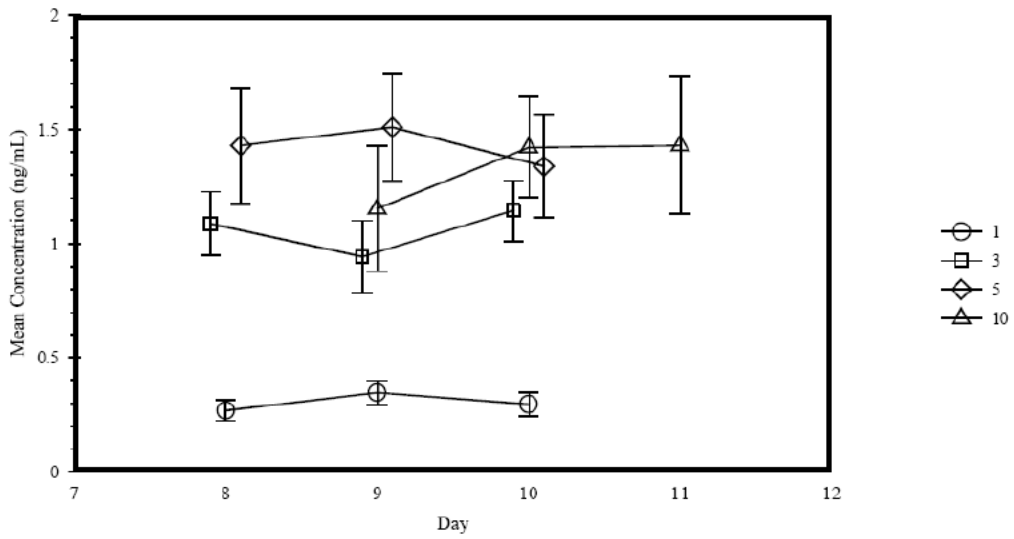


Table 2. Summary of Asenapine Pharmacokinetic Parameter Values Following q12h Administration of Sublingual Tablet Doses to Adolescent Subjects With A Psychotic Disorder, Study A7501022

Asenapine Dose	1 mg		3 mg		5 mg		10 mg	
N (n)	8 (7)		8 (5)		8 (8)		8 (8)	
	Median (Range)							
tmax, hr	0.705	(0.25-1.5)	0.890	(0.0-1.5)	1.04	(0.0-2.8)	1.28	(0.0-3.0)
	Arithmetic Mean (%CV)							
Cmax, ng/mL	1.03	(49.6)	2.64	(55.6)	3.54	(47.9)	2.77	(81.8)
Cmin, ng/mL	0.253	(53.8)	0.793	(49.8)	1.02	(41.9)	0.901	(55.8)
AUC(0-τ), hr*ng/mL	6.56	(60.8)	15.8	(49.5)	22.9	(47.5)	19.7	(54.0)
t½, hr	29.3	(40.9)	25.6	(24.6)	32.3	(37.5)	22.6	(21.7)
CL/F, mL/min	3210	(43.5)	4530	(83.5)	6810	(138)	10300	(42.8)
Vd/F, L	7750	(64.4)	12100	(90.0)	14700	(79.5)	19700	(47.3)

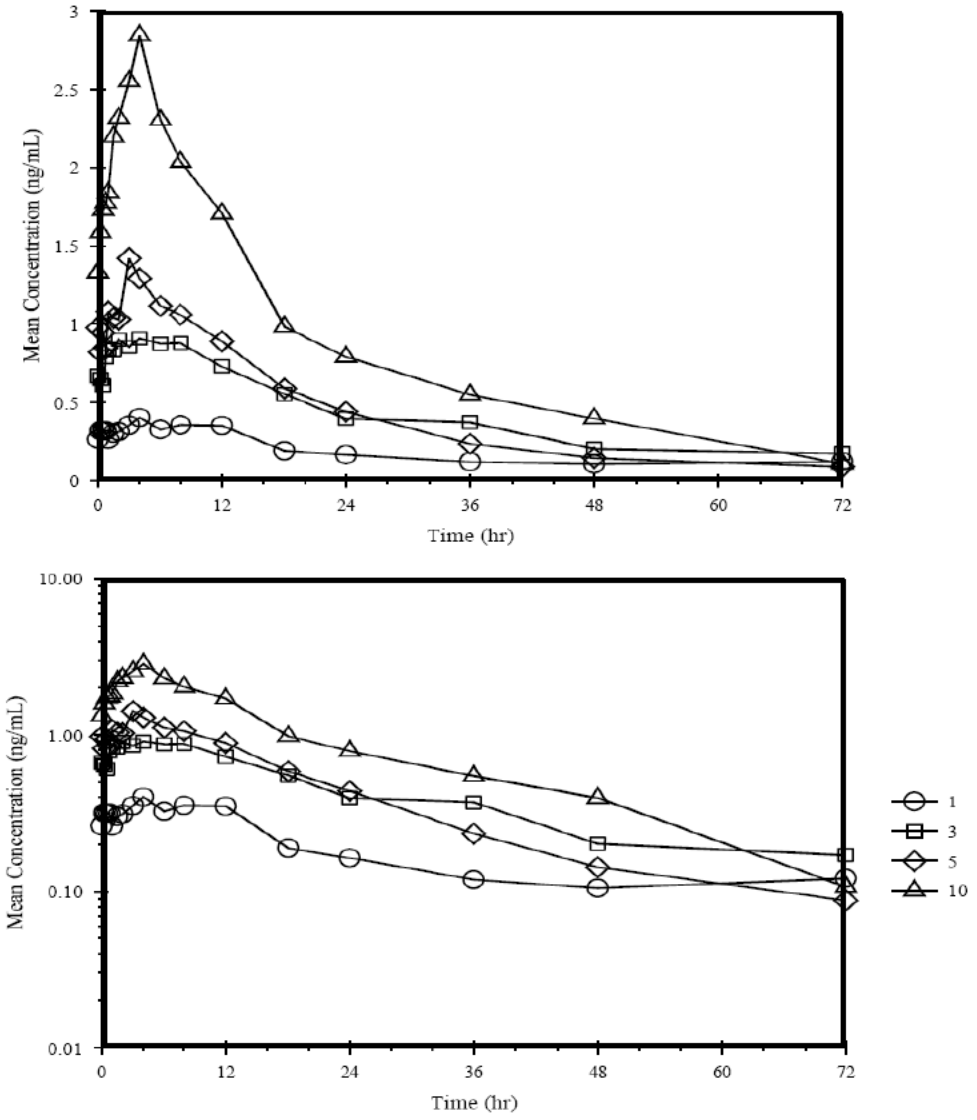
N = Number of subjects.
n = Number of subjects where t½ and Vd/F were determined.
Parameters are defined in Table 3.

Figure 3. Asenapine Morning Predose Concentrations During q12h Administration of Sublingual Asenapine Tablet Doses to Adolescent Subjects With A Psychotic Disorder, Study A7501022



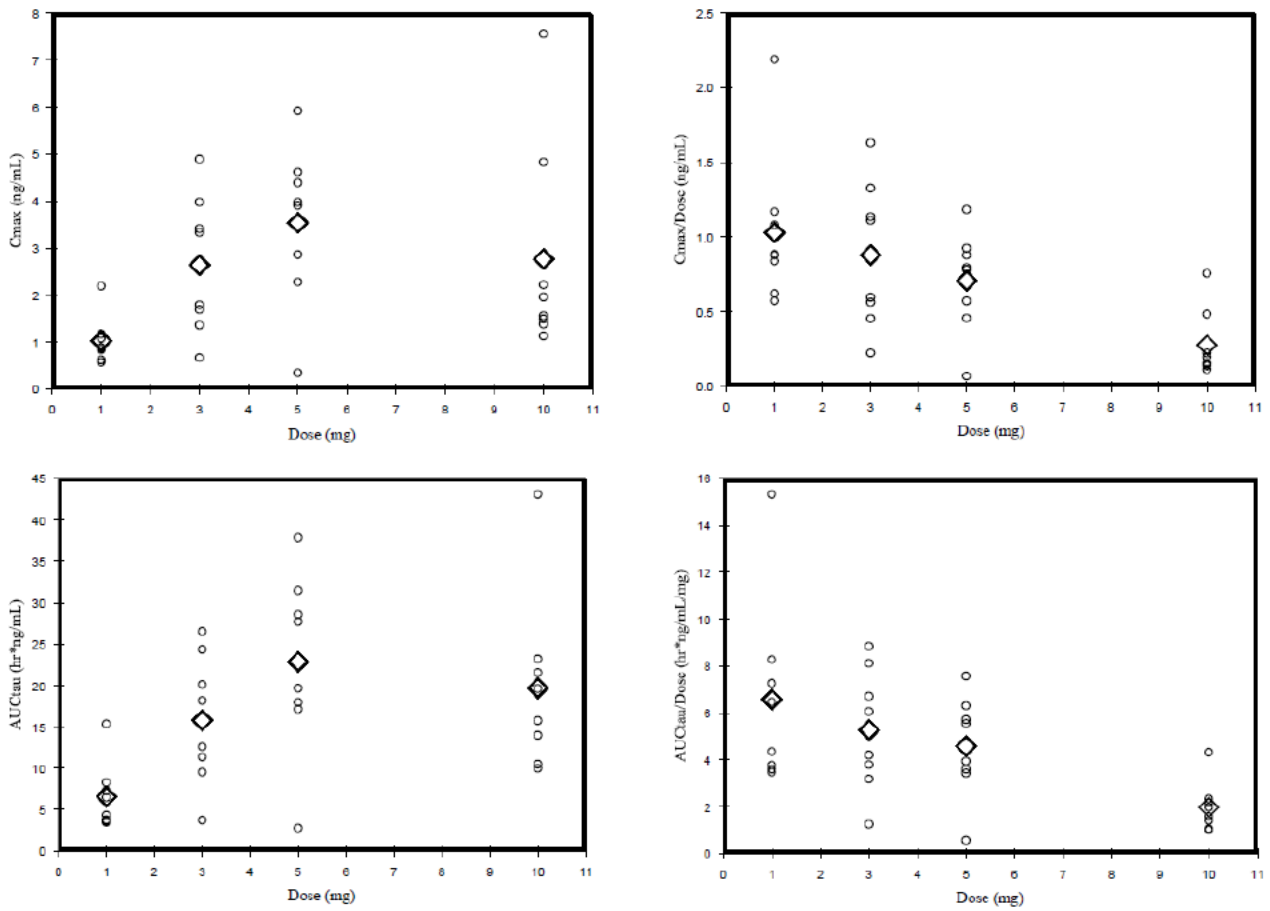
Error bars represent standard error; legend is asenapine dose (mg).

Figure 4. Mean Des-Methyl Asenapine Plasma Concentration-Time Profiles Following q12h Administration of Sublingual Asenapine Tablet Doses to Adolescent Subjects With A Psychotic Disorder, Study A7501022



Upper and lower panels are linear and semi-logarithmic scales, respectively; legend is asenapine dose (mg).

Figure 5. Asenapine Cmax (Upper Panel) and AUC(0-□) (Lower Panel)Values Following q12h Administration of Sublingual Asenapine Tablet Doses to Adolescent Subjects With A Psychotic Disorder, Study A7501022



Left panels show observed values; right panels show dose-normalized values. Circles are individual subjects, diamonds are arithmetic means.

Table 3. Summary of Des-Methyl Asenapine Pharmacokinetic Parameter Values Following q12h Administration of Sublingual Asenapine Tablet Doses to Adolescent Subjects With A Psychotic Disorder, Study A7501022

Asenapine Dose	1 mg		3 mg		5 mg		10 mg	
N (n)	8 (5)		8 (5)		8 (8)		8 (6)	
	Median (Range)							
tmax, hr	3.04	(0.50-12)	1.82	(0.28-6.0)	4.00	(0.0-11)	3.59	(0.78-4.0)
	Arithmetic Mean (%CV)							
Cmax, ng/mL	0.430	(67.7)	1.04	(63.2)	1.40	(37.4)	2.96	(74.5)
Cmin, ng/mL	0.219	(57.5)	0.621	(67.8)	0.800	(37.6)	1.07	(83.5)
AUC(0-τ), hr*ng/mL	4.03	(60.2)	10.1	(72.9)	13.3	(38.2)	25.8	(63.2)
t½, hr	23.0	(28.1)	31.2	(100.9)	21.1	(36.1)	15.2	(23.1)

N = Number of subjects.
n = Number of subjects where t½ was determined.
Parameters are defined in Table 3.

Table 4. Metabolite Ratios for Cmax and AUC(0-τ) Following q12h Administration of Sublingual Asenapine Tablet Doses

to Adolescent Subjects With A Psychotic Disorder, Study A7501022

	Mean (%CV) Metabolite Ratios (Des-Methyl Asenapine/Asenapine)	
Asenapine Dose	Cmax	AUC(0-τ)
1 mg	0.513 (85.2)	0.875 (94.2)
3 mg	0.424 (48.5)	0.639 (45.3)
5 mg	0.811 (151)	0.925 (112)
10 mg	1.67 (104.7)	1.75 (98.6)

Table 5 Comparison of asenapine AUC0-12 values in adult and adolescent patients

Study	Patients	BID dose (mg)	AUC_{0-12} (ng·h/mL)	
			Mean	CV%
A7501022	Adolescent	5	22.9	47.5
A7501001	Adult	5	26.6	38.4
041009	Adult	5	19.0	34.1
A7501022	Adolescent	10	19.7	54.0
A7501001	Adult	10	43.4	53.1
041012	Adult	10	37.3	78.8
Source: Module 2.7.1 Table A1.1 and Module 2.7.2 Table 61.				

Table 6 Comparision of Asenapine AUC(0-τ) Values (ngxhr/mL) Across Various Clinical Pharmacology Studies

		Study			
Asenapine Dose (mg BID)		A7501022 Adolescent Patients	25542 Healthy Adults Westerners	25546 Healthy Adults Japanese	25546 Healthy Adults Westerners
1	Mean	6.56	-	-	-
	CV%	60.8			
3	Mean	15.8	11.0	24.3	21.9
	CV%	49.5	26.5	26.3	11.1
5	Mean	22.9	15.5	29.4	22.1
	CV%	47.5	35.3	35.1	37.3
10	Mean	19.7	24.4	37.5	41.7
	CV%	54.0	53.3	44.3	46.2

In Table 5, the 5 mg dose appears to be comparable exposure for adolescents and adults; however, there is far less exposure for adolescents at the 10 mg dose.

1) study A7501022 was performed in the relevant age range;

2) results showed asenapine to be well tolerated in the tested dose range;

3) pharmacokinetics were shown to be similar to those in adults, up to a dose level of 5 mg BID.

These results are further supported by the data in Table 5 which again shows exposure similarity to 5 mg with dolescents decreasing from 5-10 mg whereas adults increase in AUC.

Assessment of pediatric pharmacokinetics: pooled analysis across multiple studies

The Pediatric Written Request requires the PK parameters (clearance and volume of distribution) for asenapine in pediatric patients to be estimated with sufficient precision. The sponsor plans to perform a pooled population pharmacokinetic analysis across all pediatric PK data as the basis for the assessment of the PK parameters. This analysis will include data from the available pediatric PK study (A7501022), the planned PK/tolerability study (P06522) as well as sparse sampling data from the short-term efficacy studies in schizophrenia and bipolar disorder. The totality of these data will provide estimates of clearance and volume in the different age subgroups that will have a precision that is well within the limits set by the Agency (95% CI of geometric mean within 60-140% of point estimate). However, it is expected that a pooled analysis of the two PK/tolerability studies (A7501022/P06522) already will provide estimates with a precision meeting the aforementioned criteria.

Safety Results

Table 13.6.2. Summary of TESS Adverse Events by Preferred and Investigator Terms

A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED, PARALLEL GROUP, MULTIPLE-DOSE, STUDY WITH ASENAPINE IN STABLE ADOLESCENT SUBJECTS WITH PSYCHOTIC DISORDER, TO EVALUATE SAFETY, TOLERABILITY, AND PHARMACOKINETIC PARAMETERS (Protocol A7501022)

Body System	Preferred Term	Investigator Term	Number of TESS Adverse Events	Percentage of Total (%)
Cardiac disorders	Bradycardia	BRADYCARDIA	1	0.82
	Pericarditis	PERICARDITIS	1	0.82
	Sinus bradycardia	SINUS BRADYCARDIA	1	0.82
Gastrointestinal disorders	Diarrhoea	LOOSE STOOL	1	0.82
	Dyspepsia	INTERMITTENT DYSPEPSIA	1	0.82
	Glossodynia	BURNING OF THE TONGUE	2	1.64
		BURNING SENSATION OF THE TONGUE	1	0.82
		BURNING SENSATION OF TONGUE	2	1.64
		BURNING TONGUE	2	1.64
		TONGUE BURNING	1	0.82
	Hypoaesthesia oral	NUMBNESS OF TONGUE	11	9.02
	Nausea	NAUSEA	3	2.46
	Oral pain	PAIN IN LOWER INNER CHEEK	1	0.82
	Paraesthesia oral	TINGLING OF TONGUE	1	0.82
		TINGLING SENSATION OF TONGUE	4	3.28

Table 13.6.2. Summary of TESS Adverse Events by Preferred and Investigator Terms

A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED, PARALLEL GROUP, MULTIPLE-DOSE, STUDY WITH ASENAPINE IN STABLE ADOLESCENT SUBJECTS WITH PSYCHOTIC DISORDER, TO EVALUATE SAFETY, TOLERABILITY, AND PHARMACOKINETIC PARAMETERS (Protocol A7501022)

Body System	Preferred Term	Investigator Term	Number of TESS Adverse Events	Percentage of Total (%)
Gastrointestinal disorders (cont.)	Paraesthesia oral (cont.)	TINGLING SENSATION UNDER TONGUE	1	0.82
		TONGUE TINGLING	2	1.64
	Stomach discomfort	UPSET STOMACH	1	0.82
	Tongue disorder	THICKNESS OF TONGUE	1	0.82
	Toothache	TOOTH PAIN	1	0.82
	Vomiting	VOMITING	1	0.82
General disorders and	Chest pain	BURNING IN CHEST	1	0.82
		CHEST PAIN	1	0.82
	Fatigue	FATIGUE	5	4.10
	Irritability	IRRITABLE	2	1.64
Infections and infestations	Nasopharyngitis	COLD SYMPTOM	1	0.82
Injury, poisoning and procedural complications	Animal bite	ANIMAL BITE	1	0.82
	Contusion	BRUISE ON LEFT ARM	1	0.82
		BRUISING TO BOTH FOREARMS	1	0.82
		BRUISING TO RIGHT ARM	1	0.82
		BRUISING TO SKIN ARM AREA	1	0.82

3.2 PHARMACOMETRIC REVIEW

The purpose of this review is to address key questions 2.4, 2.5 and 2.6 in the QBR.

Asenapine is approved as sublingual (SL) tablets, for the treatment of adults with schizophrenia and as monotherapy and adjunctive therapy in adults with bipolar I disorder.

Forest laboratories submitted this pediatric submission for Asenapine following a Written Request issued under BPCA. The written request was issued on September 9, 2009 to obtain pediatric information on Asenapine for pediatric schizophrenia in adolescents ages 13-17 and for pediatric mania and mixed episodes in Bipolar Disorder 1 in children 10-17.

The current submission is the sponsor's completed studies to address the written request. The submission contains 2 pharmacokinetic studies (study P06522 and study PA7501022), 1 Population PK study (study MK8274) and 4 Clinical studies (study P05896, study P06107, study P05898 and study P05897). The clinical studies had 502 Adolescent Subjects with schizophrenia ages 12-17 and 994 pediatric subjects with acute manic or mixed episodes associated with bipolar 1 ages 10-17.

The sponsor is only pursuing in pediatric patients (ages 10-17) the monotherapy treatment of manic or mixed episodes associated with bipolar l disorder based upon the efficacy established in one 3-week monotherapy trial.

Results of Sponsor's Analysis

Sponsor developed a population PK (PPK) model for asenapine in the pediatric population using data from two pharmacokinetic and safety studies (A7501022 and P06522) and two efficacy trials (P05896 and P06107) in patients aged 10 to 17 years with either schizophrenia or bipolar disorder or other psychotic disorders .The objective of PPK analysis is to explore the impact of relevant covariates on the asenapine PK in the pediatric population.

Data for PPK analysis

The PPK analysis included a total of 2451 concentration observations from 561 pediatric subjects aged 10-17 years. Covariates included in the dataset were age, body weight, body mass index (BMI), gender, and race.

Analytical Methodologies

The PPK analysis used a non-linear mixed effects modeling approach. The model previously developed on adult PK data (NDA 022-117, 2009). The final PPK model that best characterized all of the pediatric data was a 2-compartment model with first-order absorption, linear inter-compartmental clearance (Q/F) into the peripheral compartment (V3/F), and first-order elimination clearance (CL/F) from the central compartment (V2/F). Individual PK parameters were assumed to be log-normally distributed, and inter-individual variability (IIV) was estimated on CL/F, absorption (Ka), bioavailability (F1) and V2/F with exponential error models. The residual variability (RV) was expressed in an additive error model for log transformed concentrations.

The software package NONMEM (version VII) was used in the analysis. Model fitting was performed in a UNIX environment with Intel FORTRAN Compiler (version 12.01), Xpose, PsN (version 3.2.4) and R (version 3.0.2).

PPK Model Parameters

The final population PK parameter estimates are presented in Table 1.

Table 1. Final Population PK Parameters for asenapine

Parameter	Population Mean	RSE (%)
CL/F (L/h)	296	3.09
V2/F (L)	2740	13.4
Q/F (L/h)	120	14.3
V3/F (L)	2490	9.96
KA (h^{-1})	2.98	18.5
Inter-individual Variability (as %CV)		
IIV (CL/F)	66.2	19.5
Correlation $_{(CL/F-V2/F)}$	0.921	20.5
IIV (V2/F)	112.7	21.3
IIV (KA)	68.9	50.5
IIV (F1)	54.0	22.7
IIV (RV)	19.2	29.8
Residual Variability (as %)		
Phase 1 PK Studies	27.8	5.29
Phase 3 efficacy Studies	56.0	5.05
Abbreviations: RSE: Relative standard error; CL/F: apparent clearance; V2/F: apparent central volume of distribution; Q/F: apparent intercompartmental clearance; V3/F: apparent peripheral volume of distribution; KA: first-order absorption rate constant; IIV: interindividual variability; RV : residual variability; %CV, percent coefficient of variation		

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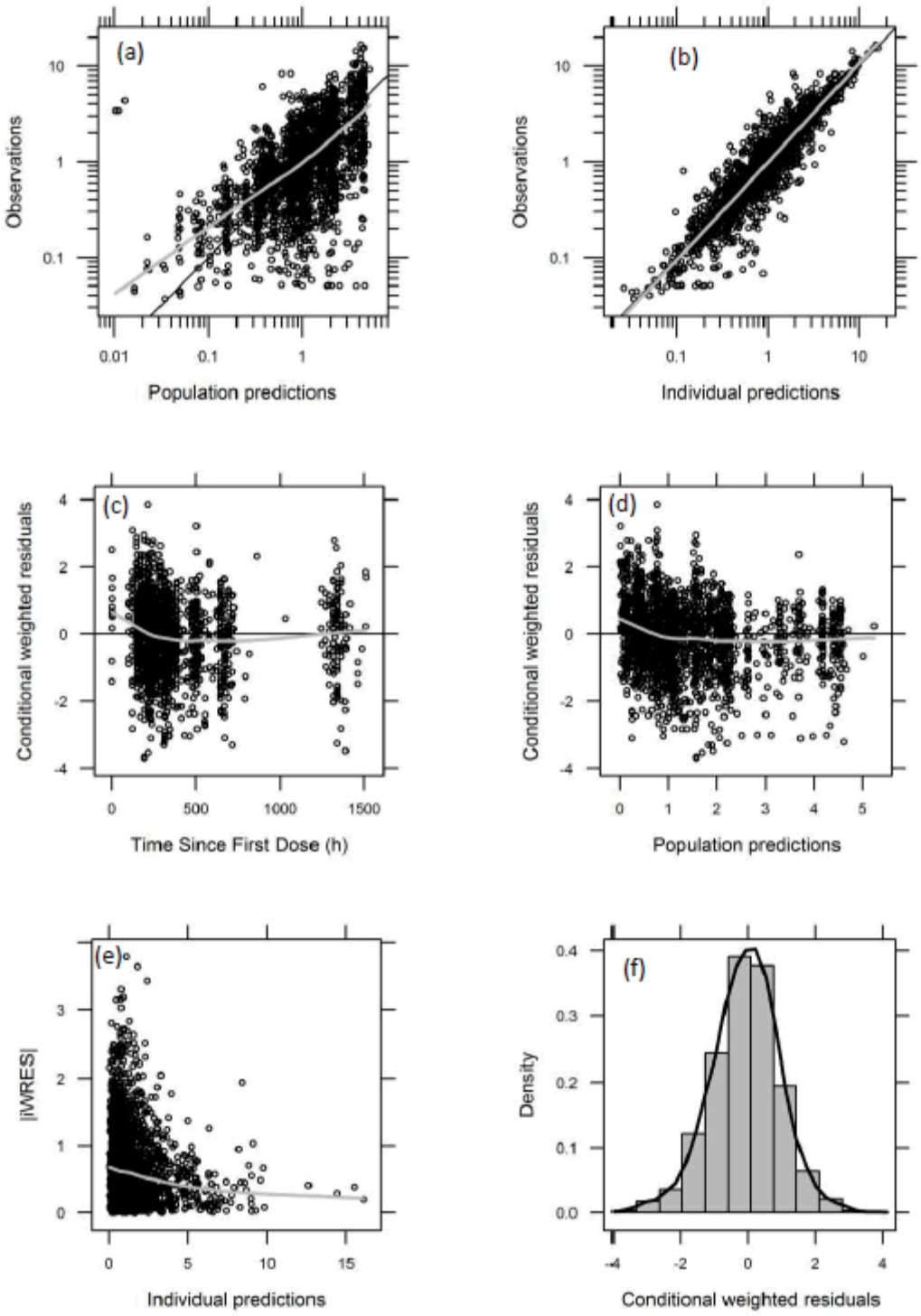
Model Evaluation

The final PPK model was mainly evaluated with standard diagnostic goodness of fit plots and visual predictive checks (VPC).

Goodness-of-fit (GOF) plots (Figure 5) for the final PPK model. Scatter plots of population predicted and individual predicted vs. observed concentrations showed an even distribution around the concord line. Scatter plots of CWRES vs. population predicted concentrations and of CWRES vs. time showed the CWRES was evenly distributed.

Figure 5 Goodness of fit plots represent the appropriateness of final PPK model to describe the time course of asenapine plasma concentration in pediatric population. Plots (a) and (b) represent the closeness of observed plasma concentrations to population and individual predictions, respectively. Plots (c) and (d) explain the trend over time and population predictions, respectively. Plot (e) depicts the relationship between absolute IWRES and individual predictions and plot (f) represent the distribution of CWRES.



Source: 03v04d.pdf, Figure 11

Visual predictive checks (VPC) showed that the PPK model accurately followed the central tendency of the observed data (Figure 6). However, VPC of the 10 mg data has some over-prediction by the model (Figure 14).

Figure 6. VPC plots displaying the adequacy of model by overlaying observations (o or *) on model predicted 95% prediction intervals (shaded area). Dots (o) represent the plasma concentration data at time since last dose (binned intervals). Solid and dashed lines represent the median of observations and model predictions, respectively.

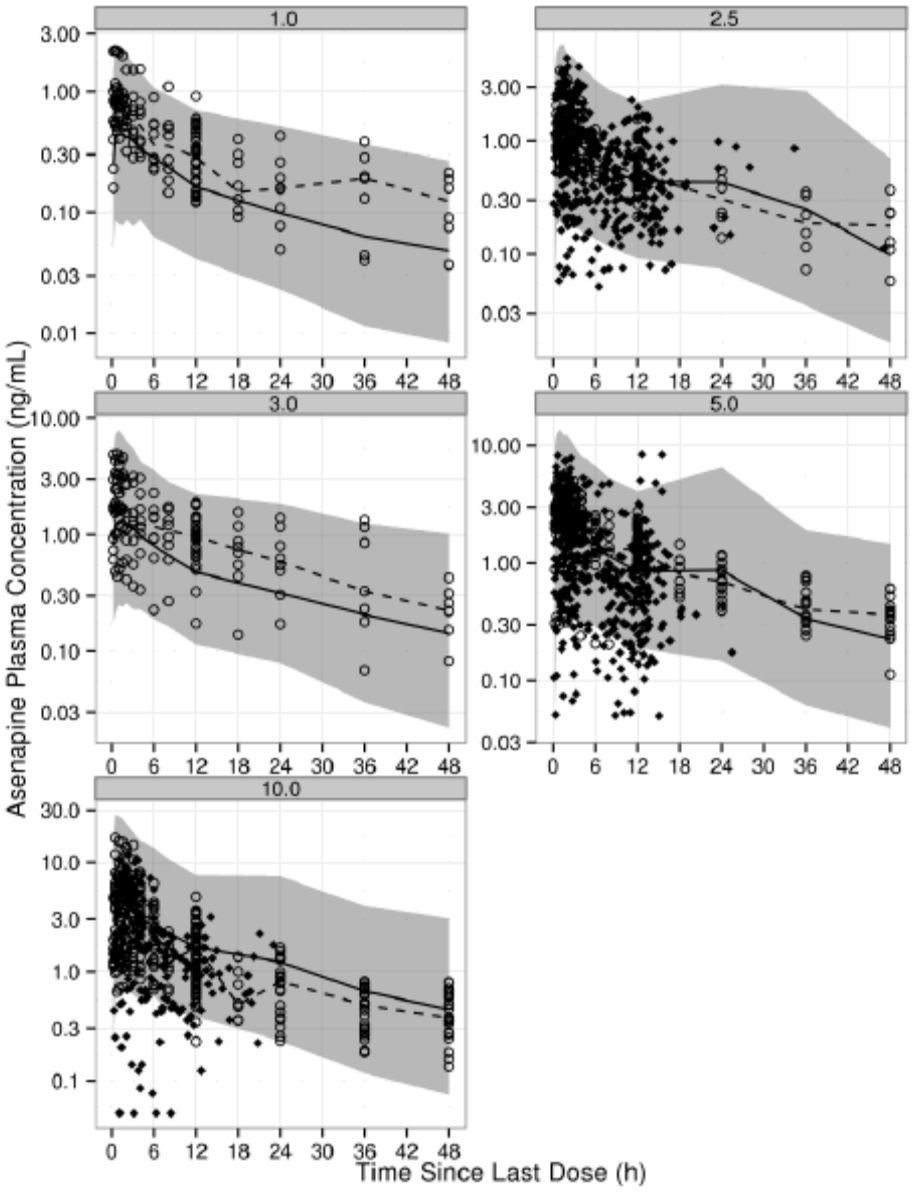


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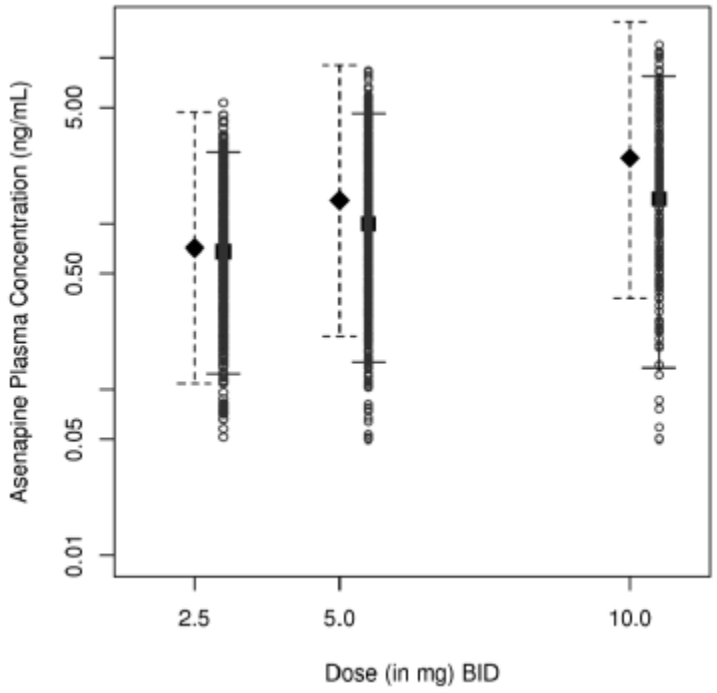
Figure 7. The adequacy of model to describe asenapine PK in phase 3 plasma concentration data is presented by comparing model predicted and observed data stratified by dose level. Symbol (◊) and (▪) represent the median of predictions and observations, respectively. Dotted and solid whiskers represent the 95% confidence intervals of predictions and observations, respectively.



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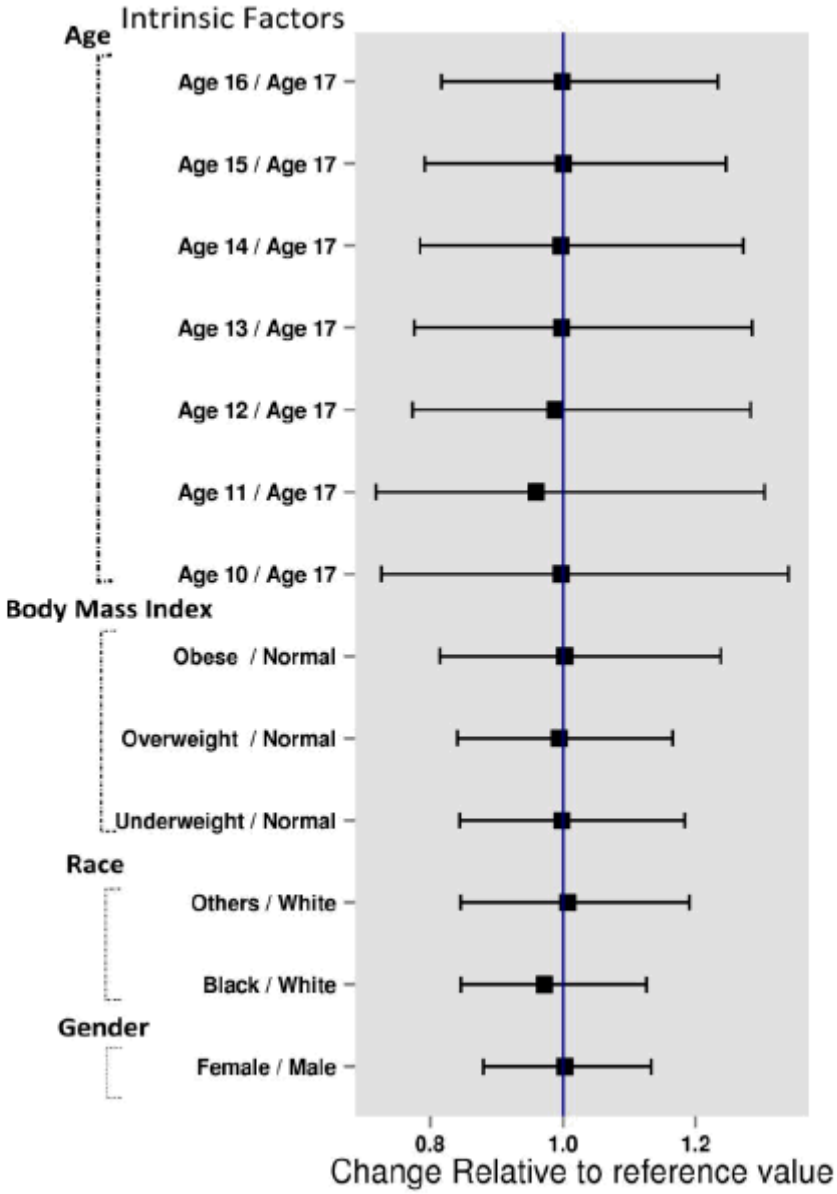
Reviewer's Comments: The identified final PPK model had no significant biases and represented an adequate fit to the data.

Magnitude of Covariate Effects

A forest plot (Figure 8) illustrated the relative differences (GMR and 90% CI) in asenapine exposure (AUC_{0-12}) as a function of intrinsic demographic features (age, BMI, race and gender). None of these factors result in clinically meaningful changes in asenapine PK indicating that no dose adjustments are required on the basis of these factors.

Figure 8 Impact of Intrinsic Factors on the Pharmacokinetics (Dose Normalized AUC0-12) of Asenapine Indicated via GMR (■) and 90% CIs (whiskers). BMI stratifications: Underweight (< 18.5 Kg/m^2), Normal (more than 18.5 and less than 25 Kg/m^2, Overweight (more than 25 and less than 30 Kg/m^2, Obese (more than 30 Kg/m^2)



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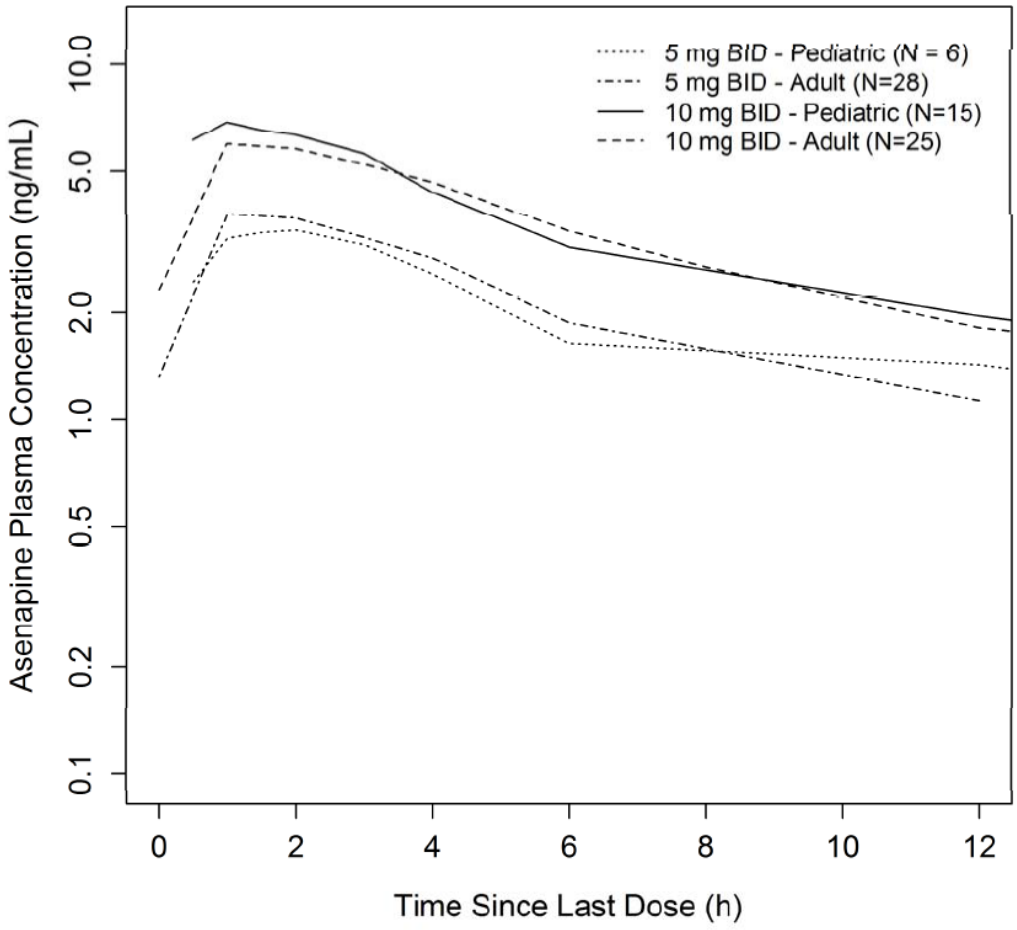
Reviewer's Comments: No covariates were identified that may have significant impact on the dose adjustments.

Comparison of adult and pediatric PK

At the same dose level, plasma asenapine concentrations in pediatrics were generally comparable to adults following repeated administration, both in bipolar 1 disorder and schizophrenia populations (Figure 9).

Figure 9, Similarity in Steady-State Asenapine Plasma-Concentration Time Profiles in the Pediatric Population (Study P06522) and Adults (Study A7501001) Following Administration of Clinically Relevant Doses



Source: summary-clin-pharm.pdf, Figure 2.7.2: 3

The comparisons were restricted to the study results from Phase 1 evaluations with 5 mg and 10 mg BID dosing. The potential differences between the pediatric and adult populations were explored through comparisons of the model-derived PK parameter estimates from each population (Table 2). The similarity in the PPK parameter estimates indicates similarity across fundamental PK properties of asenapine.

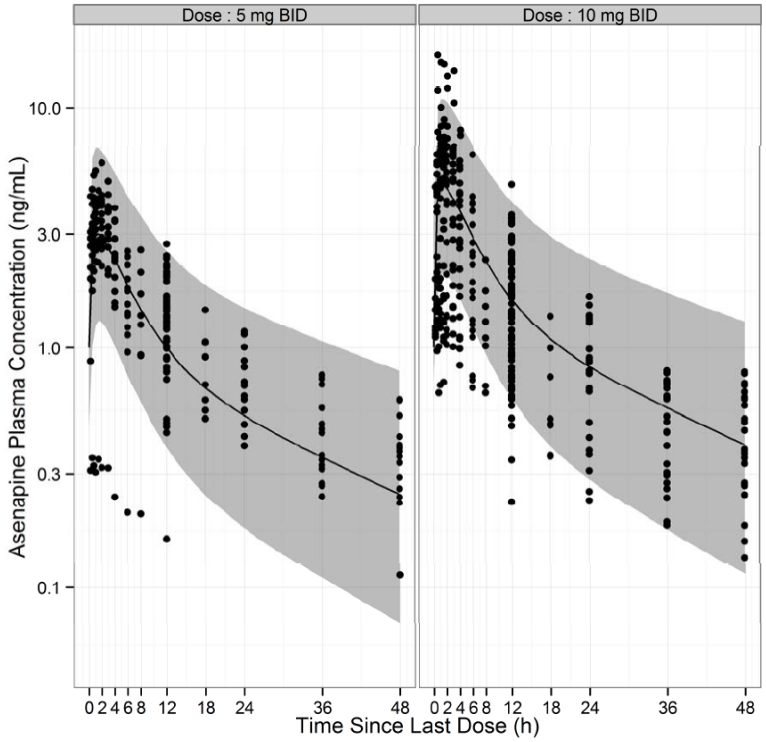
Table 2 Comparison of Population PK parameters in the Pediatric and Adult Populations

Pharmacokinetic Parameters*	Pediatric Population	Adult Population#
	Estimate (%RSE)	Estimate (%RSE)
CL/F (L/h)	296 (3.09)	288 (3.3)
V2/F (L)	2740 (13.4)	2110 (3.6)
Q/F (L/h)	120 (14.3)	124 (6.3)
V3/F (L)	2490 (9.96)	2730 (5.0)
Ka (h^{-1})	2.98 (18.5)	1.76 (11.5)

Source: summary-clin-pharm.pdf, Table 2.7.2: 5

Figure 10 displays steady-state asenapine PK profiles between the pediatric population 5 mg or 10 mg BID compared to those in adults by overlapping observed plasma concentrations from pediatric population on the prediction intervals derived from adult population PK model (NDA 022-117, 2009). It was expected that 90% of observed data were within the prediction intervals. Although some of the observed concentrations in pediatrics fall outside the prediction intervals, overall there is good concordance between the data and the independent predictions.

Figure 10. Pediatric Steady-State Asenapine Plasma Concentrations (dots) (A7501022, P06522) Compared to Adult Model-Based Predictions (90% prediction intervals (shaded), median (solid line)) Following Clinically Relevant Doses.



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Estimates of systemic exposure (AUC_{0-12} and C_{max}) were derived from the simulated steady-state concentrations and compared between the pediatric and adult populations (Table 3). Results indicated similar exposure between pediatric and adult patients at the same asenapine dose regimens.

Table 3. Comparison of asenapine PK parameters at steady-state condition in Adults and Pediatric Population

Dose Level		5 mg BID		10 mg BID	
Study Details	Population	AUC0-12(ng*h/mL)	Cmax (ng/mL)	AUC0-12(ng*h/mL)	Cmax (ng/mL)
A7501001[$]	Adult	26.6 (38.4)	4.23 (45.3)	43.4 (53.1)	6.56 (50.9)
Simulations [#]	Pediatric	19.3 (4.48 – 82.6)	4.56 (0.871 – 26.4)	37.8 (8.92 - 162)	8.64 (1.64 – 50.1)

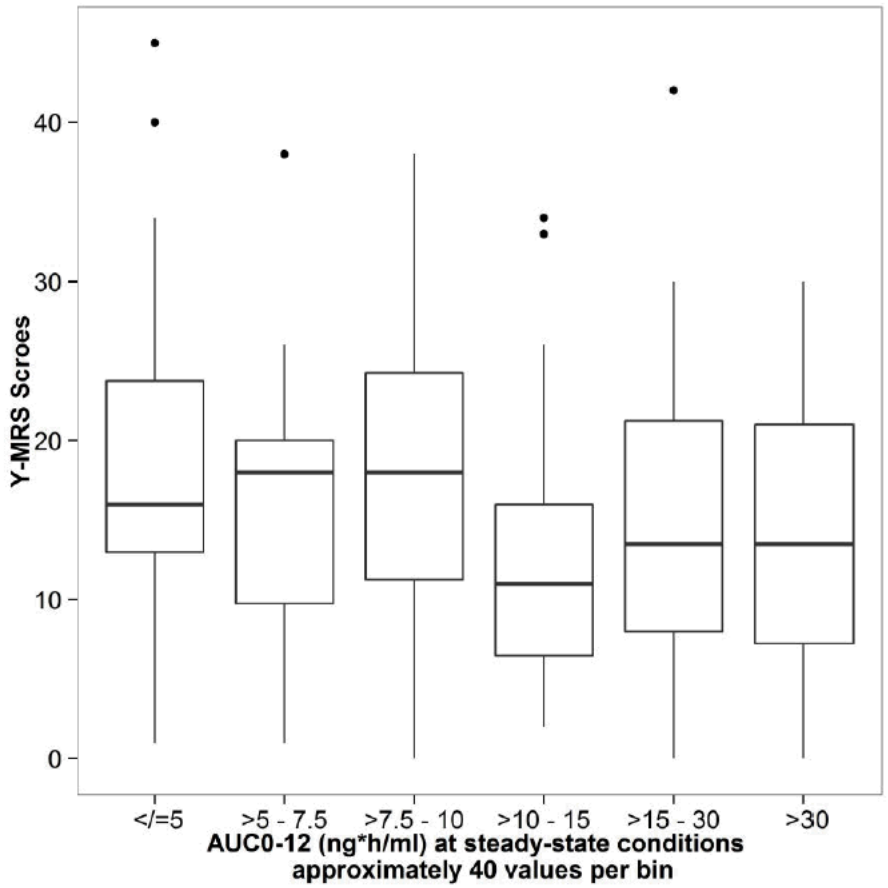
Source: 03v04d.pdf, Table 9

Reviewer's Comments: The comparisons of observed plasma concentrations from Phase 1 studies and model-estimated PK parameters show that asenapine PK in the pediatric and adult populations are largely similar at the same dose regimens. Therefore, PK properties in adults can be applied to the pediatric population.

Exposure-Response Analysis

Sponsor conducted an E-R analysis between individual predicted AUC_{0-12} and observed Y-MRS scores at Day 21 in bipolar pediatric population. Individual AUC_{0-12} estimates for subjects in study P06107 were estimated from the final PK model and binned in equally sized groups and plotted against Y-MRS scores in P06107 study. Across the exposures, a limited trend of decrease in Y-MRS score was observed (Figure 11).

Figure 11. Exposure-response relationship examined through a visual exploration of the relationship between AUC0-12 and individual Y-MRS scores in P06107. The boxes reflect the interquartile range (25-75th percentiles), the median denoted as solid line in each box, with the whiskers extending to the 5th-95th percentiles and individual data outside these percentiles presented as symbols



Source: 03v04d.pdf, Figure 17

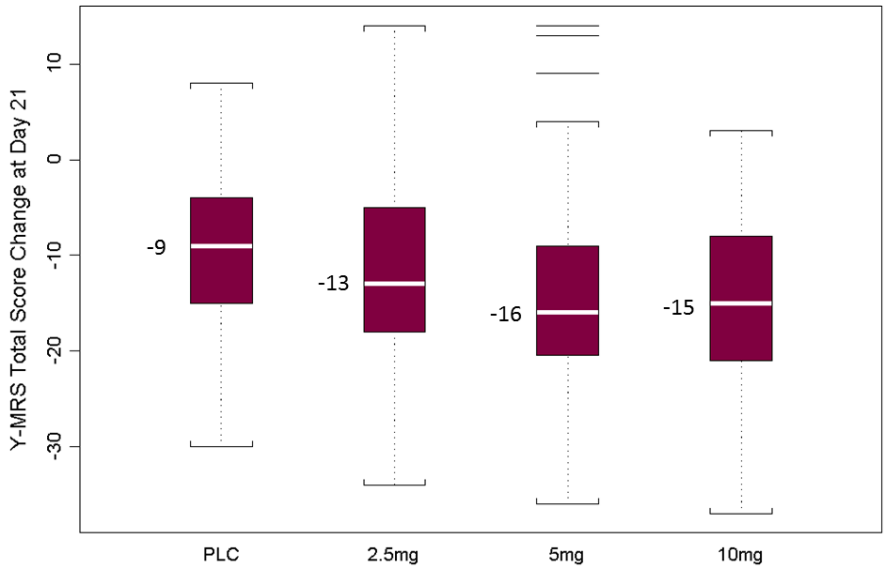
Reviewer's Analysis

FDA conducted dose/exposure-response analysis for study P06107 in bipolar patients (exposure-efficacy analysis result was demonstrated in section 1.1.1) and results showed there was a significant YMRS Total Score reduction with higher asenapine exposure. FDA also conducted dose/exposure-response relationship for study P05896 in in schizophrenia patients (exposure-efficacy analysis result was demonstrated in section 1.1.2). The exposure-response relationship was consistent with the dose-response relationship. Within asenapine-treated patients, there was no significant reduction in PANSS score with increasing asenapine concentration. In FDA exposure-response analysis, the logistic regression model was applied. The individual brexpiprazole concentration-time profiles were simulated using the sponsor's final PPK model. AUC was calculated with drug clearance divided by dose.

Dose-efficacy Analysis for Bipolar Indication:

The efficacy of Asenapine was established at doses of 2.5 mg, 5 mg and 10 mg. The three treatment arms showed noticeable decrease of YMRS Total Score compared with placebo (Figure 12**Error! Reference source not found.**).

Figure 12 Dose-YMRS Relationship in bipolar pediatric population



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Data sets used are summarized in Table 4. Analytic software includes SAS 9.3 and SPLUS 8.0.

Table 4. Analysis Data Sets

Study Number	**Name**	**Link to EDR**
P06107	S6107_effd.xpt	\\Cdsnas\pharmacometrics\ Reviews\Ongoing PM Reviews\Saphris_NDA 22117_LZ\Analysis\Exposure-efficacy for Bipolar\Dataset
P06107 and P05896	patab26.txt	

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Listing of Analyses Codes

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Sap E-R BP.ssc	Exposure-Efficacy for Bipolar	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Saphris_NDA 22117_LZ\Analysis\Exposure-efficacy for Bipolar\Code


(b) (4)

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

/s/

ANDRE J JACKSON
02/23/2015

KEVIN M KRUDYS
02/23/2015
I am signing for Li Zhang, who was the primary pharmacometrics reviewer.

HAO ZHU
02/23/2015