5.5.6.5 *Hepatic Impairment*

Two studies were conducted in subjects with hepatic impairment. The first study, study 25522, used a single 0.3 mg dose. Due to the low dose, desmethyl-asenapine could barely be detected in plasma and a second study, study A7501018 was conducted that used a single 5 mg SL dose. It appears that the sponsor used the 0.3 mg dose initially because they were concerned about the additive hepatotoxicity of asenapine.

Study 25522 only examined the effect of hepatic impairment on asenapine and desmethyl-asenapine, although the desmethyl-asenapine was largely unmeasurable due to the low dose. In contrast study A7501018, was able to examine the effect of hepatic impairment on asenapine, desmethyl-asenapine, asenapine glucuronide and unbound asenapine. Neither study examined the effects of hepatic impairment on the other primary pathway of asenapine 11-hydroxylation or on important secondary pathways.

The results of study A7501018 are more reliable due to the higher dose and longer sampling times.

In general after examination of both studies the following conclusions were reached.

- Average exposures to asenapine are increased by 2 – 5 fold in moderate and severe hepatic impairment, (see Table 93 and Table 99).
- On average there is little increase in exposure to asenapine in subjects with mild hepatic impairment, however in both studies there was 1 out of the 8 subjects with mild hepatic impairment who had an exposures two fold higher than the highest exposure in the normal group, (see Table 93 and Table 99).
- Similar results were seen with desmethyl-asenapine exposures, (see Table 100).
- There was an increase in free fraction with the degree of hepatic impairment, (see Table 96, Figure 75 and Table 102).
- The effect of hepatic impairment on exposure to unbound asenapine was even greater than the effect on total asenapine exposure, and is likely due to a greater decrease in intrinsic clearance with hepatic impairment than due to increases in free fraction. Exposures to free asenapine were almost twice as high in subjects with mild impairment compared to in normals in study A7501018, and the subject with mild impairment with the greatest exposure had exposures triple the highest expsore in the normal group, (see Table 102).
- There were indications of potentially worrisome effects of asenapine on the liver and QTc in these studies, (see Table 94 and Table 95).
- The use of only a single dose and exclusion of subjects who are more likely to be sensitive to drug induced hepatotoxicity, (additive or otherwise), biases these studies to show greater safety than would be expected in the hepatically impaired population under conditions of actual use.
- The narrow therapeutic index based on other studies for asenapine induced hepatic impairment along with the findings in the present studies argues against the use of asenapine in subjects with any degree of hepatic impairment.

5.5.6.5.1 Hepatic Impairment – Study 25522

Study 25522 was an open label, single dose study of the effects of chronic hepatic impairment on the pharmacokinetics of asenapine and its metabolite desmethyl-asenapine in 16 male and 16 female Caucasian subjects with a mild, moderate, severe, or no hepatic impairment as classified by Child-Pugh

score aged 35-52 years of age. There were 4 male and 4 female subjects per degree of hepatic impairment, and each subject was administered a single 0.3 mg dose of asenapine sublingually.

The Child-Pugh classification system is shown in Table 91.

Table 91 Child-Pugh Classification System

Class A: 5-6		Class B: 7-9	Class C: 10-15	
Measure	**1 point**	**2 points**	**3 points**	**units**
Bilirubin (total)	<34 (<2)	34-50 (2-3)	>50 (>3)	µmol/l (mg/dL)
Serum albumin	>35	28-35	<28	g/L
INR	<1.7	1.71-2.20	> 2.20	*no unit*
Ascites	None	Suppressed with medication	Refractory	*no unit*
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)	*no unit*

Exclusion criteria were as follows:

- Arterial hypertension (> 190/105 mmHg), chronic heart failure (CHF) nonstabilized (NYHA class III and IV);
- Hepatocarcinoma;
- Hepatic encephalopathy grade 3;
- Sepsis or spontaneous bacterial peritonitis;
- Gastrointestinal bleeding within one month before the study;
- Diabetes mellitus of any type requiring drug administration;
- Acute liver failure of any etiology, (surgical) portocaval shunt (primary biliary cirrhosis is allowed);
- Acute viral, toxic, or drug induced hepatitis;
- Current use of any drug intake with potentially hepatotoxicity;
- Change in used medication (prescribed by a physician and/or OTC medication) other than for liver insufficiency within 7 days prior to Org 5222 administration (for Child Pugh C patients, exceptions can be made if medically justified);
- Chronic drug induced hepatitis;
- Presence of alcohol abuse (alcohol consumption > 40 g/day)

Intake of alcohol was not allowed from 24 hours prior to dosing until the last PK blood sample. Smoking was not allowed during the entire hospitalization period. Food and drinks containing caffeine and other methylxanthines (e.g. coffee, tea, cola or chocolate) were not allowed from 48 hours prior to dosing until after the last PK blood sample. Grapefruit containing products were not allowed from 1 week prior to dosing until after the last PK blood sample

Strenuous physical exercise (including competitive sports) had to be avoided from 48 hours prior to dosing until the last PK blood sample.

Meals and snacks during hospitalization were to be provided according to the rules of Pharm PlanNet Contract Research-Ukraine.

Comments

Demographic characteristics demonstrate that subjects groups were relatively well matched with the possible exception of weight. Subjects were generally middle-aged, (see Table 92).

Exposures of asenapine assessed by AUCs were increased by over 2 fold in subjects with moderate and severe hepatic impairment, Cmax was lower and Tmax was delayed. Although the geometric mean AUC in subjects with mild impairment was 90% of the geometric mean AUC in healthy controls, the 90% confidence interval was 55% - 149% indicating that some individuals may have either exceptionally high or low exposures. In fact although the mean exposures were similar in the mild and healthy groups the subject with the largest AUCinf in the mild group had an AUC that was over twice the mean for the healthy group (see Table 93). Even more troubling however is the fact that the sampling in subjects with mild hepatic impairment was truncated and the mean concentration vs. time profiles indicate if sampling was continued, that the AUC ratio in subjects with mild impairment could be much higher, (see Figure 71).

Most demethyl-asenapine concentration values were below LLOQ. Consequently, for desmethyl-asenapine, the sponsor claims that no mean concentration values could be calculated at any time point and thus no curves were presented by the sponsor.

In the severely impaired group, (Child Pugh C), there was one case of severe jaundice in Subject 37. Subject 37 also had increases in liver function tests with a pattern that is suggestive of an acute hepatocellular injury, (see Table 94). This subject also had the 2nd highest free fraction of any subject at 2.2%.

Table 95 shows a table of adverse events as reported by the sponsor in the clinical study report. This table is included as it shows that the increase in LFTs in the patient with jaundice was not reported in this table. In addition it shows a fair number of increases in LFTs in the moderate impairment group and a case of QTc prolongation in each group of hepatically impaired subjects. Due to a lack of review time this was not pursued by this reviewer, however this should be examined more in depth by the safety reviewer.

The plasma bound asenapine fraction unbound in the Child-Pugh B and C groups (both 1.7%) was significantly higher than that in healthy subjects (1.3 %). Although no significant difference in binding was found between healthy subjects and the Child-Pugh A group (1.4%), this was not the case in study A7501018, (see Table 96 and Table 99).

According to the sponsor *'Regression analysis showed a significant positive correlation between AUC0-tlast and the Child-Pugh score. An even stronger (negative) correlation was found between AUC0-tlast and the albumin concentration which can be explained by the fact that the total Child-Pugh score is mainly determined by the albumin concentration at screening in the present study'*. This is true and can be seen by simple inspection of Figure 72, although an even clearer relationship can be seen between fraction unbound and AUCinf, (see Figure 73).

However, as a high intrinsic clearance drug this does not make sense. Instead we would expect that as free fraction increases that total AUC decreases while AUCunbound stays the same. This is clarified by examinating of AUCinf and unbound AUCinf vs. degree of hepatic impairment. From Figure 74 and Figure 75 we see a pattern that indicates that although the fraction unbound is changing the decrease in intrinsic clearance appears to be even greater in some subjects.

Blood samples were collected for genotyping however the decision whether genotyping took place was made by the sponsor. No data on genotype could be found and it is presumed that genotyping was not performed.

The exclusion criteria on the previous page demonstrate that the subjects used will likely provide a biased assessment of asenapine's safety in patients with hepatic impairment:

Virtually all of the categories of subjects who are excluded are those whose underlying cause of hepatic insufficiency indicates that they may be genetically predisposed to drug induced hepatotoxicity or whose hepatic injury is likely to be exascerbated in the face of a hepatotoxic drug.

It is this reviewer's opinion that while this may protect the small number of subjects in a particular study, the danger to the overall population of individuals with hepatic insufficiency once a drug is approved outweighs the risk from exposure to a single dose of drug in a carefully monitored population.

Table 92 Hepatic Impairment Study Subject Demographic Summary Statistics – Study 25522

	Gender	N	Healthy	Mild	Moderate	Severe	Total
Age (years)	Female	4/16	45.3 ± 7.27 (16.0) 35 - 52 [47.0]	46.0 ± 9.02 (19.6) 33 - 53 [49.0]	48.5 ± 10.34 (21.3) 33 - 54 [53.5]	51.0 ± 6.06 (11.9) 42 - 55 [53.5]	47.7 ± 7.81 (16.4) 33 - 55 [51.5]
	Male	4/16	46.8 ± 6.55 (14.0) 37 - 51 [49.5]	52.8 ± 7.27 (13.8) 46 - 60 [52.5]	46.8 ± 7.59 (16.2) 36 - 53 [49.0]	47.0 ± 7.12 (15.1) 39 - 53 [48.0]	48.3 ± 6.92 (14.3) 36 - 60 [49.5]
	Total	8/32	46.0 ± 6.46 (14.0) 35 - 52 [48.5]	49.4 ± 8.40 (17.0) 33 - 60 [49.0]	47.6 ± 8.45 (17.8) 33 - 54 [52.0]	49.0 ± 6.48 (13.2) 39 - 55 [53.0]	48.0 ± 7.26 (15.1) 33 - 60 [50.5]
Height (cm)	Female	4/16	162.3 ± 6.60 (4.1) 155 - 170 [162.0]	162.3 ± 9.84 (6.1) 154 - 175 [160.0]	166.0 ± 4.55 (2.7) 161 - 172 [165.5]	153.5 ± 4.73 (3.1) 150 - 160 [152.0]	161.0 ± 7.69 (4.8) 150 - 175 [160.5]
	Male	4/16	171.3 ± 1.50 (0.9) 170 - 173 [171.0]	173.8 ± 4.79 (2.8) 167 - 178 [175.0]	178.3 ± 2.06 (1.2) 176 - 180 [178.5]	172.5 ± 2.38 (1.4) 170 - 175 [172.5]	173.9 ± 3.80 (2.2) 167 - 180 [174.0]
	Total	8/32	166.8 ± 6.54 (3.9) 155 - 173 [170.0]	168.0 ± 9.44 (5.6) 154 - 178 [170.5]	172.1 ± 7.32 (4.3) 161 - 180 [174.0]	163.0 ± 10.73 (6.6) 150 - 175 [165.0]	167.5 ± 8.88 (5.3) 150 - 180 [170.0]
Weight (kg)	Female	4/16	63.80 ± 5.59 (8.8) 58.1 - 71.0 [63.05]	62.10 ± 2.85 (4.6) 60.0 - 66.1 [61.15]	71.82 ± 11.13 (15.5) 60.1 - 84.1 [71.55]	56.83 ± 4.69 (8.3) 50.1 - 60.1 [58.55]	63.64 ± 8.24 (12.9) 50.1 - 84.1 [60.55]
	Male	4/16	77.75 ± 7.41 (9.5) 71.0 - 88.0 [76.00]	73.28 ± 7.42 (10.1) 62.3 - 78.1 [76.35]	82.55 ± 6.55 (7.9) 75.1 - 88.1 [83.50]	84.28 ± 6.43 (7.6) 78.0 - 92.0 [83.55]	79.46 ± 7.65 (9.6) 62.3 - 92.0 [78.05]
	Total	8/32	70.78 ± 9.62 (13.6) 58.1 - 88.0 [71.00]	67.69 ± 7.92 (11.7) 60.0 - 78.1 [64.20]	77.19 ± 10.21 (13.2) 60.1 - 88.1 [78.50]	70.55 ± 15.57 (22.1) 50.1 - 92.0 [69.05]	71.55 ± 11.22 (15.7) 50.1 - 92.0 [72.50]
BMI (kg/m^2)	Female	4/16	24.20 ± 0.29 (1.2) 23.9 - 24.6 [24.15]	23.73 ± 2.229 (9.4) 21.6 - 26.2 [23.55]	26.00 ± 3.299 (12.7) 23.2 - 30.5 [25.15]	24.15 ± 1.857 (7.7) 22.3 - 26.7 [23.80]	24.52 ± 2.167 (8.8) 21.6 - 30.5 [24.10]
	Male	4/16	26.53 ± 2.734 (10.3) 24.0 - 30.4 [25.85]	24.33 ± 2.945 (12.1) 20.6 - 27.8 [24.45]	26.00 ± 2.286 (8.8) 23.2 - 28.4 [26.20]	28.40 ± 2.859 (10.1) 25.5 - 31.5 [28.30]	26.31 ± 2.86 (10.9) 20.6 - 31.5 [25.85]
	Total	8/32	25.36 ± 2.19 (8.6) 23.9 - 30.4 [24.40]	24.03 ± 2.439 (10.1) 20.6 - 27.8 [24.45]	26.00 ± 2.628 (10.1) 23.2 - 30.5 [25.80]	26.28 ± 3.185 (12.1) 22.3 - 31.5 [26.00]	25.42 ± 2.66 (10.4) 20.6 - 31.5 [24.80]

Table 93 Effect of Hepatic Impairment on Pharmacokinetics of Asenapine – Study 25522

Parameter	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
Group	Healthy Subjs	Child-Pugh A	Child-Pugh B	Child-Pugh C	HS	A	B	C	A:HS	B:HS	C:HS
N	8	8	8	8	—	—	—	—	—	—	—
Tmax (h)	1.75 (0.75 - 4.00)	1.50 (0.75 - 3.00)	3.00 (1.00 - 4.02)	1.75 (0.75 - 4.00)	—	—	—	—	—	—	—
Cmax (ng/mL)	0.284 ± 0.104 (36.7) 0.13 - 0.41 [0.26]	0.196 ± 0.053 (27.1) 0.13 - 0.275 [0.193]	0.187 ± 0.088 (47.2) 0.109 - 0.396 [161]	0.226 ± 0.074 (32.9) 0.171 - 0.390 [0.196]	0.266	0.190	0.174	0.217	0.71 0.53 - 0.95	0.66 0.49 - 0.87	0.82 0.61 - 1.09
AUC0-tlast (ng/mL x hr^{-1})	2.03 ± 0.531 (26.2) 1.16 - 3.00 [2.09]	2.14 ± 1.08 (50.6) 1.10 - 3.90 [1.68]	3.27 ± 0.686 (21.0) 2.52 - 4.43 [3.02]	3.68 ± 1.48 (40.2) 1.52 - 5.49 [3.91]	1.96	1.93	3.21	3.35	0.98 0.71 - 1.36	1.63 1.18 - 2.26	1.7 1.23 - 2.36
AUC∞ (ng*h/mL)	2.97 ± 0.865 (29.1) 1.94 - 4.51 [2.77]	2.99 ± 1.93 (64.5) 1.42 - 7.19 [2.46]	7.26 ± 4.05 [a] (55.8) 3.81 - 14.6 [4.90]	7.86 ± 5.82 (74.0) 1.73 - 17.4 [6.76]	2.87	2.58	6.43	5.96	0.90 0.55 - 1.49	2.24 1.34 - 3.77	2.08 1.26 - 3.43
AUCextrap (%)	29.8 ± 15.2 (51.0) 8.49 - 57.7 [28.4]	24.3 ± 11.9 (49.2) 11.2 - 45.8 [23.2]	44.7 ± 23.0 [a] (51.4) 9.34 - 79.0 [39.3]	39.3 ± 22.7 (57.7) 11.8 - 75.0 [36.5]	26.1	21.8	38.0	33.2	—	—	—
Tlast (h)	25.5 ± 6.21 (24.4) 12.0 - 30.0 [27.0]	29.3 ± 13.8 (47.1) 12.0 - 48.0 [27.0]	46.5 ± 4.24 (9.12) 36.0 - 48.0 [48.0]	42.0 ± 11.6 (27.5) 18.0 - 48.0 [48.0]	24.6	26.3	46.3	40.0	—	—	—
Clapp (L/h)	109 ± 30.9 (28.5) 66.6 - 155 [108]	131 ± 61.3 (46.9) 41.7 - 211 [123]	51.8 ± 23.1 [a] (44.6) 20.6 - 78.8 [61.2]	69.0 ± 60.3 (87.3) 17.2 - 174 [44.4]	105	116	46.6	50.3	1.11 0.61 - 2.03	0.45 0.24 - 0.83	0.48 0.26 - 0.88
wn-CLapp (L/h) / kg	1.55 ± 0.432 (28.0) 1.02 - 2.10 [1.55]	1.95 ± 0.899 (46.1) 0.538 - 3.19 [1.76]	0.696 ± 0.335 [a] (48.2) 0.263 - 1.16 [0.695]	1.15 ± 1.20 (105) 0.219 - 3.47 [0.631]	1.49	1.73	0.618	0.729	1.16 0.58 - 2.30	0.41 0.20 - 0.84	0.49 0.25 - 0.97
Vz,app (L)	3120 ± 1403 (45.0) 905 - 5239 [3006]	2565 ± 1063 (41.4) 1077 - 4362 [2528]	3536 ± 1251 [a] (35.4) 1003 - 4917 [3752]	2537 ± 769 (30.3) 1450 - 3358 [2674]	2792	2363	3225	2419	0.85 0.52 - 1.37	1.15 0.70 - 1.91	0.87 0.53 - 1.41
wn - Vz,app (L/kg)	—	—	—	—	39.8	35.1	42.7	35.0	0.88 0.54 - 1.45	1.07 0.64 - 1.79	0.88 0.54 - 1.45
t½ (h)	22.7 ± 13.1 (57.6) 4.06-42.8 [20.8]	19.1 ± 17.5 (91.6) 3.73-58.9 [15.45]	64.2 ± 52.7 (82.2) 11.3 – 166.0 [41.7]	48.7 ± 42.7 (87.7) 5.78 – 135.0 [38.15]	18.5	14.1	47.9	33.3	0.76 0.31 - 1.86	2.59 1.03 - 6.54	1.80 0.74 - 4.40

Figure 71 Mean Asenapine Concentration-vs.-Time Profiles after a 0.3 mg Sublingual Dose in Subjects with Various Degrees of Hepatic Function – Study 25522

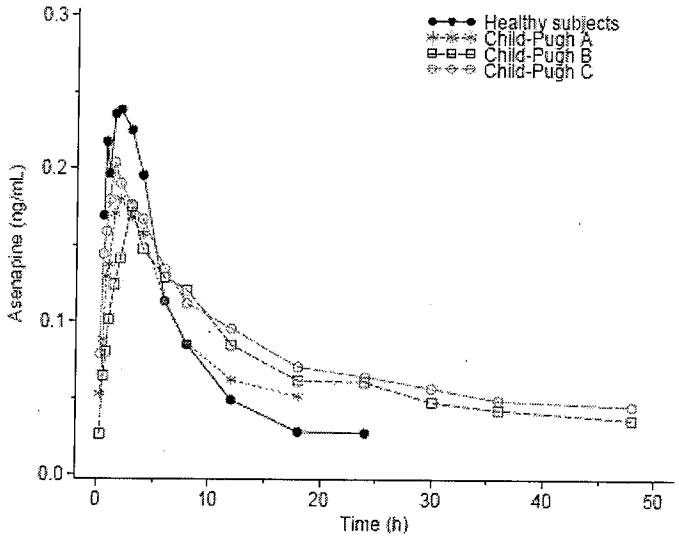


Table 94 Selected Laboratory Values in Subject 37- Study 25522

Group	Subject	Visit	Sample date	Sample time	total Bilirubin [umol/L]	Conjug Bili [umol/L]	Unconjug Bili [umol/L]	Triglycerides (TG) [mmol/L]	total Cholesterol [mmol/L]	total Protein [mmol/L]	Urea [g/L]	Albumin [g/L]	ALAT /SGPT [U/L]	ASAT /SGOT [U/L]	GGT [U/L]	AlkPhos [U/L]	LDH [U/L]	Lactate	GLDH	OCT
4	37*	Screening	22DEC2003	9:15	269.8 RH	96.2 RH	173.6 RH	6.0	0.69	2.0 RL	89 AH	23 RL	63 RH	51 RH	217 RH	265	804 RH	NR	NR	NR
		Follow-Up	26DEC2003	8:05	454.5 RH	124.0 RH	330.5 RH	5.9	0.61	1.2 RL	81	21 RL	36	123 RH	121 RH	180	762 RH	NR	NR	NR
Observed Increases						↑	↑↑							↑						
Pattern expected with Acute Hepatocellular Injury							↑						↑	↑			↑			
Pattern associated with hepatobiliary toxicity					↑										↑	↑				
Pattern expected with Mitochondrial based injury																		↑	↑	↑

* H/H at screening and followup were 90/36 abd 96/37 respectively.

Table 95 Number and Percent of Subjects with Adverse Events by MedDRA System Organ Class and Preferred Term as reported in Sponsor's Table in Clinical Study Report – Study 25522

Body system Preferred term	Group A (N = 8)	Group B (N = 8)	Group C (N = 8)	Group D (N = 8)	Total (N = 32)
Any Body System	4 (50%)	7 (88%)	5 (63%)	7 (88%)	23 (72%)
Cardiac disorders					
Sinus bradycardia	1 (13%)		1 (13%)		2 (6%)
Sinus tachycardia	1 (13%)	1 (13%)		1 (13%)	3 (9%)
Tachycardia				1 (13%)	1 (3%)
Gastrointestinal disorders					
Hypoaesthesia oral	2 (25%)				2 (6%)
General disorders and administration site conditions					
Injection site haemorrhage	1 (13%)	4 (50%)			5 (16%)
Hepatobiliary disorders					
Jaundice				1 (13%)	1 (3%)
Investigations					
Alanine aminotransferase increased			1 (13%)		1 (3%)
Aspartate aminotransferase increased			1 (13%)		1 (3%)
Blood albumin decreased		1 (13%)	1 (13%)		2 (6%)
Blood cholesterol decreased		1 (13%)			1 (3%)
Blood lactate dehydrogenase increased			1 (13%)	2 (25%)	3 (9%)
Electrocardiogram QRS complex prolonged	1 (13%)	1 (13%)			2 (6%)
Electrocardiogram QT corrected interval prolonged		1 (13%)	1 (13%)	1 (13%)	3 (9%)
Haematocrit decreased			1 (13%)		1 (3%)
Haemoglobin decreased		2 (25%)			2 (6%)
Protein urine present			1 (13%)	2 (25%)	3 (9%)
Red blood cell count decreased			1 (13%)		1 (3%)
Red blood cells urine positive			1 (13%)		1 (3%)
Urine bilirubin increased				2 (25%)	2 (6%)
White blood cells urine positive			1 (13%)	1 (13%)	2 (6%)
Nervous system disorders					
Headache	1 (13%)				1 (3%)
Respiratory, thoracic and mediastinal disorders					
Throat irritation				1 (13%)	1 (3%)

Table 96 Asenapine Fraction Bound to Plasma Proteins at 1.5 and 12 Hours Post-Dose – Study 25522

Sampling Time (hours)		Summary Statistics				Geometric Means			
		Normal	Child-Pugh Classification			Normal	Child-Pugh Classification		
			A (mild)	B (moderate)	C (severe)		A	B	C
1.5 hours	N	8	7	8	8	8	7	8	8
	Stats	98.7 ± 0.12 (0.120) 98.6 - 98.9 [98.7]	98.6 ± 0.15 (0.153) 98.4 - 98.8 [98.7]	98.3 ± 0.26 (0.269) 98.0 - 98.7 [98.4]	98.3 ± 0.32 (0.326) 97.9 - 98.9 [98.4]	98.7	98.6	98.3	98.3
12 hours	N	8	7	8	7	8	7	8	7
	Stats	98.7 ± 0.20 (0.203) 98.3 - 99.0 [98.7]	98.6 ± 0.15 (0.152) 98.3 - 98.8 [98.6]	98.3 ± 0.35 (0.353) 97.6 - 98.7 [98.3]	98.2 ± 0.24 (0.248) 97.8 - 98.6 [98.2]	98.6	98.6	98.2	98.2

Figure 72 Asenapine AUCinf vs. Albumin by Degree of Hepatic Impairment – Study 25522

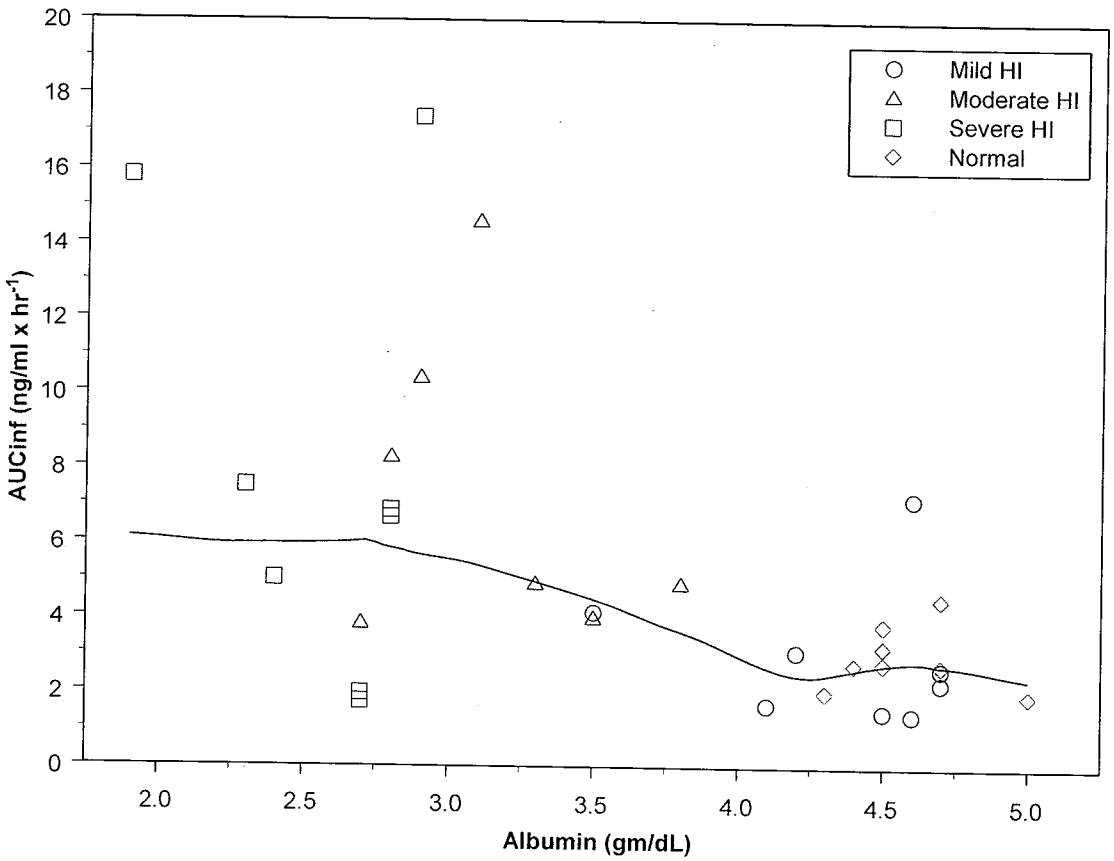


Figure 73 Asenapine AUCinf vs. Fraction Unbound (%) – Study 25522

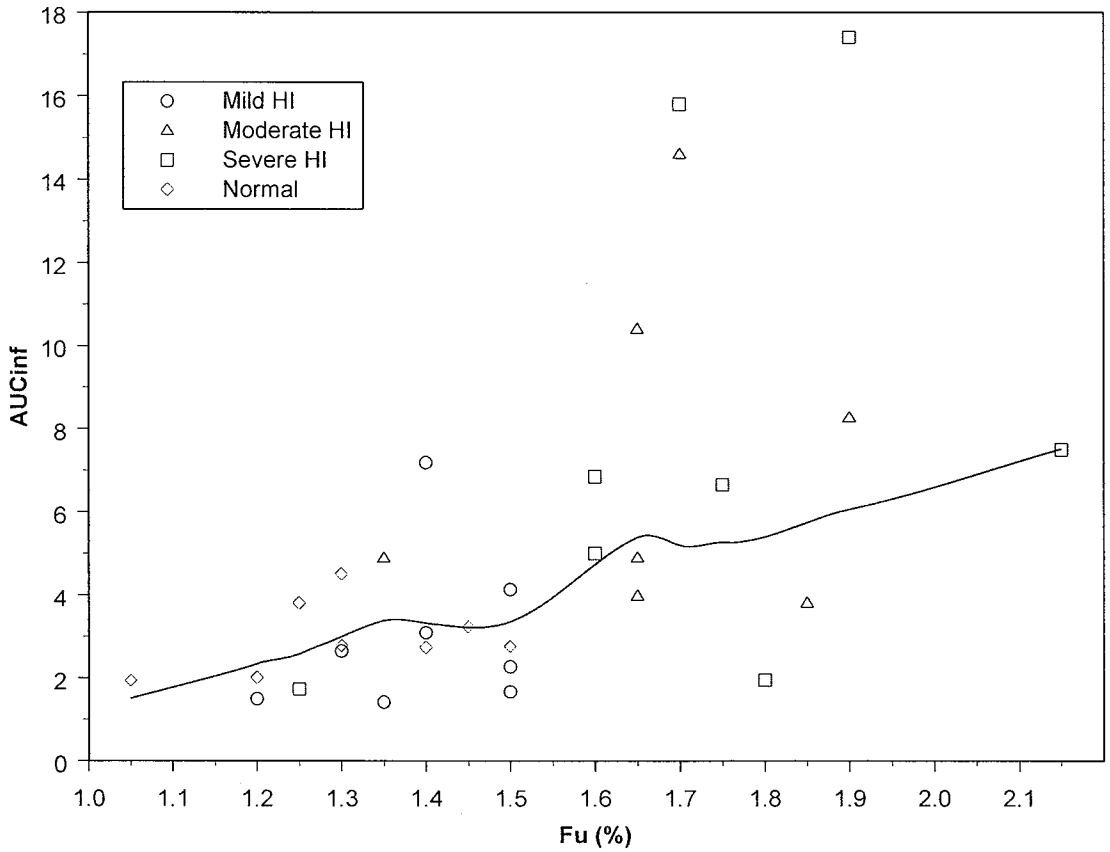


Figure 74 Asenapine AUCinf vs. Degree of Hepatic Impairment – Study 25522

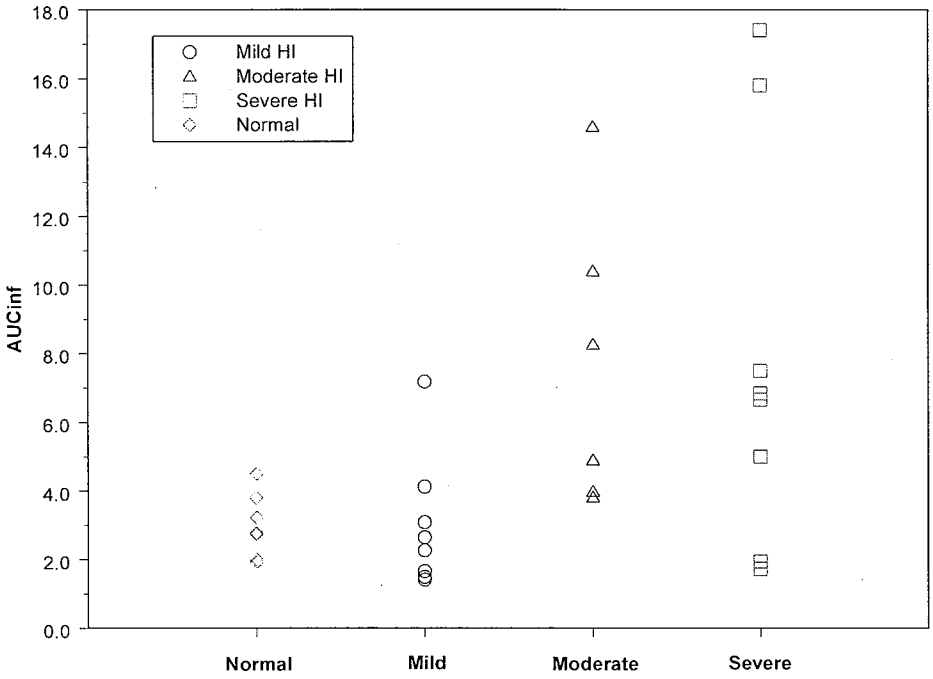
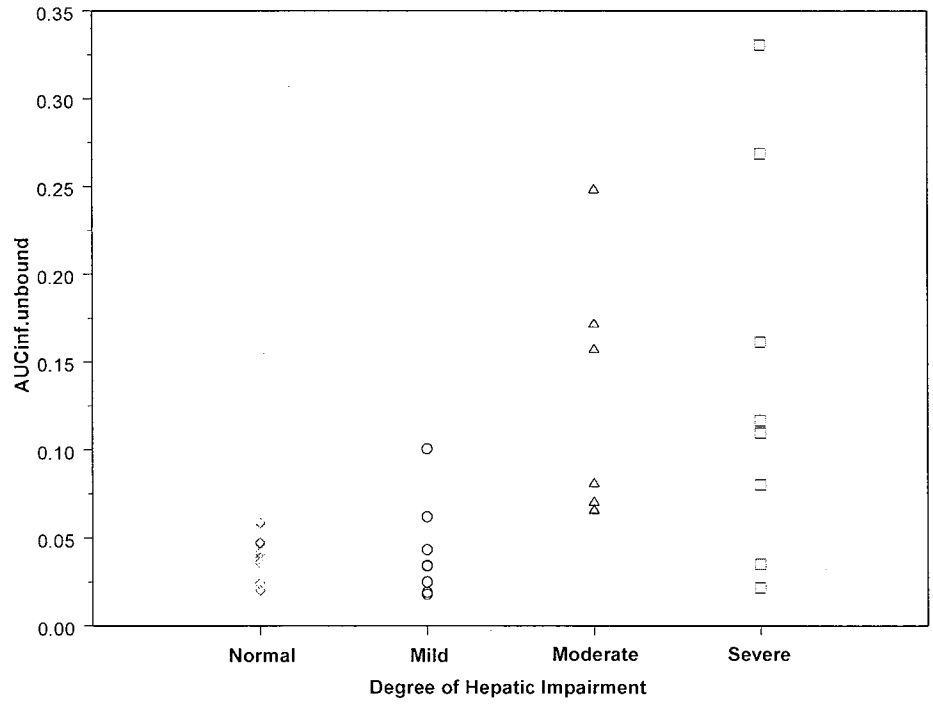


Figure 75 Asenapine Unbound AUCinf vs. Degree of Hepatic Impairment – Study 25522



5.5.6.5.2 Hepatic Impairment – Study A7501018

Study A7501018 was a single-center, open-label, single-dose study that examined the effect of varying degrees of hepatic impairment on the pharmacokinetics of asenapine, desmethyl-asenapine, and asenapine N-glucoronide.

Thirty subjects were enrolled (8 each in the normal hepatic function and Child-Pugh A and B groups, and 6 in the Child-Pugh C group). The study population included 20 men and 10 women with a mean age of 55.7 years (range 46 - 72 years) and a mean BMI of 28.4 kg/m^2 (range 18.1 - 32.7 kg/m^2). One subject was black and 29 were white, (see Table 97).

Each subject received a single dose of asenapine 5 mg sublingually (Phase III formulation), and pharmacokinetic samples were obtained up to 96-hours postdose in Groups 1 and 2, and up to 240-hours postdose in Groups 3 and 4.

Comparison of demographics by degree severity reveals that the healthy group contained the lowest proportion of women, males in the mild hepatic impairment group weighed more, and the mild and especially the moderate group had a high proportion of smokers, (see Table 98). It's this reviewer's impression from other NDAs that women and the elderly are likely to have higher exposures with CYP1A2 substrates. In addition it is well documented that smokers are likely to have lower exposures due to induction of CYP1A2.

When exposures to asenapine are compared there is a mean 5.5 fold increase in severe hepatic impairment with an upper 90% CI of 8.6. Even more concerning is that exposures to unbound asenapine are 8 fold higher. There's only a 1.12 fold mean increase in exposure to bound asenapline in moderate and mild impairment however, the 90% confidence intervals are quite wide going up to 1.68 and 1.71 fold in the mild and moderate groups respectively, (see Table 99).

Similar results are seen with the N-desmethyl metabolite, but with much lower Cmaxs in all groups, (see Table 100). For asenapine glucuronide there are increases in all three groups of hepatic impairment, (see Table 101).

The results in the moderate group are inconsistent with what was seen in study 25522 where exposures in the moderate group were double those in the healthy controls, (see Table 93). However, most troubling of all is that when unbound asenapine exposures are compared the mean exposure is nearly doubled in the mild group with some individuals having exposures 3 fold higher than any of the healthy subjects and this is in spite of free fractions being much higher, (see Table 102). This is in contrast to study 25522, (see §5.5.6.5.1), however the present study uses a higher dose and sampling is longer than in study 25522 thus the results of the present study should be considered more reliable.

Thus, it appears that some patients with mild hepatic impairment may have much higher exposures to asenapine and this is confirmed by comparing plots of individual exposures as compared with mean exposures, (see Figure 76 to Figure 81), although the subject with high exposure to asenapine (subject 1001006 in Figure 79) also has much higher exposure to the N-desmethyl-metabolite (Figure 81). Possibly indicating that this subject is a CYP2D6 poor metabolizer, this may not be a mitigating factor and could actually increase the risk, as the exposure to free drug in this subject is much higher, (see Figure 82). Since only slightly higher than the likely clinical doses appear to be associated with hepatotoxicity, the presence of even 1 or 2 individuals in the mild hepatic impairment groups with much higher total exposures and others with normal total exposures and much higher free exposures leaves no margin of safety. Thus even if the risk : benefit ratio turns out to be acceptable for patients with normal hepatic function, it is unlikely to be acceptable for patients with even mild degrees of hepatic function.

Safety and laboratory data was not closely inspected but even in passing it's noteworthy that several subjects had acute changes in lab tests, e.g. BUN, LFTs, as well as possibly significant AEs. A more detailed review will be needed and will need to be documented if there is any discussion on whether subjects with mild hepatic impairment should be allowed to take asenapine.

Table 97 Subject Demographics for Hepatic Impairment Study – Study A7501018

Site	Subj No.	Age	Gender	Menopausal Status	Race	Ht (cm)	Wt (kg)	BMI (kg/m^2)	Smoking Status	EtOH (U/wk)	Group
1001	10011009	56	Male		Caucasian	167.6	80.0	28.5	NS	0	Group 1
1001	10011010	66	Male		Caucasian	177.8	82.7	26.2	NS	0	Group 1
1001	10011011	60	Male		Caucasian	170.2	82.7	28.5	Current Smoker	0	Group 1
1001	10011012	53	Female	(Postmenopausal)	Black	157.5	70.5	28.4	Current Smoker	0	Group 1
1002	10021008	63	Female	(Postmenopausal)	Caucasian	168.0	73.8	26.1	Past Smoker	4	Group 1
1002	10021014	54	Male		Caucasian	170.0	80.0	27.7	NS	9	Group 1
1002	10021015	52	Male		Caucasian	165.0	87.7	32.2	Past Smoker	0	Group 1
1002	10021016	46	Male		Caucasian	171.5	95.7	32.5	NS	10	Group 1
1001	10011005	55	Female	(Postmenopausal)	Caucasian	172.7	54.1	18.1	Current Smoker	0	Group 2
1001	10011006	57	Female	(Postmenopausal)	Caucasian	160.0	70.5	27.5	Current Smoker	0	Group 2
1001	10011007	56	Male		Caucasian	182.9	88.2	26.4	Current Smoker	0	Group 2
1001	10011008	53	Male		Caucasian	177.8	91.8	29	NS	0	Group 2
1002	10021009	47	Male		Caucasian	182.0	92.3	27.9	NS	0	Group 2
1002	10021010	64	Female	(Postmenopausal)	Caucasian	161.0	76.4	29.5	Past Smoker	0	Group 2
1002	10021012	51	Male		Caucasian	183.5	99.1	29.4	NS	0	Group 2
1002	10021013	52	Male		Caucasian	175.0	88.8	29	NS	0	Group 2
1001	10011001	52	Male		Caucasian	165.1	75.5	27.7	NS	0	Group 3
1001	10011002	72	Female	(Postmenopausal)	Caucasian	162.6	86.4	32.7	NS	0	Group 3
1001	10011003	65	Male		Caucasian	162.6	84.5	32	Current Smoker	0	Group 3
1001	10011004	55	Male		Caucasian	175.3	98.2	32	Current Smoker	0	Group 3
1002	10021002	63	Female	(Postmenopausal)	Caucasian	165.5	78.2	28.6	NS	0	Group 3
1002	10021003	48	Female	(Postmenopausal)	Caucasian	157.0	71.8	29.1	Current Smoker	0	Group 3
1002	10021004	50	Male		Caucasian	188.5	94.1	26.5	Past Smoker	0	Group 3
1002	10021005	53	Male		Caucasian	169.0	84.5	29.6	Current Smoker	0	Group 3
1001	10011013	46	Female	(Postmenopausal)	Caucasian	167.6	80.9	28.8	NS	0	Group 4
1001	10011014	54	Male		Caucasian	182.9	88.2	26.4	NS	0	Group 4
1002	10021006	51	Male		Caucasian	169.0	79.1	27.7	NS	0	Group 4
1002	10021007	66	Male		Caucasian	176.0	98.2	31.7	NS	0	Group 4
1002	10021011	48	Male		Caucasian	175.2	92.6	30.2	NS	0	Group 4
1002	10021017	46	Female	(Premenopausal)	Caucasian	168.0	60.9	21.6	Current Smoker	0	Group 4

Table 98 Summary Statistics for Subject Demographics by Degree of Hepatic Impairment and Gender – Study A7501018

Group	Gender	Menopausal Status	N	Race W/B/A/H/NA	Age	Ht (cm)	Wt (kg)	BMI (kg/m^2)	Smoking Status Current/Past/NS	EtOH (U/wk)
1 Normal	Female	Post	2	1/1	58 ± 7.1 (12.2) 53 - 63 [58]	162.75 ± 7.4 (4.6) 157.5 - 168 [162.75]	72.15 ± 2.3 (3.2) 70.5 - 73.8 [72.15]	27.25 ± 1.6 (6.0) 26.1 - 28.4 [27.25]	1/1/0	0/4
	Male		6		55.7 ± 6.9 (12.3) 46 - 66 [55]	170.4 ± 4.3 (2.5) 165 - 177.8 [170.1]	84.8 ± 6.0 (7.1) 80 - 95.7 [82.7]	29.3 ± 2.5 (8.7) 26.2 - 32.5 [28.5]	1/1/4	4x0/9/10
2 Mild	Female	Post	3		58.7 ± 4.7 (8.1) 55 - 64 [57]	164.6 ± 7.1 (4.3) 160 - 172.7 [161]	67.0 ± 11.6 (17.2) 54.1 - 76.4 [70.5]	25.0 ± 6.1 (24.3) 18.1 - 29.5 [27.5]	2/1/0	0
	Male		5	5/	51.8 ± 3.3 (6.3) 47 - 56 [52]	180.2 ± 3.7 (2.0) 175 - 183.5 [182]	92.0 ± 4.3 (4.7) 88.2 - 99.1 [91.8]	28.3 ± 1.2 (4.3) 26.4 - 29.4 [29]	1/0/4	0
3 Moderate	Female	Post	3	3/	61 ± 12.1 (19.9) 48 - 72 [63]	161.7 ± 4.3 (2.7) 157 - 165.5 [162.6]	78.8 ± 7.3 (9.3) 71.8 - 86.4 [78.2]	30.1 ± 2.2 (7.4) 28.6 - 32.7 [29.1]	1/0/2	0
	Male		5	5/	55.0 ± 5.9 10.7 50 - 65 53	172.1 ± 10.3 6.0 162.6 - 188.5 169	87.4 ± 8.9 10.2 75.5 - 98.2 84.5	29.6 ± 2.5 8.4 26.5 - 32 29.6	3/1/1	0
4 Severe	Female	1 Pre 1 Post	2	2/	46 ± 0.0 0.0 46 - 46 [46]	167.8 ± 0.3 0.2 167.6 - 168 [167.8]	70.9 ± 14.1 19.9 60.9 - 80.9 [70.9]	25.2 ± 5.1 20.2 21.6 - 28.8 [25.2]	1/0/1	0
	Male		4	4	54.8 ± 7.9 (14.4) 48 - 66 [52.5]	175.8 ± 5.7 (3.2) 169 - 182.9 [175.6]	89.5 ± 8.1 (9.0) 79.1 - 98.2 [90.4]	29.0 ± 2.4 (8.30 26.4 - 31.7 [28.95]	0/0/4	0

Table 99 Asenapine Pharmacokinetic Summary Metrics with Varying Degrees of Hepatic Impairment Values – Study A7501018

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
	Normal	Mild	Moderate	Severe	Normal	Mild	Moderate	Severe	Mild : NI	Mod : NI	Severe : NI
N	8	8	8	6							
Tmax (hr)	0.94 ± 0.66 (70.9) 0.50 - 2.0 [0.625]	1.09 ± 0.38 (34.4) 0.50 - 1.5 [1.00]	2.09 ± 1.13 (54.1) 0.75 - 4.0 [1.75]	2.21 ± 1.90 (86.0) 0.75 - 6.0 [1.50]							
Cmax (ng/mL)	6.85 ± 2.51 (36.6) 4.06 - 11.6 [5.92]	6.12 ± 1.78 (29.2) 3.44 - 8.59 [6.30]	4.06 ± 1.79 (44.1) 2.17 - 6.60 [4.24]	7.50 ± 4.58 (61.1) 3.60 - 16.6 [6.21]	6.49	5.87	3.71	6.67	0.904 0.641 – 1.28	0.571 0.405 – 0.806	1.03 0.708 – 1.49
AUC(0-tlast) (ng/mL x hr^{-1})	50.9 ± 15.3 (30.0) 31.7 - 71.6 [46.7]	58.2 ± 27.2 (46.7) 25.3 - 105 [53.3]	63.1 ± 34.2 (54.2) 20.4 - 115 [49.2]	247 ± 55.3 (22.4) 156 - 304 [260]	49.0	52.8	54.8	241	1.08 0.742 – 1.56	1.12 0.771 – 1.63	4.92 3.29 – 7.37
AUC∞ (ng/mL x hr^{-1})	55.0 ± 15.9 (28.9) 33.6 - 75.9 [51.3]	68.4 ± 39.6 (57.9) 26.9 - 130 [56.4]	68.9 ± 37.3 [a] (54.1) 22.0 - 121 [55.7]	304 ± 85.0 (27.9) 164 - 412 [319]	52.9	59.2	59.5	293	1.12 0.744 – 1.68	1.12 0.736 – 1.71	5.53 3.56 – 8.59
%extrap (%)	7.42 ± 3.45 (46.5) 3.96 - 13.6 [6.15]	10.4 ± 10.2 (98.6) 2.12 - 31.8 [6.98]	4.76 ± 1.53 [a] (32.1) 3.15 - 7.46 [4.78]	17.0 ± 11.1 (65.2) 4.48 - 32.3 [16.8]							
CL/F (mL/min)	1640 ± 490 (29.9) 1100 - 2480 [1630]	1610 ± 856 (53.1) 642 - 3100 [1510]	1660 ± 1090 [a] (65.7) 690 - 3780 [1500]	299 ± 110 (37.0) 202 - 509 [261]	1570	1410	1400	285	0.894 0.594 – 1.34	0.89 0.583 – 1.36	0.181 0.116 – 0.281
Vd/F (L)	5470 ± 3010 (55.0) 2670 - 12000 [4570]	4900 ± 2220 (45.3) 2920 - 9750 [4350]	6440 ± 2930 [a] (45.5) 3600 - 12000 [5740]	2240 ± 442 (19.8) 1670 - 2760 [2160]							
t½ (hr)	39.1 ± 17.8 (45.5) 16.7 - 76.4 [37.1]	39.9 ± 16.6 (41.6) 22.8 - 72.4 [33.9]	49.8 ± 9.53 [a] (19.1) 36.6 - 60.4 [48.1]	94.3 ± 31.7 (33.6) 51.6 - 124 [105]							

a n = 7

Table 100 Desmethyl-Asenapine Pharmacokinetic Metrics with Varying Degrees of Hepatic Impairment Values - Study A7501018

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
	NI	Mild	Moderate	Severe	NI	Mild	Moderate	Severe	Mild : NI	Mod : NI	Severe : NI
N	8a	8a	8	6b							
Tmax (hr)	7.25 ± 2.38 (32.8) 4 - 12 [7]	13 ± 11.2 (85.9) 6 - 36 [7]	13.3 ± 11.1 (83.3) 6 - 36.2 [8]	40 ± 29.1 (72.6) 12 - 96 [36]							
Cmax (ng/mL)	0.537 ± 0.163 (30.4) 0.299 - 0.782 [0.569]	0.399 ± 0.186 (46.6) 0.153 - 0.696 [0.343]	0.365 ± 0.131 (35.9) 0.167 - 0.564 [0.352]	0.179 ± 0.066 (37.2) 0.101 - 0.267 [0.176]	0.513	0.360	0.342	0.168	0.702 0.495 - 0.995	0.667 0.471 - 0.946	0.327 0.225 - 0.477
AUC(0-tlast) (ng/mL x hr^{-1})	12 ± 5.5 (45.6) 4.03 - 22.3 [12.1]	13.5 ± 5.21 (38.6) 6.35 - 24.4 [13.9]	15.5 ± 11.3 (72.8) 4.95 - 38.8 [12]	20.3 ± 8.73 (42.9) 5.89 - 31.8 [21.4]	10.9	12.7	12.5	18.1	1.17 0.727 – 1.87	1.15 0.718 – 1.85	1.67 1.00 – 2.78
AUC∞ (ng/mL x hr^{-1})	15.3 ± 6.22 [a] (40.7) 4.83 - 24.6 [15.4]	16.8 ± 7.36 [a] (43.8) 8.07 - 32 [15.7]	18.4 ± 12.2 (66.5) 6.27 - 43.6 [15.2]	47.8 ± 20.5 [b] (43) 29.5 - 70 [43.9]	13.9	15.6	15.4	44.9	1.13 0.693 – 1.83	1.11 0.695 – 1.78	3.24 1.73 – 6.06
%extrap (%)	19.8 ± 7.03 [a] (35.5) 9.63 - 30.2 [17.7]	17.3 ± 6.65 [a] (38.5) 6.08 - 25 [16]	18.5 ± 7.64 (41.2) 10.7 - 28.8 [17.4]	53.5 ± 16.5 [b] (30.8) 34.6 - 64.7 [61.2]							
t½ (hr)	21.1 ± 7.82 [a] (37.1) 7.67 - 31.4 [20.4]	24.8 ± 12.2 [a] (49.1) 11.3 - 44.6 [24.3]	31.5 ± 17.7 (56.3) 14.4 - 63.9 [23.5]	252 ± 147 [b] (58.2) 90.4 - 377 [289]							

a n = 7
b n = 3

Table 101 Asenapine Glucuronide Pharmacokinetic Metrics with Varying Degrees of Hepatic Impairment Values – Study A7501018

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
	Normal	Mild	Moderate	Severe	Normal	Mild	Moderate	Severe	Mild : NI	Mod : NI	Severe : NI
	8	8	8	6							
Tmax (hr)	4.75 ± 1.39 (29.2) 3 - 6 [5]	4.38 ± 1.51 (34.4) 2 - 6 [4]	4.63 ± 1.6 (34.6) 2 - 6 [5]	7.15 ± 3.01 (42.1) 3 - 12 [7]							
Cmax (ng/mL)	8.19 ± 3.84 (46.8) 1.11 - 13.5 [8.32]	13.8 ± 17.8 (130) 2.26 - 56.7 [9.23]	8.04 ± 4.88 (60.7) 2.71 - 17.2 [5.64]	3.84 ± 1.54 (40.1) 2.47 - 6.42 [3.36]	6.84	8.28	6.87	3.61	1.21 0.635 – 23.1	1.01 0.527 – 1.92	0.528 0.263 – 1.06
AUC(0-tlast) (ng/mL x hr^{-1})	103 ± 46 (44.7) 8.06 - 153 [113]	210 ± 307 (146) 18.5 - 951 [108]	109 ± 83.4 (76.5) 20.8 - 227 [87]	119 ± 63.2 (53.1) 47.7 - 225 [111]	81.5	111	79.6	105	1.36 0.612 – 3.03	0.97.6 0.438 – 2.17	1.29 0.544 - .307
AUC∞ (ng/mL x hr^{-1})	105 ± 51.1 [a] (48.5) 9.3 - 159 [114]	232 ± 341 (147) 24.3 - 1060 [114]	119 ± 91 (76.8) 22.9 - 253 [95.5]	198 ± 131 [b] (66.2) 50.6 - 348 [196]	82.0	127	86.6	157	1.55 0.650 – 3.68	1.06 0.444 – 2.51	1.92 0.672 – 5.49
%extrap (%)	6.13 ± 3.84 [a] (62.7) 2.27 - 13.4 [5.11]	12 ± 8.69 (72.2) 4.43 - 26 [8.18]	8.08 ± 3.66 (45.3) 2.59 - 14.2 [8.18]	29 ± 16.3 [b] (56.1) 5.75 - 43.4 [33.4]							
t½ (hr)	7.44 ± 3.37 [a] (45.3) 3.07 - 13.1 [7.51]	20.8 ± 14.4 (69.1) 5.05 - 42 [19]	15 ± 18.8 (125) 2.23 - 58.6 [6.46]	90.7 ± 84.4 [b] (93) 5.91 - 207 [74.8]							

a n = 7
b n = 4

Table 102 Effect of Hepatic Impairment on the Pharmacokinetics of Unbound Asenapine – Study A7501018

	Normal	Mild	Moderate	Severe
N	8	8	8/7	6
Cmaxu (ng/mL)	0.317 ± 0.105 (33.1) 0.217-0.487 [0.278]	0.364 ± 0.148 (40.6) 0.206 - 0.659 [0.336]	0.229 ± 0.0948 (41.4) 0.119 - 0.347 [0.238]	0.524 ± 0.419 (80.1) 0.248 - 1.36 [0.353]
AUCu(0 - tlqc) (ng/mL x hr^{-1})	2.38 ± 0.686 (28.8) 1.55-3.17 [2.38]	3.65 ± 2.45 (67.1) 1.52 - 8.38 [2.78]	3.64 ± 2.16 (59.5) 1.20 - 7.69 [3.00]	16.5 ± 5.06 (30.7) 8.44 - 22.5 [16.4]
AUCu(0-∞) (ng/mL x hr^{-1})	2.57 ± 0.717 (27.9) 1.65-3.42 [2.61]	4.38 ± 3.44 (78.6) 1.61 - 10.4 [2.93]	3.93 ± 2.41 (61.2) 1.30 - 8.09 [3.34]	20.6 ± 7.71 (37.5) 8.83 - 28.4 [22.1]
CL/Fu (mL/min)	35000 ± 10400 (29.9) 24300-50600 [32200]	29400 ± 16900 (57.3) 8020 - 51600 [28600]	29900 ± 18900 (63.2) 10300 - 64100 [25000]	4790 ± 2480 (51.9) 2930 - 9430 [3860]
fu (%)	0.047 ± 0.005 0.040 - 0.057	0.059 ± 0.012 0.046 - 0.080	0.057 ± 0.007 0.046 - 0.067	0.066 ± 0.013 0.053 - 0.082

Figure 76 Linear and Semi-log Plots of Asenapine Concentration vs. Time Profiles for a Single 5 mg Sublingual Dose by Degree of Hepatic Impairment – Study A7501018

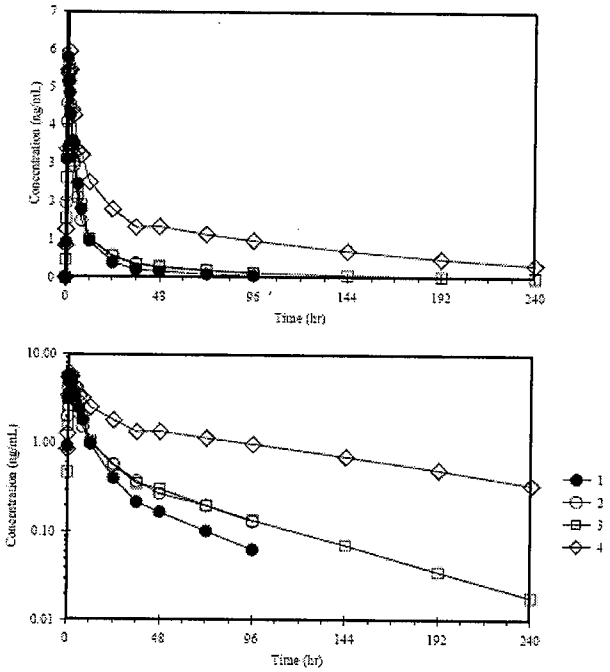


Figure 77 Linear and Semi-log Plots of Asenapine Glucuronide Concentration vs. Time Profiles for a Single 5 mg Sublingual Dose by Degree of Hepatic Impairment – Study A7501018

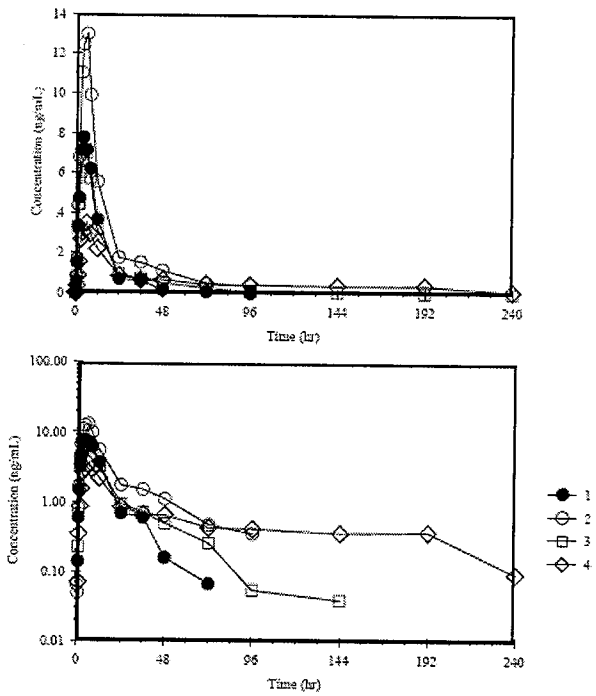


Figure 78 Linear and Semi-log Plots of Desmethyl-Asenapine Concentration vs. Time Profiles for a Single 5 mg Sublingual Dose by Degree of Hepatic Impairment – Study A7501018

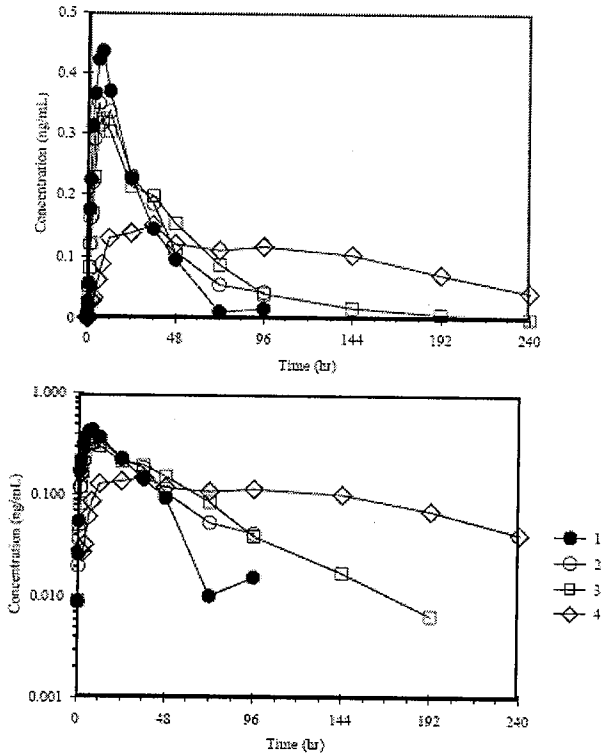


Figure 79 Individual Asenapine Cmax and AUC∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018

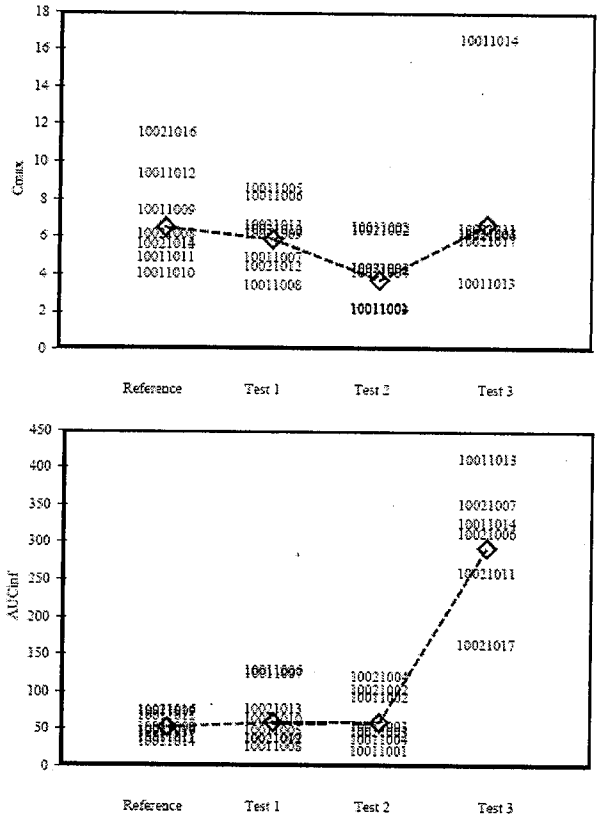


Figure 80 Individual Asenapine Glucuronide Cmax and AUC∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018

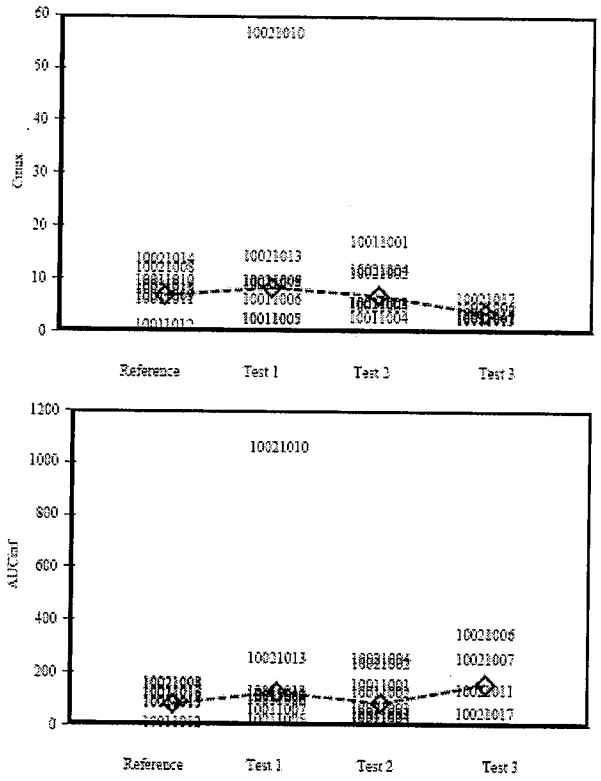


Figure 81 Individual Desmethyl-Asenapine Cmax and AUC∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018

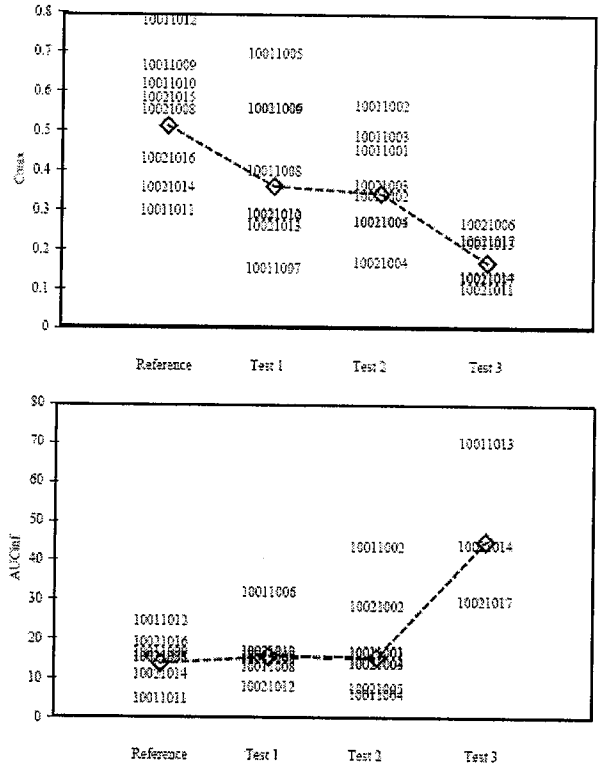
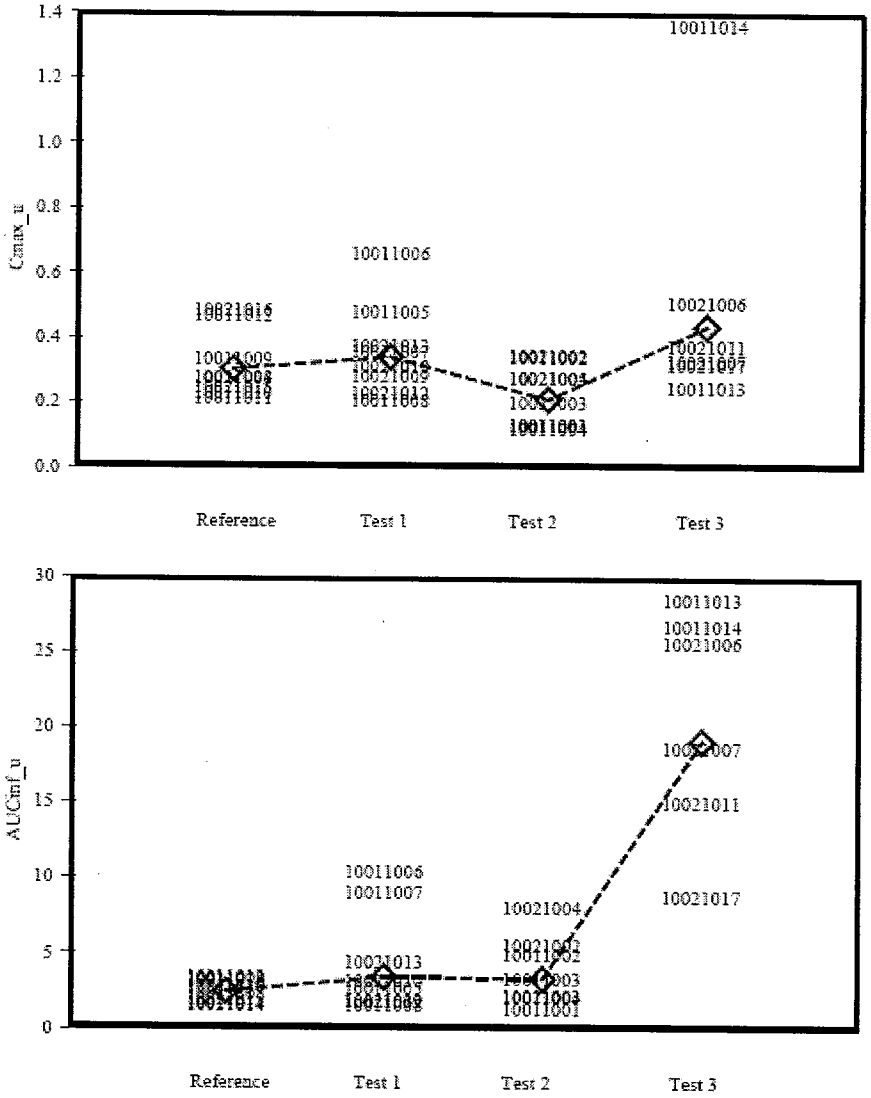


Figure 82 Individual Unbound Asenapine Cmax,u and AUCu∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018



5.5.6.6 *Renal Impairment*

Two studies were conducted on the effects of renal impairment on the pharmacokinetics of asenapine and desmethyl-asenapine. The only finding was that desmethyl-asenapine exposures were lower in moderate and severe renal insufficiency, possibly indicating a decreased formation of desmethyl-asenapine.

Other metabolites such as the derivatives of the 11-hydroxy-asenapine and N-glucuronides were not assessed so the alterations in other major active metabolites cannot be assessed.

5.5.6.6.1 Renal Impairment – Study 25521

Study 25521 was a single dose, open label study to assess the effect of varying degrees of renal impairment on the pharmacokinetics of asenapine and desmethyl-asenapine following a 0.3 mg sublingual dose in 16 male and 16 female Caucasian subjects with varying levels of renal function aged 25 - 65 years old.

Renal function was assessed at screening by a 24 hour creatinine clearance, and subjects were grouped per degree of impaiment as follows:

- Normal renal function — Clcr ≥ 82.0 mL/min/1.73 m^2 — n = 8
- Mild renal insufficiency — Clcr ≥ 52.0 and < 78.0 mL/min/1.73 m^2 — n = 8
- Moderate renal insufficiency — Clcr ≥ 32.0 and < 48.0 mL/min/1.73 m^2 — n = 8
- Severe renal insufficiency — Clcr < 28.0 mL/min/1.73 m^2 — n = 8

Mean concentration vs. Time profiles are shown in Figure 83, AUCt vs. Clcr in Figure 84, and weight normalized Clapp vs. Clcr in Figure 85.

Due to the low dosage used desmethyl-asenapine was largely unmeasurable. This as well as differences in subject weight by group may also account for the truncated concentration vs. time profiles in Figure 83. The low body weight of subjects in the severe renal impairment group might account for higher exposures in this group, however low exposures in the mild group argues against this, (see Table 104, Figure 83, and Table 105). Another possibility is that severe renal insufficiency inhibits metabolism of asenapine. This is known to occur with CYP2D6.

AUCt and Cmax were largely independent of renal function although there were two individuals with higher Cmax's in the moderate and severe renal insufficiency groups although the reason for this is unclear, (see Figure 86 and Table 106).

Free fraction was unchanged with renal impairment, (see Table 107).

Figure 83 Asenapine Mean Concentration vs. Time Profiles for Various Degrees of Renal Function - Study 25521

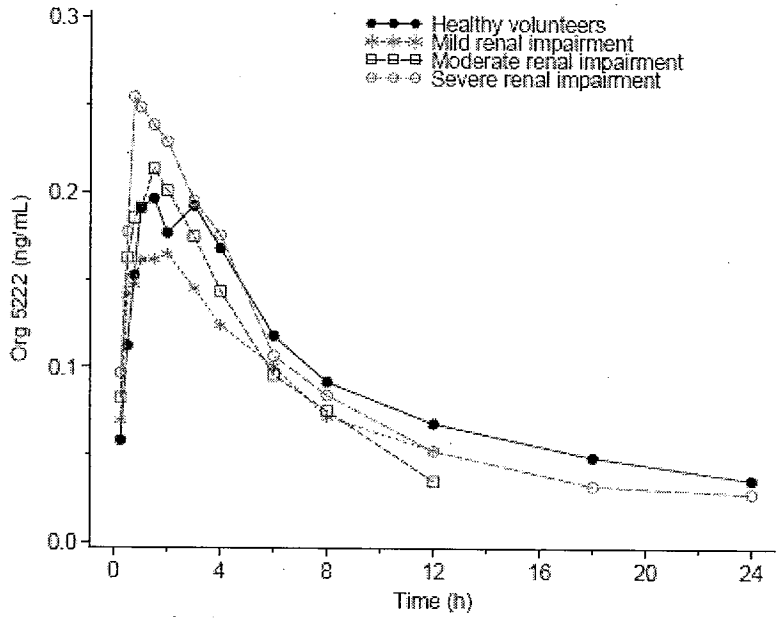


Figure 84 Asenapine AUCt vs. Creatinine Clearance - Study 25521

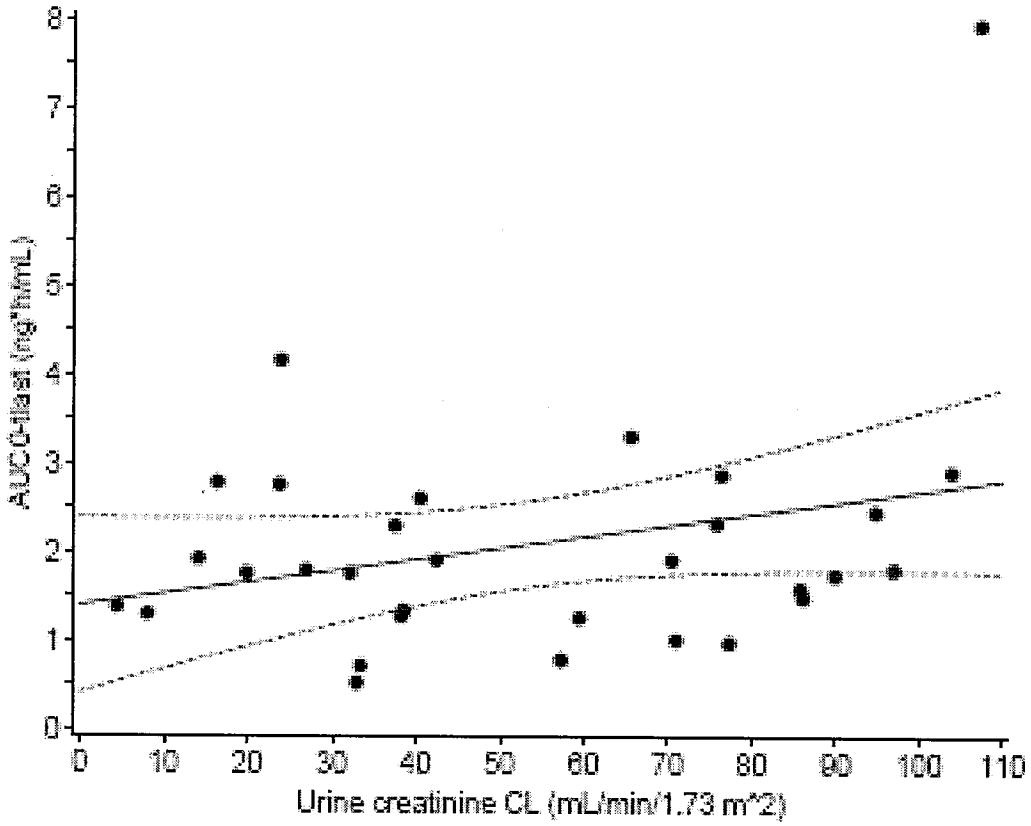


Figure 85 Asenapine Weight Normalized Apparent Clearance vs. Creatinine Clearance – Renal Impairment Study 25521

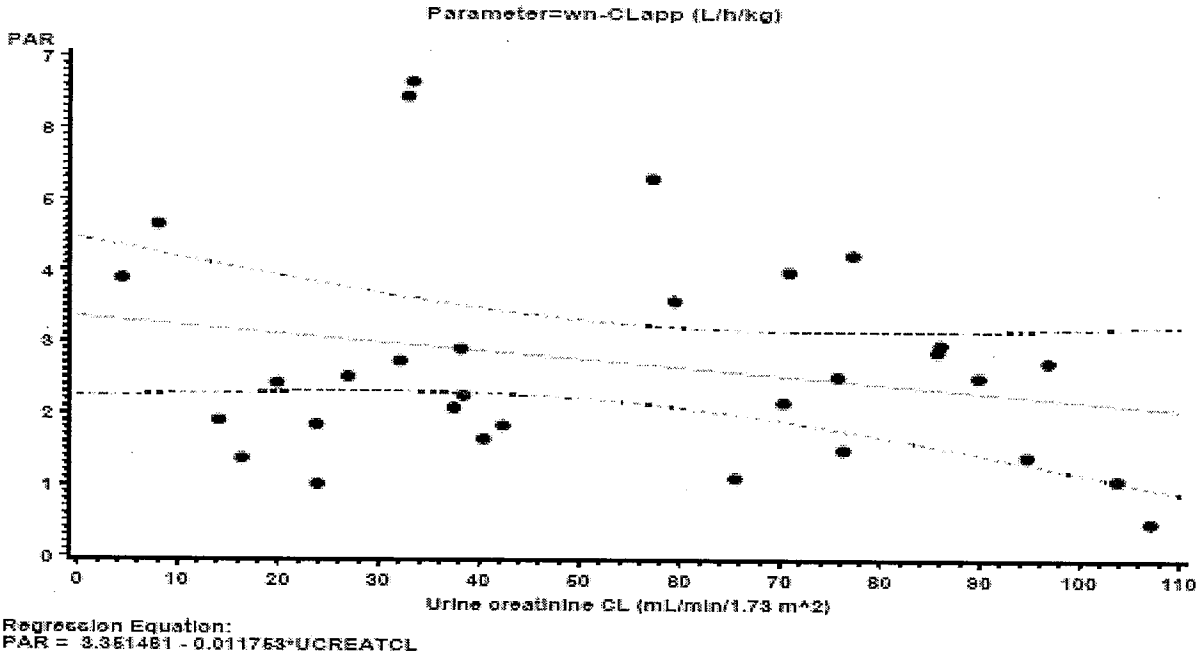


Table 103 Renal Impairment Study Individual Subject Demographic Characteristics- Study 25521

Group	Subj	Sex	Race	Age	Ht	Wt	BMI	BSA	Smoker?
Normal Renal Function CIcr ≥ 82.0 mL/min/1.73 m^2	1	Female	Caucasian	49	155	58.0	24.1	1.60	YES
	2	Female	Caucasian	50	158	68.1	27.3	1.78	NO
	3	Male	Caucasian	52	167	66.0	23.7	1.75	YES
	4	Female	Caucasian	43	156	61.2	25.1	1.65	NO
	5	Female	Caucasian	43	161	69.0	26.6	1.78	YES
	6	Male	Caucasian	48	185	96.0	28.0	2.23	YES
	7	Male	Caucasian	49	185	78.8	23.0	2.03	NO
	8	Male	Caucasian	50	176	87.1	28.1	2.06	NO
Mild Renal Impairment CLcr ≥ 52.0 and <78.0 mL/min/1.73 m^2	11	Male	Caucasian	26	183	70.0	20.9	1.93	NO
	12	Male	Caucasian	45	171	82.6	28.2	1.99	NO
	13	Male	Caucasian	43	172	75.0	25.4	1.88	NO
	14	Female	Caucasian	54	165	73.0	26.8	1.86	NO
	15	Female	Caucasian	49	163	51.4	19.3	1.52	YES
	16	Male	Caucasian	65	170	73.0	25.3	1.88	NO
	17	Female	Caucasian	31	165	67.0	24.6	1.75	YES
	18	Female	Caucasian	42	167	73.0	26.2	1.86	YES
Moderate Renal Impairment CLcr ≥ 32.0 and <48.0 mL/min/1.73 m^2	21	Male	Caucasian	38	183	100.0	29.9	2.28	NO
	22	Male	Caucasian	54	177	86.0	27.5	2.06	NO
	23	Female	Caucasian	63	153	70.0	29.9	1.76	NO
	24	Female	Caucasian	62	145	62.5	29.7	1.64	NO
	25	Male	Caucasian	27	177	81.5	26.0	2.01	NO
	26	Male	Caucasian	33	182	90.0	27.2	2.13	NO
	27	Female	Caucasian	57	166	63.0	22.9	1.70	NO
	28	Female	Caucasian	28	164	63.8	23.7	1.70	NO
Severe Renal Impairment CLcr < 28.0 mL/min/1.73 m^2	31	Female	Caucasian	61	155	50.0	20.8	1.48	NO
	32	Female	Caucasian	56	164	71.2	26.5	1.81	YES
	33	Female	Caucasian	41	160	58.9	23.0	1.62	NO
	34	Female	Caucasian	54	151	56.0	24.6	1.58	YES
	35	Male	Caucasian	55	169	78.6	27.5	1.94	NO
	36	Male	Caucasian	47	178	82.2	25.9	2.04	NO
	37	Male	Caucasian	31	172	66.5	22.5	1.78	YES
	38	Male	Caucasian	54	169	70.5	24.7	1.83	YES

Table 104 Demographic Summary Statistics by Degree of Renal Impairment - Study 25521

Degree of Renal Impairment	Gender	n	Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m^2)	BSA (m^2)
Normal Renal Function CLcr ≥ 82.0 mL/min/1.73 m^2	Female	4	46.3 ±3.77 43 - 50 [46.0]	158 ±2.65 155 - 161 [157]	64.1 ±5.34 58.0 - 69.0 [64.7]	25.8 ±1.42 24.1 - 27.3 [25.9]	1.70 ±0.0918 1.60 - 1.78 [1.72]
	Male	4	49.8 ±1.71 48 - 52 [49.5]	178 ±8.62 167 - 185 [181]	82.0 ±12.8 66.0 - 96.0 [83.0]	25.7 ±2.75 23.0 - 28.1 [25.9]	2.02 ±0.199 1.75 - 2.23 [2.05]
	Total	8	48.0 ±3.30 43 - 52 [49.0]	168 ±12.6 155 - 185 [164]	73.0 ±13.2 58.0 - 96.0 [68.6]	25.8 ±2.03 23.0 - 28.1 [25.9]	1.86 ±0.221 1.60 - 2.23 [1.78]
Mild Renal Impairment CLcr ≥ 52.0 and <78.0 mL/min/1.73 m^2	Female	4	44.0 ± 9.97 31 - 54 [45.5]	165 ± 1.63 163 - 167 [165]	66.1 ± 10.2 51.4 - 73.0 [70.0]	24.2 ± 3.39 19.3 - 25.4 [26.8]	1.75 ± 0.160 1.52 - 1.81 [1.86]
	Male	4	44.8 ± 16.0 26 - 65 [44.0]	174 ± 6.06 170 - 183 [172]	75.2 ± 5.37 70.0 - 82.6 [74.0]	24.9 ± 3.03 20.9 - 28.2 [25.3]	1.92 ± 0.0523 1.88 - 1.99 [1.91]
	Total	8	44.4 ± 12.3 26 - 65 [44.0]	170 ± 6.32 163 - 183 [169]	70.6 ± 8.96 51.4 - 82.6 [73.0]	24.6 ± 3.00 19.3 - 28.2 [25.3]	1.83 ± 0.144 1.52 - 1.87 [1.99]
Moderate Renal Impairment CLcr ≥ 32.0 and <48.0 mL/min/1.73 m^2	Female	4	52.5 ± 16.5 28 - 63 [59.5]	157 ± 9.83 145 - 166 [159]	64.8 ± 3.49 62.5 - 70.0 [63.4]	26.6 ± 3.78 22.9 - 29.9 [26.7]	1.70 ± 0.0490 1.64 - 1.76 [1.70]
	Male	4	38.0 ± 11.6 27 - 54 [35.5]	180 ± 3.20 177 - 183 [180]	89.4 ± 7.89 81.5 - 100 [88.0]	27.6 ± 1.62 26.0 - 29.9 [27.3]	2.12 ± 0.117 2.01 - 2.28 [2.10]
	Total	8	45.3 ± 15.3 27 - 63 [46.0]	168 ± 13.9 145 - 183 [172]	77.1 ± 14.3 62.5 - 100 [75.8]	27.1 ± 2.75 22.9 - 29.9 [27.3]	1.91 ± 0.239 1.64 - 2.28 [1.89]
Severe Renal Impairment CLcr < 28.0 mL/min/1.73 m^2	Female	4	53.0 ± 8.52 41 - 61 [55.0]	158 ± 5.69 151 - 164 [158]	59.0 ± 8.92 50.0 - 71.2 [57.5]	23.7 ± 2.40 20.8 - 26.5 [23.8]	1.62 ± 0.138 1.48 - 1.81 [1.60]
	Male	4	46.8 ± 11.1 31 - 55 [50.5]	172 ± 4.24 169 - 178 [171]	74.5 ± 7.21 66.5 - 82.2 [74.6]	25.2 ± 2.13 22.5 - 27.5 [25.3]	1.90 ± 0.116 1.78 - 2.04 [1.89]
	Total	8	49.9 ± 9.75 31 - 61 [54.0]	165 ± 9.04 151 - 178 [167]	66.7 ± 11.2 50.0 - 82.2 [68.5]	24.4 ± 2.24 20.8 - 27.5 [24.6]	1.76 ± 0.189 1.48 - 2.04 [1.80]

Table 105 Asenapine Pharmacokinetic Metric Summary Statistics in Various Degrees of Renal Insufficiency – Study 25521

Degree of Renal Impairment	Summary Statistics				Geometric Means				Geometric Mean Ratio (90% CI)		
	Normal	Mild	Moderate	Severe	NI	Mild	Mod	Sev	Mild : NI	Mod : NI	Sev : NI
Clcr (ml/min / 1.73 m^2)	≥ 82.0	≥ 52.0 + <78.0	≥ 32.0 + <48.0	< 28.0							
n	8/7 [a]	8	8	8							
Tmax (h)	2.25 ± 1.13 (50.4) 1.00 - 4 [2.25]	1.56 ± 0.50 (31.7) 0.5 - 2 [1.50]	1.53 ± 0.81 (52.7) 0.50 - 3.00 [1.50]	1.56 ± 1.08 (69.0) 0.75 - 4.00 [1.23]	1.99	1.46	1.34	1.33			
Cmax (ng/mL)	0.224 ± 0.069 (30.80 0.161 - 0.363 [0.193]	0.189 ± 0.043 (22.9) 0.112 - 0.233 [0.196]	0.259 ± 0.120 (46.2) 0.129 - 0.497 [0.245]	0.309 ± 0.167 (54.2) 0.123 - 0.675 [0.292]	0.216	0.184	0.237	0.276	0.85 0.61 - 1.18	1.09 0.79 - 1.52	1.28 0.92 - 1.77
AUC0-12h (ng*h/mL)	1.51 ± 0.45 (29.6) 1.14 - 2.48 [1.40]	1.20 ± 0.35 (29.3) 0.716 - 1.68 [1.24]	1.31 ± 0.51 (38.7) 0.639 - 2.05 [1.30]	1.54 ± 0.33 (21.2) 0.959 - 1.98 [1.52]	1.47	1.15	1.22	1.51	0.79 0.60 - 1.03	0.83 0.63 - 1.09	1.03 0.78 - 1.35
CLapp (L/h)	142 ± 58 (40.9) 37.7 - 202 [167]	214 ± 109 (51.1) 90.8 - 386 [198]	255 ± 163 (64.1) 115 - 580 [198]	154 ± 55.5 (36.0) 72.0 - 232 [162]	127	189	219	145			
wn-CLapp (L/h) / kg	2.00 ± 1 (49.9) 0.479 - 2.97 [2.51]	3.04 ± 1.46 (47.9) 1.10 - 5.29 [3.05]	3.32 ± 2.04 (61.4) 1.65 - 6.65 [2.49]	2.45 ± 1.24 (50.7) 1.01 - 4.65 [2.16]	1.71	2.7	2.88	2.19			
CrCLurine (mL/min/1.73 $m^{\wedge 2}$)	96.6 ± 9.16 (9.48) 85.8 - 109 [95.8]	69.1 ± 7.69 (11.1) 57.3 - 77.3 [68.7]	36.9 ± 3.75 (10.2) 32.1 - 42.4 [36.8]	17.2 ± 8.01 (46.5) 4.4 - 27 [15]	96.3	70.7	37.9	18.2			
dn-Cmax (ng/mL)/mg	0.75 ± 0.23 (30.8) 0.54 - 1.21 [0.642]	0.63 ± 0.14 (22.9) 0.37 - 0.78 [0.612]	0.86 ± 0.4 (46.2) 0.43 - 1.66 [0.789]	1.03 ± 0.558 (54.2) 0.41 - 2.25 [0.919]	0.721	0.653	0.817	0.973			
dn-AUC0-12h (ng*h/mL)/mg	5.04 ± 1.49 (29.6) 3.82 - 8.27 [4.66]	4.01 ± 1.18 (29.3) 2.39 - 5.58 [3.85]	4.35 ± 1.69 (38.7) 2.13 - 6.83 [4.05]	5.13 ± 1.09 (21.2) 3.2 - 6.59 [5.02]	4.89	4.13	4.33	5.05			

a n = 8 for Cmax and Tmax

Figure 86 Asenapine AUCt and Cmax vs. Creatinine Clearance – Study 25521

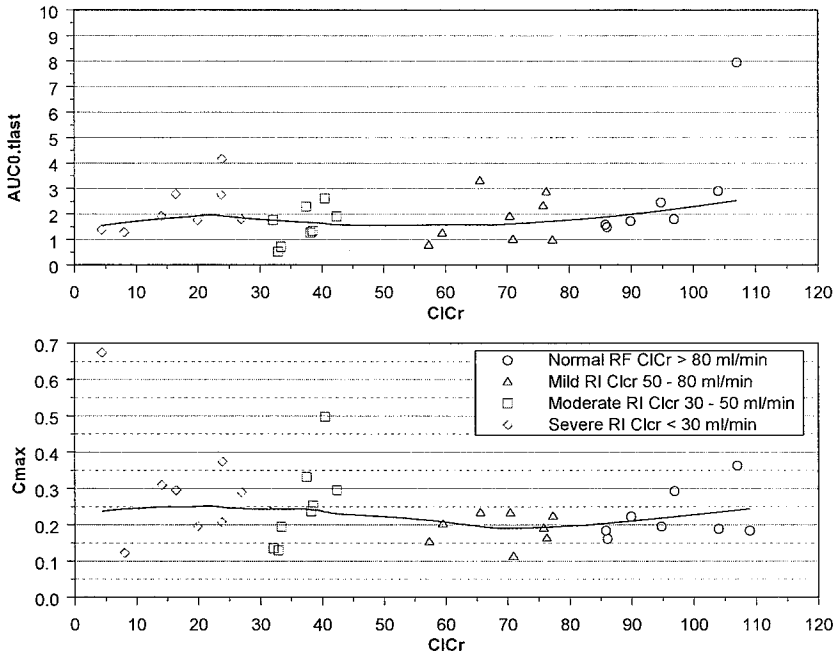


Table 106 Individual Asenapine Pharmacokinetic Metrics – Study 25521

Group	Subject	Cmax (ng/mL)	Tmax (h)	AUC0-12h (ng*h/mL)	AUC0-tlast (ng*h/mL)	Clapp (L/h)	wn-Clapp (L/h)/kg	Tlast (hr)	Urine Creatinine CL (mL/min / 1.73 m^2)
Healthy volunteers	1	0.184	1.5					6.0	109
	2	0.161	4.0	1.14	1.48	202	2.97	23.0	86.1
	3	0.184	3.0	1.21	1.58	189	2.87	23.0	85.8
	4	0.293	1.5	1.44	1.80	167	2.72	24.0	96.9
	5	0.223	1.0	1.54	1.73	173	2.51	18.0	89.9
	6	0.189	1.0	1.38	2.91	103	1.07	48.0	104
	7	0.363	3.0	2.48	7.95	37.7	0.479	48.0	107
	8	0.196	3.0	1.40	2.46	122	1.40	48.0	94.8
Mild renal impairment	11	0.163	1.5	1.30	2.87	104	1.49	48.0	76.3
	12	0.233	1.5	1.68	3.30	90.8	1.10	48.0	65.6
	13	0.112	2.0	0.819	1.00	299	3.98	18.0	70.9
	14	0.232	2.0	1.23	1.91	157	2.15	48.0	70.4
	15	0.190	2.0	1.65	2.32	129	2.52	24.0	75.8
	16	0.223	0.5	0.974	0.974	308	4.22	12.0	77.3
	17	0.202	1.5	1.25	1.25	239	3.57	12.0	59.5
	18	0.153	1.5	0.716	0.777	386	5.29	30.0	57.3
Moderate renal impairment	21	0.253	1.5	1.33	1.33	225	2.25	12.0	38.5
	22	0.295	0.75	1.55	1.90	158	1.83	24.0	42.4
	23	0.497	1.0	2.05	2.61	115	1.65	30.0	40.5
	24	0.135	2.0	0.929	1.76	171	2.73	36.0	32.1
	25	0.237	3.0	1.27	1.27	237	2.91	12.0	38.2
	26	0.129	1.5	0.639	0.517	580	6.44	8.00	32.9
	27	0.331	2.0	1.88	2.29	131	2.08	24.0	37.5
	28	0.194	0.5	0.798	0.707	424	6.65	8.00	33.4
Severe renal impairment	31	0.123	4.0	0.959	1.29	232	4.65	24.0	8.05
	32	0.374	2.0	1.98	4.17	72.0	1.01	48.0	23.9
	33	0.208	1.5	1.47	2.76	109	1.85	48.0	23.8
	34	0.675	0.75	1.47	1.38	218	3.89	6.00	4.40
	35	0.295	0.75	1.95	2.78	108	1.37	36.0	16.4
	36	0.310	1.0	1.56	1.92	156	1.90	24.0	14.1
	37	0.289	1.0	1.56	1.79	167	2.51	18.0	27.0
	38	0.196	1.47	1.36	1.75	171	2.43	24.0	19.9

Table 107 Summary Statistics for Protein Binding of Asenapine by Degree of Renal Function – Study 25521

Group	Metrics	AsenapineFraction Bound (%)	
		Time Post Dose	
		1 hour	8 hours
Normal Renal Function CLcr ≥ 82.0 mL/min/1.73 m^2	N	8	8
	Summary Statistics	98.2 ± 0.196 (0.200) 97.9 - 98.5 [98.2]	98.1 ± 0.196 (0.200) 97.7 - 98.3 [98.2]
Mild Renal Impairment CLcr ≥ 52.0 and <78.0 mL/min/1.73 m^2	N	7	8
	Summary Statistics	98.1 ± 0.162 (0.165) 97.9 - 98.3 [98.1]	98.2 ± 0.191 (0.194) 98.0 - 98.5 [98.2]
Moderate Renal Impairment CLcr ≥ 32.0 and <48.0 mL/min/1.73 m^2	N	8	8
	Summary Statistics	98.2 ± 0.223 (0.227) 97.8 - 98.4 [98.3]	98.2 ± 0.177 (0.180) 97.9 - 98.4 [98.2]
Severe Renal Impairment CLcr < 28.0 mL/min/1.73 m^2	N	8	8
	Summary Statistics	98.2 ± 0.205 (0.209) 97.9 - 98.5 [98.1]	98.2 ± 0.245 (0.249) 97.7 - 98.5 [98.3]
Normal	Geometric mean	98.2	98.1
Mild	Geometric mean	98.1	98.2
Moderate	Geometric mean	98.2	98.2
Severe	Geometric mean	98.2	98.2

5.5.6.6.2 Renal Impairment - Study A7501017

Study A7501017 was a single dose, open label study to assess the effect of varying degrees of renal impairment on the pharmacokinetics of asenapine and desmethyl- asenapine following a 5 mg sublingual dose in 15 male and 18 female subjects aged 36 - 78 years old with varying levels of renal function*.

* Renal function was assessed at screening based on the mean value of 2 estimated CLcr values determined at least 72 hours apart with the Cockcroft-Gault equation:

Subjects were originally grouped per degree of impaiment as follows:

- Normal renal function — Clcr* > 80.0 mL/min — n = 8
- Mild renal insufficiency — Clcr* ≥ 51.0 ≤ 80.0 mL/min — n = 8
- Moderate renal insufficiency — Clcr* ≥ 30.0 and ≤ 50.0 mL/min — n = 8
- Severe renal insufficiency † — Clcr* < 30.0 mL/min — n = 8

† (Not on dialysis - The study center attempted to enroll at least 3 subjects with estimated CLcr < 20 mL/min, but not requiring dialysis.)

However 3 subjects had differing Clcr on the Day of testing and were assigned to a different analysis group as follows.

Subject	Enrollment Group	(CLcr range)	Day 1 CLcr Value	Analysis Group	(CLcr range)
10011034	2	(51 - 80 mL/min)	94.8 mL/min	1	(>80 mL/min)
10011036	2	(51 - 80 mL/min)	48.9 mL/min	3	(30 - 50 mL/min)
10011038	3	(30 - 50 mL/min)	69.9 mL/min	2	(51 - 80 mL/min)

Thus, data were analyzed for 9 subjects in Group 1 and 8 subjects each in Groups 2 through 4.

Blood samples for analysis of asenapine and des-methyl-asenapine were collected for 72 hours after the asenapine dose, with an additional sample collected at 96 hours for Groups 3 and 4. Samples for plasma protein binding were collected at 4 hours postdose and protein binding was determined by equilibrium dialysis.

Results are shown in Figure 87 to Figure 90 and Table 108 to Table 113. Mean plasma concentration vs. time profiles for both asenapine and desmethyl-asenapine in Figure 87 and Figure 88 appear higher in normals and subjects with mild renal impairment, however this is not borne out by plots of exposure and clearance vs. creatinine clearance, (see Figure 89 and Figure 90), or pharmacokinetic metrics or their geometric mean ratios for asenapine, (see Table 109 and Table 110). The reason for this apparent discrepancy is that although Cmaxs are higher in healthy subjects and subjects with mild renal insufficiency with time terminal exposures are higher in the subjects with moderate and severe insufficiency, (see Figure 87 and Figure 88).However, mean exposures to desmethyl-asenapine goes down in severe renal impairment possibly suggesting a decreased formation, (see Table 112).

Figure 91 to Figure 94 show that AUCfree is more variable than total AUC and that there is a complex relationship but upon close examination it is as expected, e.g. for desmethyl-asenapine mean unbound AUC is independent of renal function, even though total AUC and fraction are inversely related.

Figure 87 Mean Asenapine Concentration vs. Time Profiles by Degree of Renal Function – Study A7501017

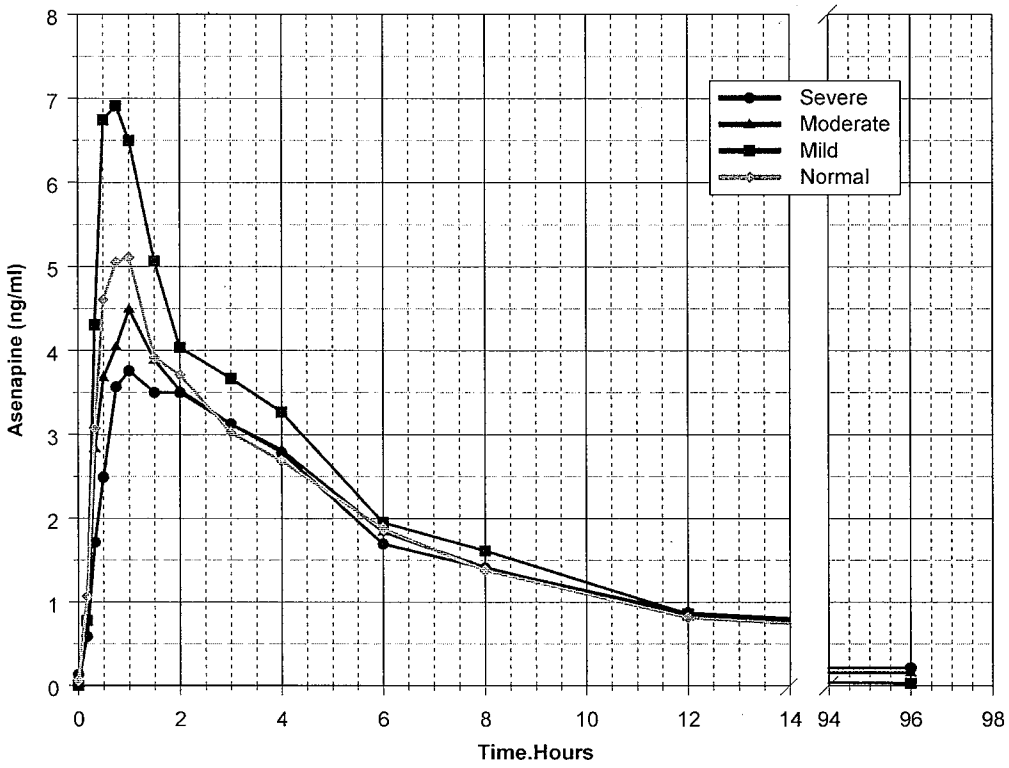


Figure 88 Mean Desmethyl-Asenapine Concentration vs. Time Profiles by Degree of Renal Function – Study A7501017

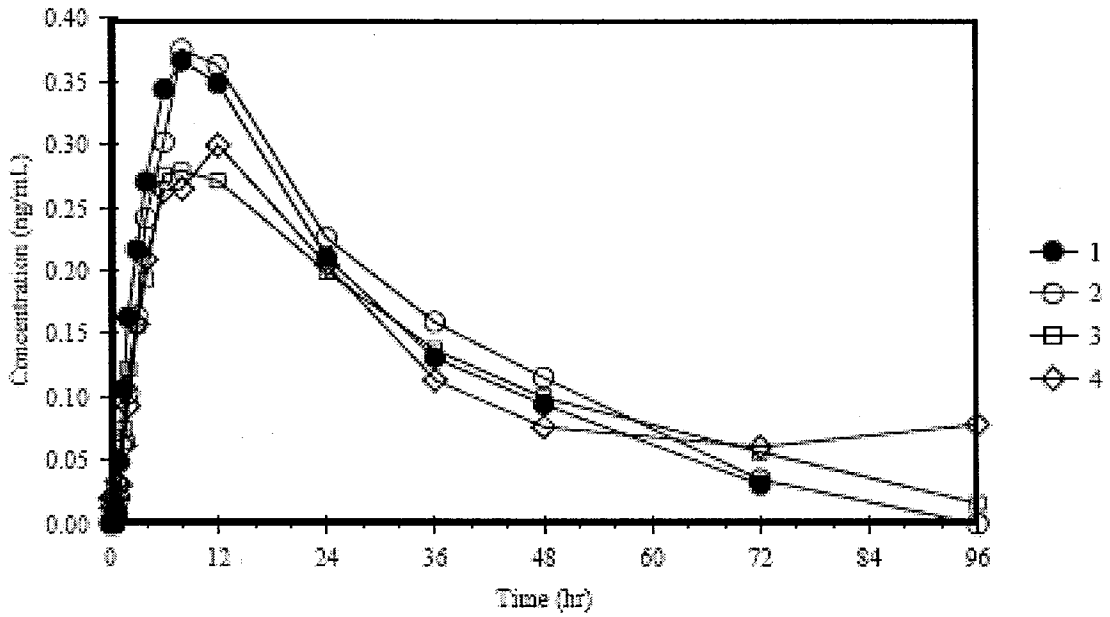


Figure 89 Plots of Asenapine AUCt, AUCinf, and Cl/F vs. Clcr – Study A7501017A

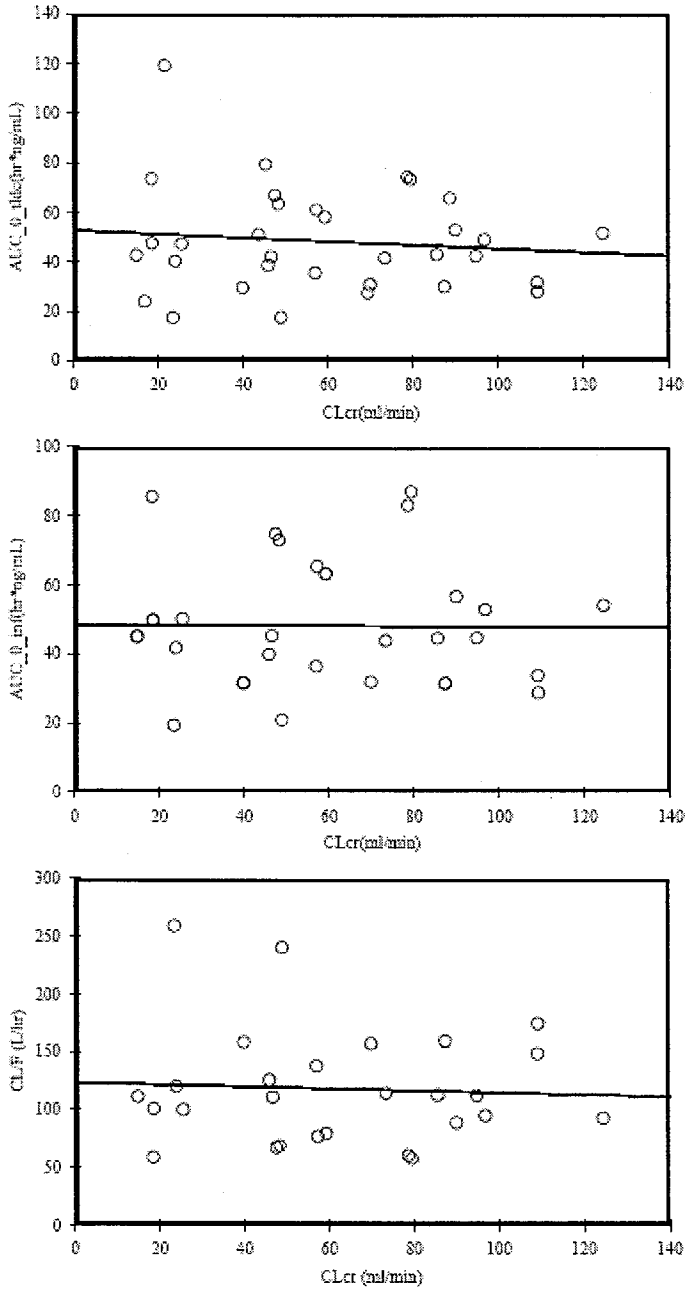


Figure 90 Plots of Desmethyl-Asenapine AUCt and AUCinf vs. Clcr – Study A7501017A

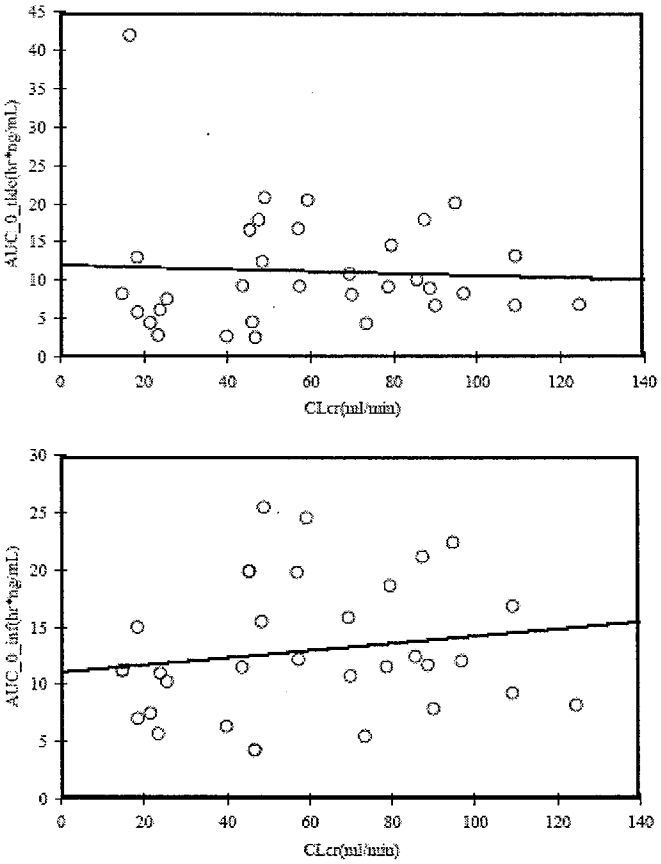


Table 108 Individual Subject Demographics for Renal Impairment Study A7501017

Renal Function	Renal Function Analysis Group	Subject	Age	Sex	(Hormonal Status)	Race	Height (cm)	Weight (kg)	BMI (kg/m2)	Smoking Status	Alcohol (Units / Wk)
Normal Renal Function Clcr* > 80.0 mL/min	Group 1	10011026	65	Female	(Postmenopausal)	Caucasian	167.6	77.3	27.5	Never Smoked	0
	Group 1	10011040	60	Female	(Postmenopausal)	Caucasian	162.5	84.5	32	Never Smoked	0
	Group 1	10011041	58	Female	(Postmenopausal)	Caucasian	165.1	63.2	23.2	Never Smoked	0
	Group 1	10011045	59	Female	(Postmenopausal)	Caucasian	156.5	75.3	30.7	Current Smoker	0
	Group 1	10011031	72	Female	(Postmenopausal)	Caucasian	160.0	68.6	26.8	Never Smoked	7
	Group 1	10011032	61	Male		Caucasian	176.5	88.4	28.4	Never Smoked	4
	Group 1	10011033	60	Male		Caucasian	187.3	104.5	29.8	Never Smoked	0
	Group 1	10011037	69	Male		Caucasian	171.4	88.4	30.1	Never Smoked	0
	Group 1	10011042	58	Male		Caucasian	182.8	86.3	25.8	Never Smoked	0
Mild Renal Insufficiency Clcr* ≥ 51.0 ≤ 80.0 mL/min	Group 2	10011002	71	Female	(Postmenopausal)	Caucasian	158.7	63.0	25	Never Smoked	0
	Group 2	10011034	64	Female	(Postmenopausal)	Caucasian	160.0	63.4	24.8	Never Smoked	0
	Group 2	10011035	64	Female	(Postmenopausal)	Caucasian	149.8	70.9	31.6	Never Smoked	0
	Group 2	10011043	65	Female	(Postmenopausal)	Caucasian	151.7	53.6	23.3	Never Smoked	0
	Group 2	10011038	56	Female	(Postmenopausal)	Caucasian	160.0	63.4	24.8	Never Smoked	0
	Group 2	10011011	63	Male		Black, Non Hispanic	177.8	75.5	23.9	Current Smoker	0
	Group 2	10011009	48	Male		Caucasian	170.2	92.3	31.9	Never Smoked	0
	Group 2	10011028	66	Male		Caucasian	176.5	83.6	26.8	Never Smoked	0
Moderate Renal Insufficiency Clcr ≥ 30.0 & ≤ 50.0 mL/min	Group 3	10011036	36	Female	(Premenopausal)	Black, Non Hispanic	161.3	83.6	32.1	Never Smoked	0
	Group 3	10011012	45	Female	(Premenopausal)	Caucasian	160.0	62.3	24.3	Current Smoker	0
	Group 3	10011014	60	Female	(Postmenopausal)	Caucasian	160.0	75.5	29.5	Never Smoked	0
	Group 3	10011024	50	Male		Black, Non Hispanic	184.1	108.6	32	Never Smoked	0
	Group 3	10011005	73	Male		Caucasian	179.0	89.0	27.8	Never Smoked	1
	Group 3	10011006	73	Male		Caucasian	167.6	69.0	24.6	Current Smoker	0
	Group 3	10011027	67	Male		Caucasian	184.8	110.0	32.2	Never Smoked	0
	Group 3	10011030	75	Male		Caucasian	172.7	96.4	32.3	Never Smoked	0
Severe Renal Insufficiency † Clcr* < 30.0 mL/min	Group 4	10011017	72	Female	(Postmenopausal)	Black, Non Hispanic	158.7	70.9	28.2	Never Smoked	0
	Group 4	10011023	74	Female	(Postmenopausal)	Black, Non Hispanic	162.5	54.0	20.4	Never Smoked	0
	Group 4	10011008	77	Female	(Postmenopausal)	Caucasian	160.0	61.8	24.1	Never Smoked	0
	Group 4	10011013	65	Female	(Postmenopausal)	Caucasian	166.4	90.5	32.7	Never Smoked	0
	Group 4	10011018	78	Female	(Postmenopausal)	Caucasian	163.8	65.4	24.4	Never Smoked	0
	Group 4	10011003	57	Male		Black, Non Hispanic	170.0	72.3	25	Current Smoker	0
	Group 4	10011020	52	Male		Black, Non Hispanic	166.4	68.6	24.8	Never Smoked	0
	Group 4	10011001	77	Male		Caucasian	176.5	87.3	28	Past Smoker	1

Table 109 Individual Asenapine Pharmacokinetic Metrics by Degree of Renal Impairment – Study A7501017

Groupa	CLcr (mL/min)	Subject	Cmax (ng/mL)	Tmax (hr)	AUCtlast (hr*ng/mL)	AUC(0 - ∞) (hr*ng/mL)	%AUC(0 - ∞) extrapolated	t½ (hr)	Vd/F (L)	CL/F (L/hr)	Fu
Renal Function Normal Renal Function Clcr* > 80.0 mL/min	85.6	10011026	6.57	0.700	42.9	44.5	3.74	15.0	2430	112	0.032
	109	10011032	5.64	0.530	31.6	33.8	6.32	28.6	6110	148	0.033
	96.8	10011033	4.52	0.750	48.9	52.9	7.62	31.5	4290	94.5	0.027
	94.8	10011034	4.93	1.00	42.3	44.7	5.39	21.9	3540	112	0.055
	125	10011037	7.92	1.05	51.5	54.1	4.69	19.0	2530	92.5	0.039
	88.7	10011040	3.76	1.00	65.7						0.039
	87.4	10011041	5.14	1.00	29.9	31.4	4.93	24.6	5660	159	0.038
	109	10011042	2.83	0.330	27.9	28.7	2.90	17.8	4470	174	0.036
	90.0	10011045	6.74	0.700	52.8	56.5	6.63	26.4	3370	88.4	0.037
Mild Renal Insufficiency Clcr* ≥ 51.0 ≤ 80.0 mL/min	57.0	10011002	6.27	1.05	35.5	36.4	2.35	12.3	2440	137	0.032
	69.4	10011009	2.54	1.97	27.4						0.095
	73.4	10011011	5.56	0.730	41.5	43.9	5.52	24.6	4040	114	0.044
	57.3	10011028	8.93	0.500	61.0	65.4	6.70	20.0	2200	76.5	0.04
	78.7	10011031	11.6	0.750	74.3	83.0	10.5	26.1	2270	60.3	0.029
	79.5	10011035	12.0	0.720	73.2	87.0	15.8	33.7	2800	57.5	0.028
	69.9	10011038	4.04	0.700	30.7	31.9	3.90	29.2	6610	157	0.031
	59.3	10011043	10.8	0.750	58.0	63.2	8.15	24.3	2770	79.1	0.028
Moderate Renal Insufficiency Clcr ≥ 30.0 & ≤ 50.0 mL/min	43.6	10011005	4.70	1.00	50.9						0.039
	45.9	10011006	3.21	2.00	38.6	39.8	3.12	13.3	2410	125	0.066
	46.6	10011012	4.54	1.47	41.9	45.3	7.41	40.8	6510	110	0.041
	47.5	10011014	5.73	0.750	66.9	74.7	10.5	35.7	3450	66.9	0.036
	45.3	10011024	7.09	1.00	79.2						0.032
	39.8	10011027	2.74	0.750	29.5	31.6	6.71	37.0	8450	158	0.047
	48.3	10011030	8.31	0.500	63.4	73.0	13.2	42.2	4170	68.5	0.036
	48.9	10011036	1.55	2.00	17.5	20.9	16.3	31.0	10700	240	0.039
Severe Renal Insufficiency † Clcr* < 30.0 mL/min	23.9	10011001	3.21	0.750	40.2	41.7	3.70	18.5	3190	120	0.036
	18.5	10011003	3.59	2.02	47.4	49.8	4.67	17.1	2470	100	0.046
	25.5	10011008	3.46	1.00	47.2	50.2	5.97	26.3	3780	99.6	0.039
	14.8	10011013	6.80	1.00	42.6	45.1	5.58	25.8	4130	111	0.038
	16.7	10011017	2.26	2.03	23.9						0.052
	18.4	10011018	6.79	2.97	73.4	85.5	14.2	42.0	3540	58.5	0.049
	21.5	10011020	6.06	0.750	119						0.047
	23.4	10011023	1.25	4.00	17.3	19.3	10.4	48.9	18300	259	0.037

Table 110 Asenapine Pharmacokinetic Metric Summary Statistics in Subjects with Varying Degrees of Renal Insufficiency after a Single 5 mg Sublingual Dose – Study A7501017

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
	Group 1 (>80 mL/min)	Group 2 (51 - 80 mL/min)	Group 3 (30 - 50 mL/min)	Group 4 (<30 mL/min)	Group 1 (>80 mL/min)	Group 2 (51 - 80 mL/min)	Group 3 (30 - 50 mL/min)	Group 4 (<30 mL/min)	Mild : Normal	Moderate : Normal	Severe : Normal
N	9/8	8/7	8/6	8/6							
Tmax (hr)	0.8 ± 0.2 (31.8) 0.33 - 1.05 [0.75]	0.9 ± 0.5 (51.2) 0.5 - 1.97 [0.74]	1.2 ± 0.6 (48.7) 0.5 - 2 [1.00]	1.8 ± 1.2 (65.2) 0.75 - 4 [1.51]	0.74	0.82	1.06	1.51			
Cmax (ng/mL)	5.3 ± 1.6 (29.5) 2.83 - 7.92 [5.14]	7.7 ± 3.6 (46.8) 2.54 - 12 [7.6]	4.7 ± 2.3 (47.8) 1.55 - 8.31 [4.62]	4.2 ± 2.1 (50.6) 1.25 - 6.8 [3.525]]	5.12	6.84	4.21	3.65	1.34 0.878 - 2.04	0.822 0.54 – 1.25	0.713 0.468 – 1.09
AUC(0 - tlqc)[a] (hr*ng/mL)	43.7 ± 12.5 (28.5) 27.9 - 65.7 [42.9]	50.2 ± 18.8 (37.5) 27.4 - 74.3 [49.75]	48.5 ± 20.6 (42.5) 17.5 - 79.2 [46.4]	51.4 ± 32.1 (62.5) 17.3 - 119 [44.9]	42.1	47.0	44.1	43.9	1.12 0.767 – 1.62	1.05 0.719 – 1.52	1.04 0.716 – 1.52
AUC(0 - ∞) (hr*ng/mL)	43.3 ± 10.9 (25.2) 28.7 - 56.5 [44.6]	58.7 ± 22.0 (37.4) 31.9 - 87 [63.2]	47.6 ± 22.0 (46.2) 20.9 - 74.7 [42.55]	48.6 ± 21.4 (44.0) 19.3 - 85.5 [47.45]	42.1	55.0	43.2	44.5	1.31 0.911 – 1.87	1.03 0.705 – 1.50	1.06 0.726 - 1.54
% extrap	5.3 ± 1.6 (29.4) 2.9 - 7.62 [5.16]	7.6 ± 4.5 (59.7) 2.35 - 15.8 [6.7]	9.5 ± 4.8 (50.0) 3.12 - 16.3 [8.955]	7.4 ± 4.0 54.5 3.7 - 14.2 [5.775]	5.1	6.4	8.4	6.6			
Vd/F (L)	4050 ± 1348 (33.3) 2430 - 6110 [3915]	3304 ± 1584 (47.9) 2200 - 6610 [2770]	5948 ± 3196 (53.7) 2410 - 10700 [5340]	5902 ± 6100 103.4 2470 - 18300 [3660]	3854	3062	5227	4469			
L/kg	51.5 ± 20.2 (39.2) 28.6 - 89.6 [48.3]	49.6 ± 26.0 (52.3) 26.3 - 104.3 [39.5]	72.2 ± 37.7 (52.2) 34.9 - 128.0 [61.3]	95.1 ± 119.9 126.1 34.2 - 338.9 [49.9]	48.3	45.2	64.3	63.2			
CL/F (L/hr)	122.6 ± 33.2 (27.1) 88.4 - 174 [112]	97.3 ± 39.0 (40.1) 57.5 - 157 [79.1]	128.1 ± 64.9 (50.7) 66.9 - 240 [117.5]	124.7 ± 69.1 55.4 58.5 - 259 [105.5]	118.8	90.9	115.6	112.3	0.765 0.533 – 1.10	0.974 0.669 – 1.42	0.945 0.649 – 1.38
t½ (hr)	23.1 ± 5.7 (24.6) 15 - 31.5 [23.25]	24.3 ± 6.8 (28.0) 12.3 - 33.7 [24.6]	33.3 ± 10.6 (31.8) 13.3 - 42.2 [36.35]	29.8 ± 12.9 43.3 17.1 - 48.9 [26.05]	22.5	23.3	31.3	27.6			

a tlqc not defined by sponsor, abbreviation may indicate 'Time of Last Quantifiable Concentration'.

Table 111 Individual Desmethyl-Asenapine Pharmacokinetic Metrics by Degree of Renal Impairment– Study A7501017

Groupa	Groupa	CLcr (mL/min)	Subject	Cmax (ng/mL)	Tmax (hr)	AUC(0-tlqc) (hr*ng/mL)	AUC(0-∞) (hr*ng/mL)	%AUC(0-∞) Extrapolated	λz (1/hr)	t½ (hr)	Fu
Renal Function Normal Renal Function Clcr* > 80.0 mL/min	1	85.6	10011026	0.454	5.93	10.1	12.5	19.0	0.0333	20.8	0.032
	1	109	10011032	0.308	2.95	6.77	9.26	26.9	0.0327	21.2	0.033
	1	96.8	10011033	0.220	8.0	8.34	12.0	30.8	0.0172	40.3	0.027
	1	94.8	10011034	0.720	7.93	20.1	22.4	10.1	0.0365	19.0	0.055
	1	125	10011037	0.248	8.07	6.89	8.21	16.0	0.0463	15.0	0.039
	1	88.7	10011040	0.274	12.0	8.99	11.7	23.3	0.0205	33.7	0.039
	1	87.4	10011041	0.712	12.0	18.0	21.2	15.1	0.0454	15.3	0.038
	1	109	10011042	0.343	12.0	13.2	16.9	21.5	0.0217	32.0	0.036
	1	90.0	10011045	0.310	6.00	6.76	7.90	14.4	0.0608	11.4	0.037
Mild Renal Insufficiency Clcr* ≥ 51.0 ≤ 80.0 mL/min	2	57.0	10011002	0.543	5.95	16.8	19.8	15.4	0.0286	24.2	0.032
	2	69.4	10011009	0.400	12.0	10.9	15.8	31.3	0.0300	23.1	0.095
	2	73.4	10011011	0.327	4.12	4.41	5.48	19.5	0.0520	13.3	0.044
	3	39.8	10011027	0.150	7.97	2.75	6.36	56.7	0.0266	26.0	0.04
	2	57.3	10011028	0.287	7.93	9.25	12.2	24.1	0.0372	18.6	0.029
	2	78.7	10011031	0.386	8.0	9.21	11.6	20.4	0.0370	18.7	0.028
	2	79.5	10011035	0.392	7.97	14.6	18.6	21.5	0.0223	31.1	0.031
	2	69.9	10011038	0.312	12.0	8.16	10.7	24.1	0.0332	20.9	0.028
	2	59.3	10011043	0.625	12.0	20.5	24.6	16.6	0.0256	27.1	0.032
Moderate Renal Insufficiency Clcr ≥ 30.0 & ≤ 50.0 mL/min	3	43.6	10011005	0.389	6.0	9.32	11.5	19.1	0.0349	19.9	0.039
	3	45.9	10011006	0.268	11.9	4.58					0.066
	3	46.6	10011012	0.159	5.97	2.58	4.28	39.6	0.0434	16.0	0.041
	3	47.5	10011014	0.265	24.0	17.9					0.036
	3	45.3	10011024	0.456	6.0	16.6	19.9	16.5	0.0242	28.6	0.032
	3	48.3	10011030	0.274	12.0	12.5	15.5	19.5	0.0196	35.3	0.047
	3	48.9	10011036	0.473	6.00	20.8	25.5	18.3	0.0266	26.0	0.036
Severe Renal Insufficiency † Clcr* < 30.0 mL/min	4	23.9	10011001	0.251	12.0	6.17	11.0	43.9	0.0272	25.5	0.036
	4	18.5	10011003	0.272	12.0	5.86	7.03	16.6	0.0581	11.9	0.046
	4	25.5	10011008	0.390	8.0	7.60	10.3	26.0	0.0284	24.4	0.039
	4	14.8	10011013	0.311	5.97	8.28	11.2	26.3	0.0279	24.9	0.038
	4	16.7	10011017	0.742	12.0	42.0					0.052
	4	18.4	10011018	0.396	12.0	13.0	15.0	13.2	0.0339	20.4	0.049
	4	21.5	10011020	0.162	12.0	4.49	7.49	40.1	0.0237	29.3	0.047
	4	23.4	10011023	0.114	12.0	2.87	5.68	49.5	0.0232	29.8	0.037

Table 112 Desmethyl-Asenapine Pharmacokinetic Metric Summary Statistics in Subjects with Varying Degrees of Renal Insufficiency after a Single 5 mg Sublingual Dose – Study A7501017

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
Group	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4	Mild : Normal	Moderate : Normal	Severe : Normal
CLcr Range	>80 mL/min	51 - 80 mL/min	30 - 50 mL/min	<30 mL/min	>80 mL/min	51 - 80 mL/min	30 - 50 mL/min	<30 mL/min			
N	9	8	8/6	8/7							
Tmax (hr)	8.32 ± 3.18 (38.2) 2.95 - 12 [8]	8.73 ± 2.98 (34.1) 4.12 - 12 [7.99]	9.99 ± 6.24 (62.5) 5.97 - 24 [6.99]	10.7 ± 2.38 (22.1) 5.97 - 12 [12]	7.68	8.24	8.78	10.4	0	-1	4
Cmax (ng/mL)	0.399 ± 0.192 (48.1) 0.22 - 0.72 [0.31]	0.409 ± 0.117 (28.7) 0.287 - 0.625 [0.389]	0.304 ± 0.124 (40.7) 0.15 - 0.473 [0.271]	0.33 ± 0.194 (58.7) 0.114 - 0.742 [0.292]	0.365	0.396	0.281	0.286	1.09 0.754 - 1.56	0.771 0.535 - 1.11	0.785 0.545 – 1.13
AUC_{0-t} (ng/mL)	11.0 ± 5.02 (45.6) 6.76 - 20.1 [8.99]	11.7 ± 5.21 (44.4) 4.41 - 20.5 [10.1]	10.9 ± 7.18 (66) 2.58 - 20.8 [10.9]	11.3 ± 12.8 (113) 2.87 – 42.0 [6.88]	10.2	10.7	8.34	7.95	1.05 0.61 - 1.81	0.822 0.477 – 1.42	0.783 0.455 – 1.35
AUC_{∞} (ng/mL x hr^{-1})	13.6 ± 5.4 (39.8) 7.9 - 22.4 [12]	14.9 ± 6.05 (40.8) 5.48 - 24.6 [14]	13.8 ± 8.1 (58.5) 4.28 - 25.5 [13.5]	9.67 ± 3.18 (32.9) 5.68 – 15.0 [10.3]	12.7	13.6	11.6	9.23	1.08 0.729 - 1.59	0.917 0.601 – 1.40	0.728 0.486 – 1.09
AUCextrap (%)	19.7 ± 6.57 (33.4) 10.1 - 30.8 [19]	21.6 ± 5.02 (23.3) 15.4 - 31.3 [21]	28.3 ± 16.4 (57.8) 16.5 - 56.7 [19.3]	30.8 ± 13.9 (45.2) 13.2 - 49.5 [26.3]	18.7	21.1	25.1	27.9			
$t_{½}$ (hr)	23.2 ± 9.85 (42.5) 11.4 - 40.3 [20.8]	22.1 ± 5.52 (24.9) 13.3 - 31.1 [22]	25.3 ± 6.77 (26.8) 16 - 35.3 [26]	23.8 ± 6.1 (25.7) 11.9 - 29.8 [24.9]	21.4	21.5	24.5	22.9			

Table 113 Asenapine Fraction Unbound by Degree of Renal Impairment – Study A7501017

Degree of Renal Function	Group 1 Normal >80 mL/min	Group 2 Mild 51 - 80 mL/min	Group 3 Moderate 30 - 50 mL/min	Group 4 Severe <30 mL/min
N	9	8	8	8
Summary Statistics	3.7 ± 0.8 (20.6) 2.7 - 5.5 [3.7]	4.1 ± 2.3 (55.4) 2.8 - 9.5 [3.2]	4.2 ± 1.1 (25.3) 3.2 - 6.6 [3.9]	4.3 ± 0.6 (14.4) 3.6 - 5.2 [4.3]
Geometric Mean	3.7	3.7	4.1	4.3

Figure 91 Fraction Unbound of Asenapine and Desmethyl-Asenapine vs. AUCinf by Renal Function – Study A7501017

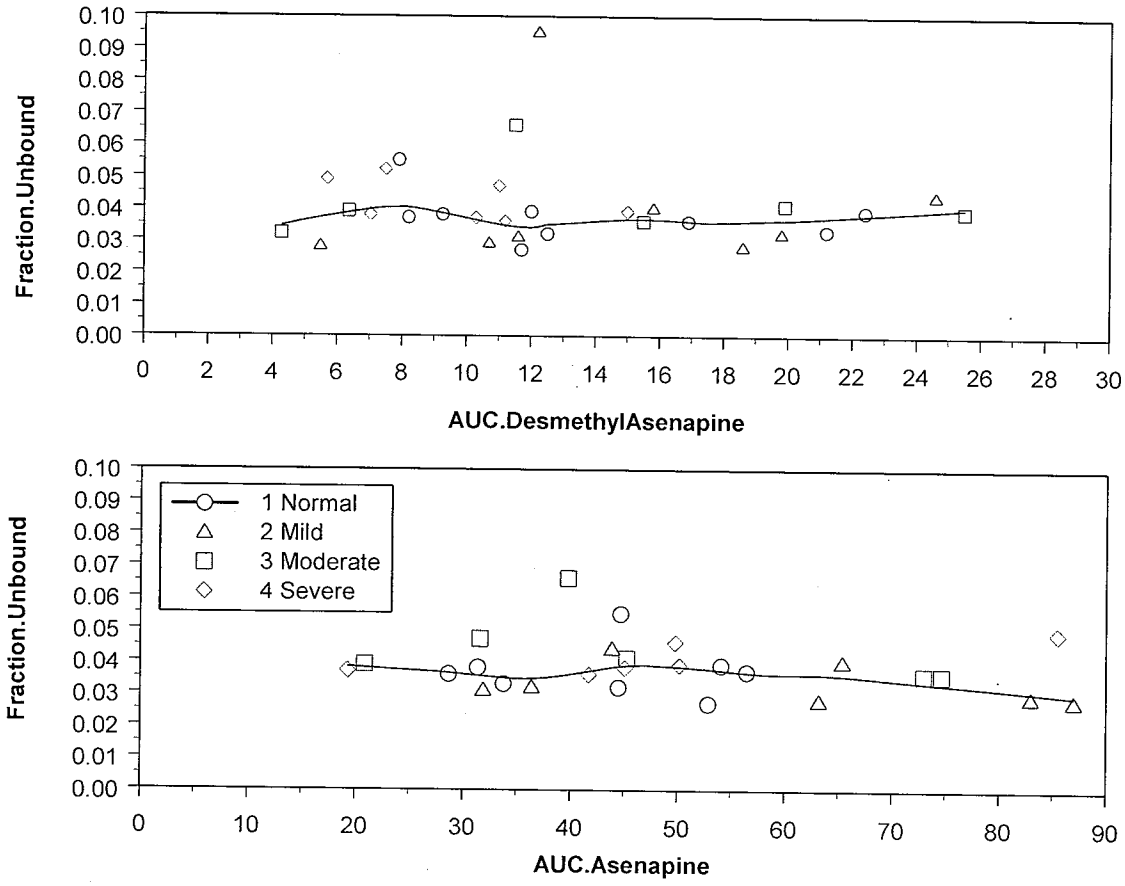


Figure 92 Desmethyl-Asenapine Unbound AUC vs. Creatinine Clearance – Study A7501017

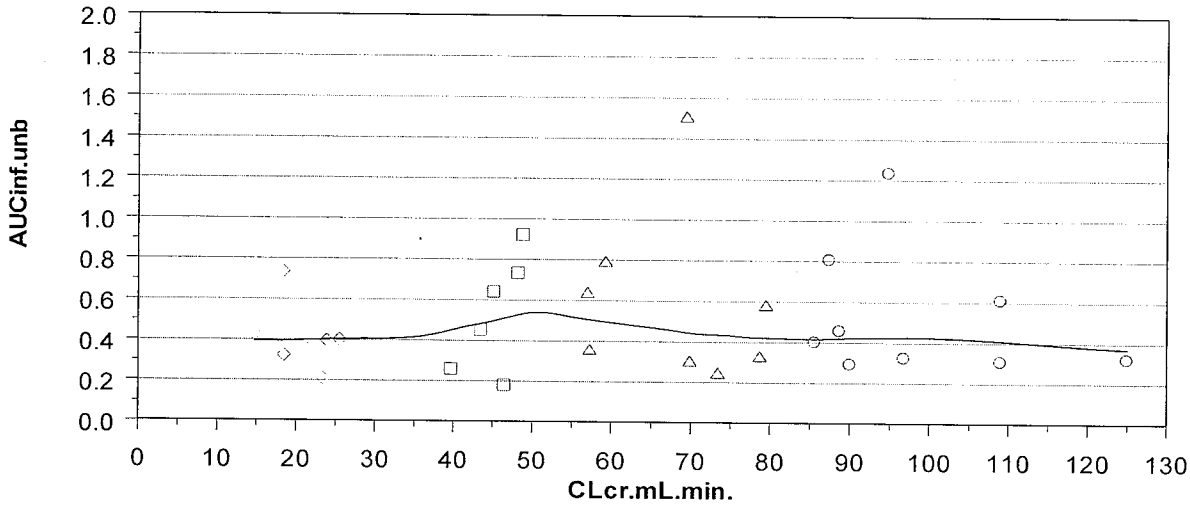


Figure 93 Desmethyl-Asenapine Total AUC vs. Creatinine Clearance – Study A7501017

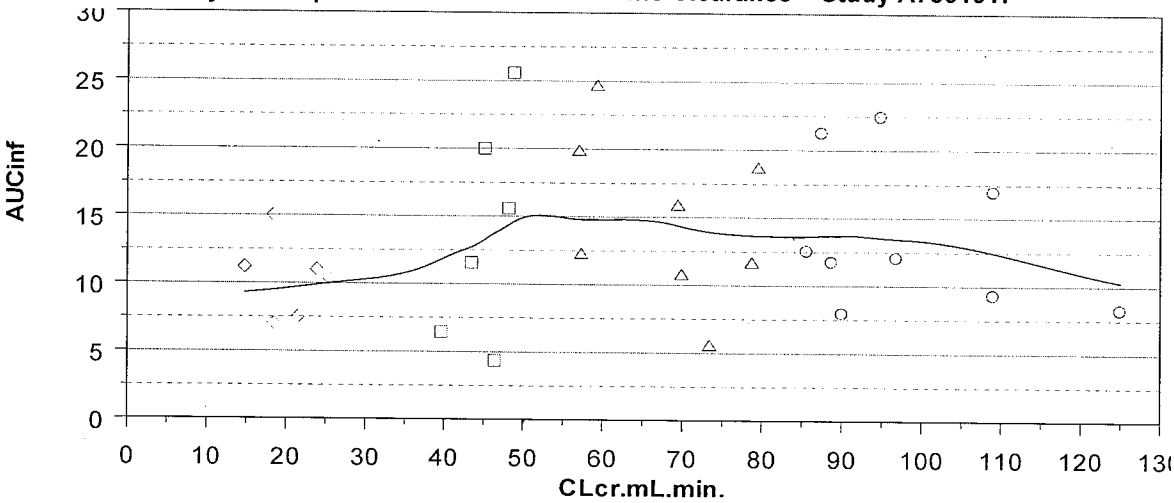
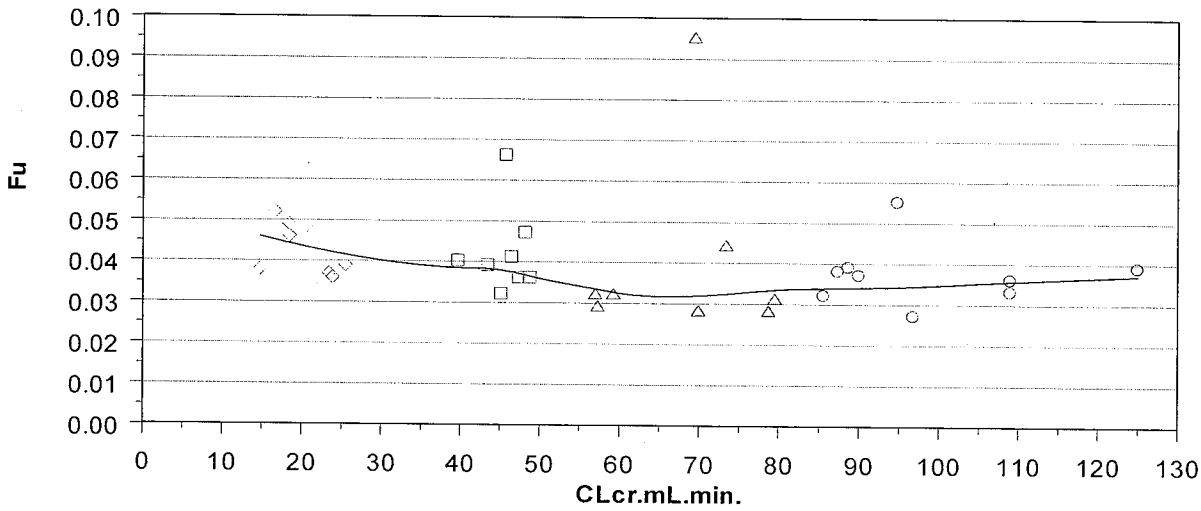


Figure 94 Asenapine Free Fraction vs. Creatinine Clearance



5.5.7 Extrinsic Factors

5.5.7.1 Effect of Water on Sublingual Bioavailability - Study 25537

Study 25537 examined the effect of drinking water at varying time intervals after a 10 mg QD dose of asenapine administered sublingually in 16 healthy male volunteers in a 4 x 4 latin square design.

As shown in Figure 95, Figure 96 and Table 114 there is little to no difference in mean exposures to asenapine and desmethyl-asenapine when water administration is administered 10 or 30 minutes after dose administration. However when water is taken less than 10 minutes after asenapine administration the exposure to asenapine decreases, presumably due to transfer of unabsorbed asenapine from the oral cavity to the stomach and increased first pass effect by way of GI absorption as compared to sublingual administration.

As an arm without water was not included and as dosing was QD rather than BID it is difficult to compare exposures in this study to exposures in other studies however, comparison of pharmacokinetic metrics of asenapine and desmethyl-asenapine from this study for the doses taken with water 10 or more minutes after the administration of asenapine as shown in shown in Table 114 appear to be comparable to their pharmacokinetic metrics when taken without water under a BID regimen, (see Table 53, Table 54, and Table 55).

Since, taking asenapine orally appears to be related to acute hepatotoxicity and since there appears to be a very narrow therapeutic index, water should not be taken for at least 10 minutes after the administration of asenapine.

Figure 95 Asenapine Mean Steady-State 0 – 6 hour Concentration vs. Time Profiles when Water is taken at Various Times after Drug Administration – Study 25537

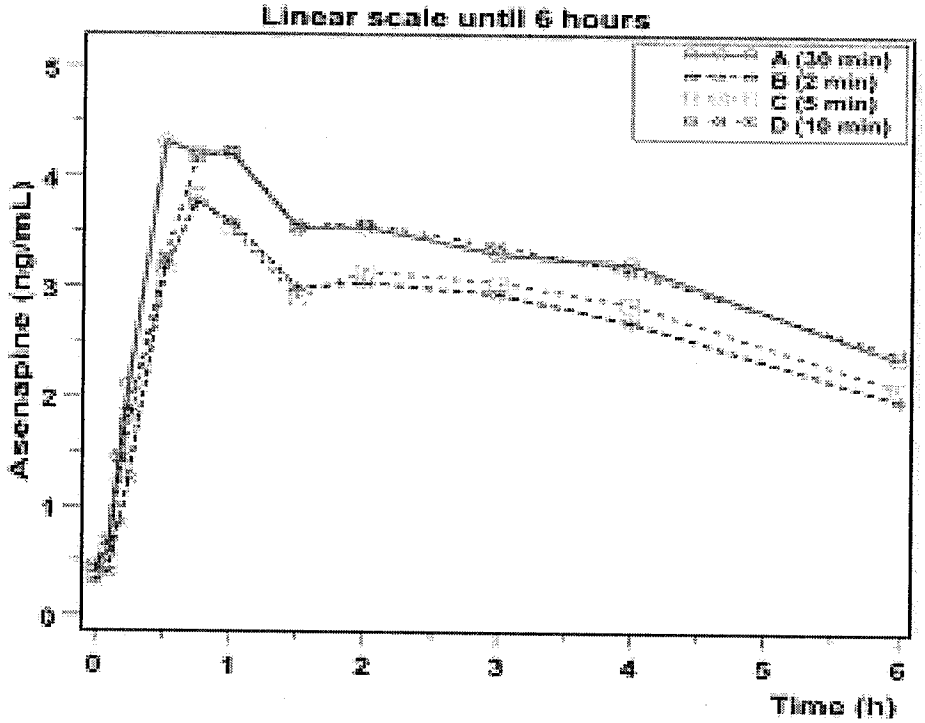


Figure 96 Asenapine Mean Steady-State 0 - 24 hour Concentration vs. Time Profiles when Water is taken at Various Times after Drug Administration – Study 25537

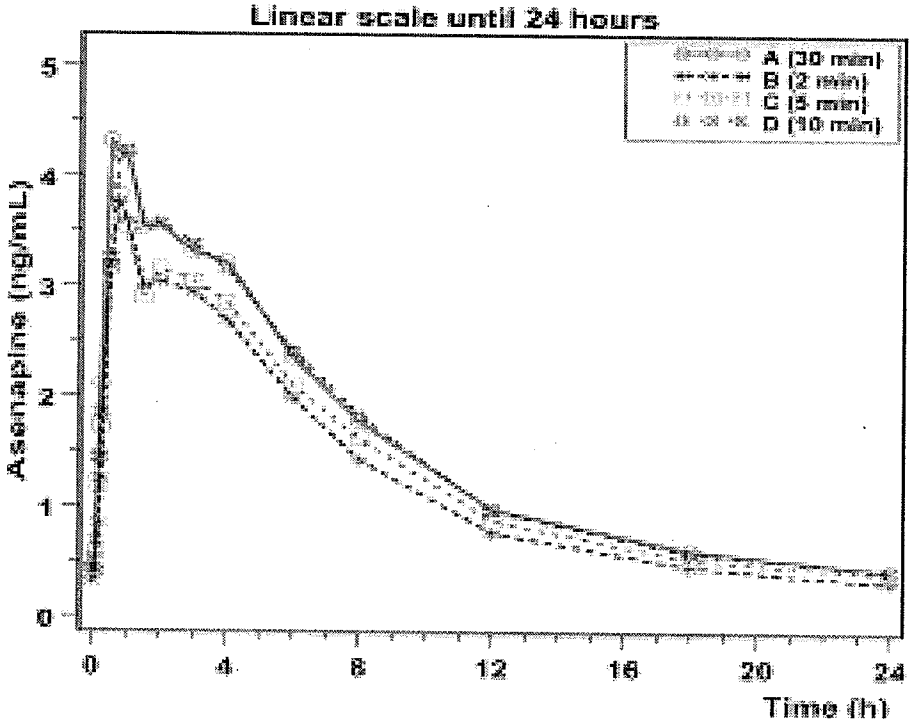


Table 114 Effect of Water at Varying Times on Asenapine and Desmethyl-aseanpine Pharmacokinetics after Asenapine 10 mg Sublingually – Study 25537

	Treatments				Geometric Mean Ratio (90% CI)		
	A (30 min)	B (2 min)	C (5 min)	D (10 min)	B : A	C : A	D : A
N	20	17	22	18			
Asenapine							
Tmax (h)	0.750 0.517 - 4.00	1.00 0.75 - 4.00	0.875 0.50 - 4.0	0.75 0.517 - 3.00			
Cmax (ng/mL)	4.99 ± 2.05	4.15 ± 2.09	4.38 ± 1.91	4.69 ± 2.22	0.79 0.62 - 1.01	0.88 0.69 - 1.12	0.98 0.77 - 1.24
AUC_{0-24} (ng*h/mL)	36.3 ± 11.3	29.8 ± 10.2	32.5 ± 11.1	35.9 ± 15.6	0.81 0.65 - 1.00	0.90 0.73 - 1.11	0.99 0.80 - 1.23
CL/f (L/h)	313 ± 149	414 ± 305	371 ± 241	354 ± 218			
wn - CL/f (L/h/kg)	4.01 ± 1.89	5.28 ± 3.84	4.80 ± 3.48	4.59 ± 3.05			
Cmin,av (ng/mL)	0.427 ± 0.135	0.309 ± 0.0927	0.390 ± 0.133	0.408 ± 0.196			
t½ (h)*	30.5 ± 8.20	27.6 ± 16.5	30.8 ± 12.4	37.4 ± 14.4			
Desmethyl-Asenapine							
Tmax (h)	6.00 2.03 - 8.02	6.00 2.00 - 8.02	4.00 2.00 - 12.0	6.00 2.00 - 12.0			
Cmax (ng/mL)	1.49 ± 0.867	1.49 ± 0.520	1.42 ± 0.642	1.38 ± 0.586	1.04 0.85 - 1.26	0.93 0.77 - 1.14	0.92 0.76 - 1.12
AUC_{0-24} (ng*h/mL)	23.4 ± 13.8	21.6 ± 7.49	20.6 ± 8.54	21.8 ± 9.90	0.95 0.80 - 1.14	0.86 0.72 - 1.03	0.92 0.77 - 1.10
Cmin,av (ng/mL)	0.492 ± 0.255	0.431 ± 0.181	0.415 ± 0.152	0.437 ± 0.227			
t½ (h)*	18.5 ± 4.21	13.9 ± 2.46	23.6 ± 7.38	15.4 ± 5.82			

* n=3 for B, n=4 for A and C and n=6 for D.
ANOVA based on n=15 subjects ('completers' group). ∫: population mean.
Source: Appendix BI, Listing 8 - 1 and 9 - 1.

5.5.7.2 *Effect of Charcoal on Relative Bioavailability – SL vs. Oral – Study 25540*

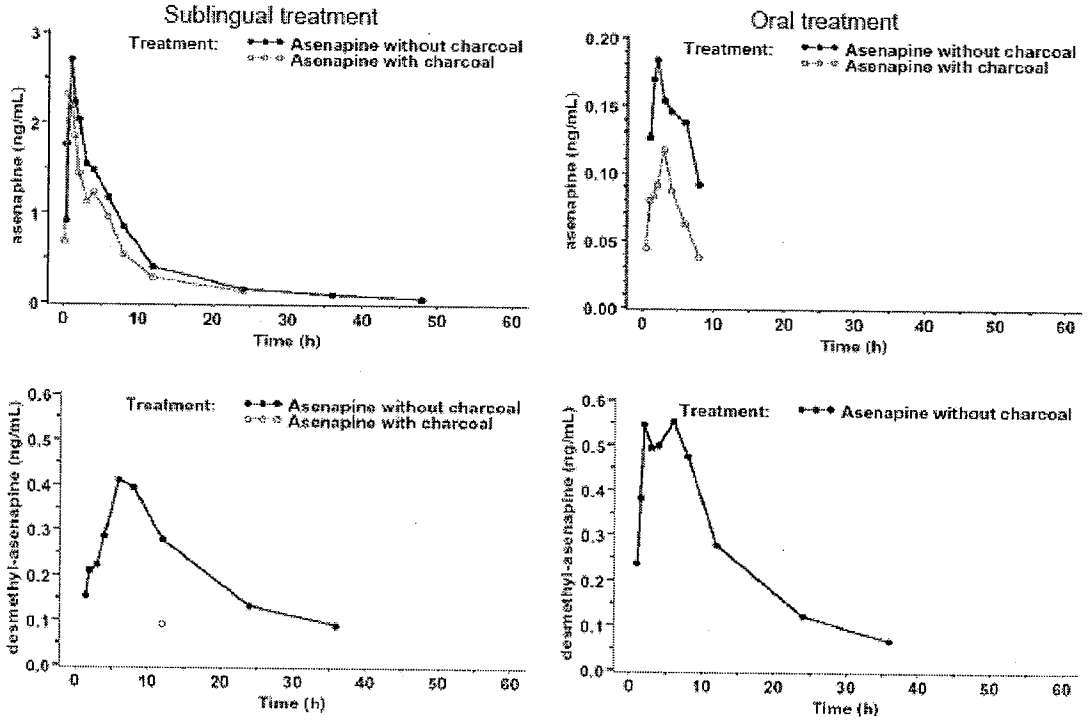
Study 25540 was an open label, randomized, parallel design single dose study in 16 healthy male volunteers to investigate the effect of concurrently administered activated charcoal to prevent gastro-intestinal absorption and to effect asenapine and desmethyl-asenapine pharmacokinetics after sublingual and oral administration of asenapine 5 mg.

Figure 97 and
Table 115 show the following:

- In the absence of activated charcoal, exposure to asenapine is lower after oral administration and peak exposure to desmethyl-asenapine is higher.
- After sublingual administration exposure to asenapine is only slighty affected by activated charcoal.
- In contrast after oral administration exposure to asenapine is significantly decreased by activated charcoal.
- Activated charcoal decreases exposure to desmethyl-asenapine after both sublingual and oral adminstration.

Although the results are specific to concurrently administered activated charcoal a similar effect albeit to a smaller degree is expected to delayed administration of activated. Thus activated charcoal should always be considered in an overdose situation with asenapine.

Figure 97 Asenapine and Desmethyl-Asenapine Mean Concentration vs. Time Profiles for Sublingual and Oral Administration of a Single 5 mg Dose when Administered with and without Activated Charcoal – Study 25540



Curves based on n = 7 subjects for the sublingual treatment and based on n=8 subjects for the oral treatment.

Data were taken from Figures 4.2-1 to 4.2-4 in Appendix BI.

Table 115 Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics for Sublingual and Oral Administration of a Single 5 mg Dose when Administered with and without Activated Charcoal – Study 25540

Route of Administration	Parameter (unit)	Asenapine		Desmethyl-Asenapine	
		with charcoal	without charcoal	with charcoal	without charcoal
Sublingual (n=7)	Tmax (h)	0.53 (0.33 - 2.0)	1.0 (0.5 - 2.0)	12.0 (8.00 - 12.0)	6.0 (4.0 - 8.0)
	Cmax (ng/mL)	2.58 (1.88)	3.02 (1.38)	0.0963 (0.0476)	0.428 (0.210)
	$AUC_{0\text{-tlast}}$ (ng·h/mL)	15.4 (12.0)	20.3 (5.75)	0.882 (0.981)	7.59 (4.13)
	$AUC_{0\text{-}\infty}$ (ng·h/mL)	16.2 (12.4)	21.3 (6.11)	—	10.3 ** (3.34)
	$t_{1/2}$ (h)	11.1 (5.46)	15.9 (5.04)	—	15.1 ** (4.32)
Oral (n=8)	Tmax (h)	3.0 (1.0 - 4.0)	2.0 (1.5 - 4.0)	—	3.00 (1.98 - 8.07)
	Cmax (ng/mL)	0.138 (0.0627)	0.204 (0.0791)	—	0.598 (0.117)
	$AUC_{0\text{-tlast}}$ (ng·h/mL)	0.612 (0.275)	1.38 (0.621)	—	8.38 (1.47)
	$AUC_{0\text{-}\infty}$ (ng·h/mL)	0.868 * (0.287)*	1.87 (0.768)	—	9.56 (1.63)
	$t_{1/2}$ (h)	4.19 * (0.671)*	6.75 (3.72)	—	10.5 (2.72)

* n = 7
** n = 6

5.5.7.3 *Effect of Food Administered Concurrently and 4 hours after Administration – Study 41029*

Study 41029 was an open-label, randomized, 3 way cross-over study to investigate the effect of a high-fat high-caloric meal eaten either concurrently or 4 hours after a single 5 mg sublingual dose of asenapine on the pharmacokinetics of asenapine and desmethyl-asenapine in 26 healthy males 18 - 55 years of age.

Although the control treatment was stated as being under fasted conditions, all subjects ingested 200 ml of a 'liquid breakfast' and 200 ml of an 'isotonic-sports' drink 1 hour prior to dosing.

All subjects received the following three treatments in randomized order:

Treatment A: Asenapine 5 mg SL "fasted"
Treatment B: Asenapine 5 mg SL after consumption of a high-fat meal. *
Treatment C: Asenapine 5 mg SL followed by a high-fat meal 4 h after dosing. *

* No further meals were allowed until 8 h post-dose

There was a seven day interperiod washout.

Figure 98, Figure 99, and Table 116 show not only that food decreases exposure to asenapine when administered concurrently (~ 20%), but also decreases exposures (but not peak concentrations) when administered 4 hours after the dose (~ 10%). However as this study was not conducted under true fasted conditions the magnitude of the decrease may actually be larger. As asenapine has a narrow therapeutic window with regards to hepatotoxicity even small changes and metabolic shunting could be clinically significant.

In fact the pattern of the concentration vs. time profiles indicated that this is likely due to an increase in clearance. Since asenapine is a high intrinsic clearance drug this may be due to slower blood flow through the liver and more stripping of drug off of plasma proteins as it passes through the liver or splanchic blood vessels.

Figure 98 Effect of Food Administration on Asenapine Mean Concentration vs. Time Profiles – Study 41029

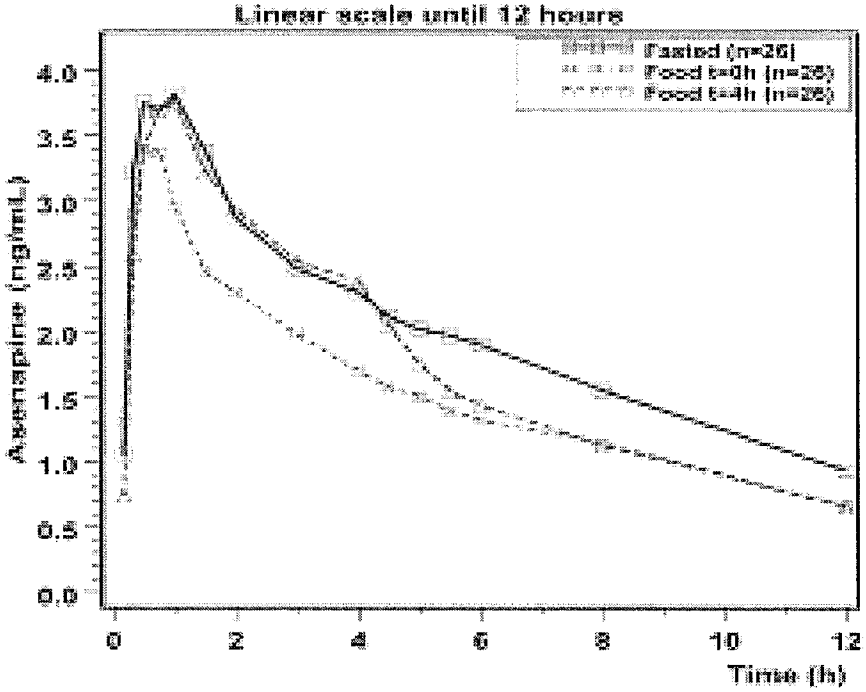


Figure 99 Effect of Food Administration on Desmethyl-Asenapine Mean Concentration vs. Time Profiles – Study 41029

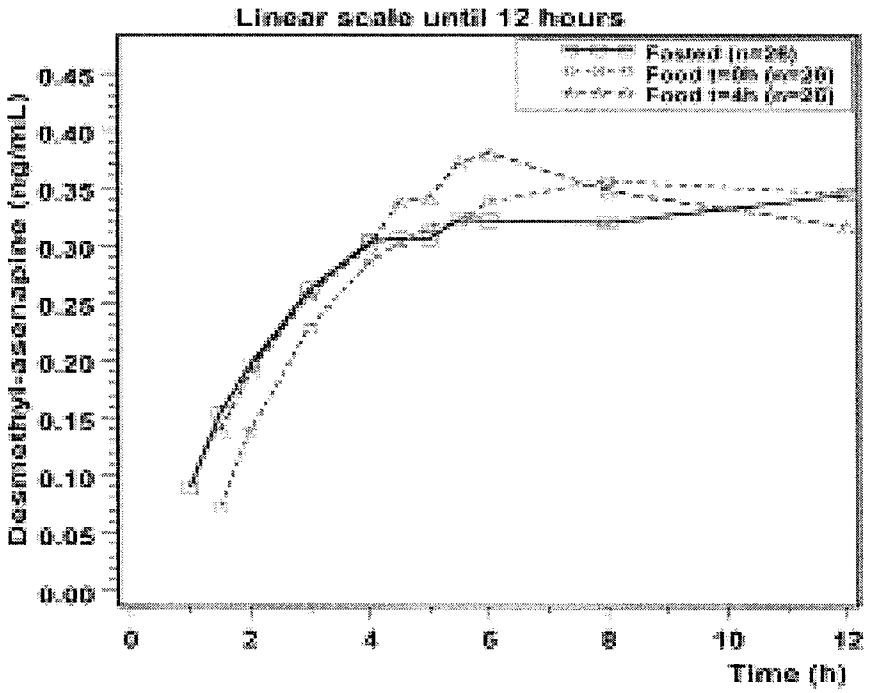


Figure 100 Effect of Food Administration on Asenapine Semi-log Mean Concentration vs. Time Profiles – Study 41029

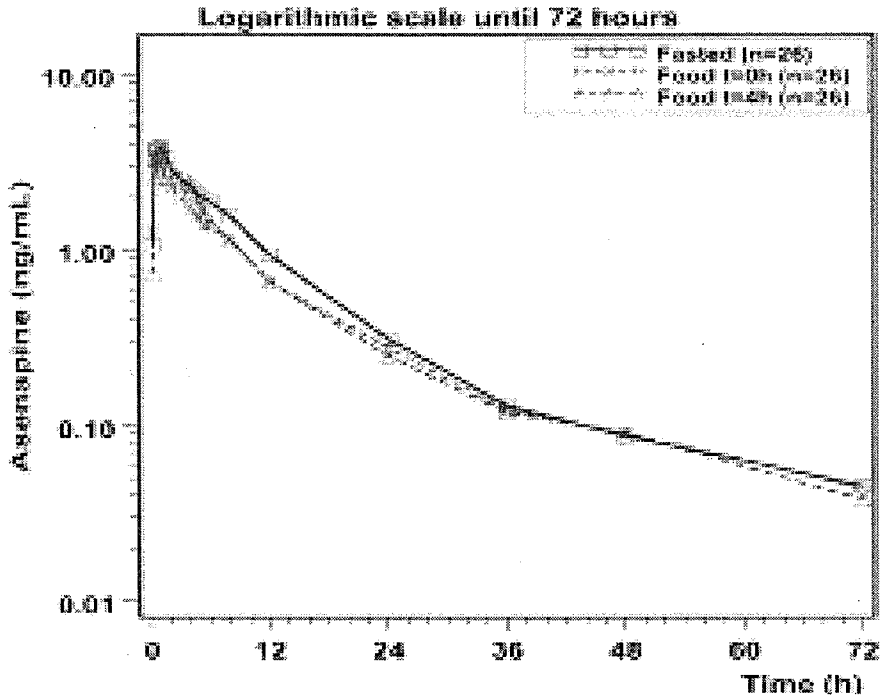


Figure 101 Effect of Food Administration on Desmethyl-Asenapine Semi-log Mean Concentration vs. Time Profiles – Study 41029

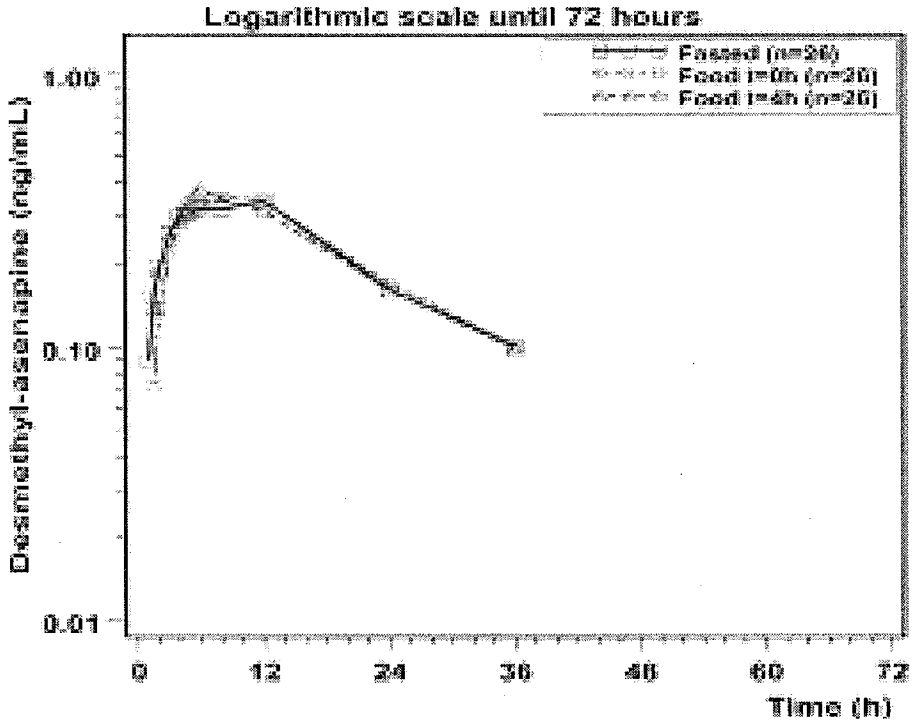


Table 116 Effect of Food on the Pharmacokineticsof Asenapine and N-Desmethyl-Asenapine after a Single Dose of Asenapine 5 mg Sublingually – Study 41029

Analyte (n)	Metric	Summary Statistics			Geometric Mean Ratios (90% CI)	
		(A) Fasted	(B) Fed t=0h	(C) Fed t=4h	B : A	C : A
Asenapine (n=26)	Tmax (h)	0.98 0.38 - 3.00	0.75 0.32 - 4.00	0.76 0.33 - 4.00		
	Cmax (ng/mL)	4.46 ± 2.57	3.89 ± 2.24	4.27 ± 2.10	0.90 0.73 - 1.11	1.02 0.83 - 1.26
	AUC∞ (ng/mL x hr^{-1})*	38.5 ± 15.6	30.8 ± 14.1	32.6 ± 11.7	0.79 0.66 - 0.94	0.87 0.73 - 1.03
	CL/f (L/h)*	163 ± 107	203 ± 105	182 ± 95.0		
	wn - CL/f (L/h/kg)*	2.16 ± 1.44	2.71 ± 1.57	2.44 ± 1.44		
	t½ (h)*	22.4 ± 12.3	22.6 ± 10.2	20.6 ± 6.75		
N - Desmethyl - Asenapine (n=26)	Tmax (h)	7.00 4.00 - 12.0	7.9 8.00 - 12.0	6.00 3.00 - 12.0		
	Cmax (ng/mL)	0.395 0.167	0.402 ± 0.139	0.407 ± 0.192		
	AUC∞ (ng/mL x hr^{-1})*	10.9 ± 3.68	11.0 ± 3.30	10.9 ± 4.23		
	CL/f (L/h)*	489 ± 182	478 ± 163	634 ± 829		
	wn - CL/f (L/h/kg)*	6.60 ± 3.13	6.37 ± 2.54	8.16 ± 10.3		
	t½ (h)*	16.4 ± 7.03	16.3 ± 5.81	15.6 ± 5.28		

Presented mean refers to arithmetic mean.

* for N - desmethyl - asenapine n=24 for Treatments A and B and n=23 for Treatment C.

5.5.7.4 Effect of Smoking a Cigarette in Chronic Smokers on Asenapine – Study 25545

Study 25545 was an open label, randomized, two-way cross-over, bioequivalence trial to assess the effect of smoking during sublingual asenapine dosing on the pharmacokinetics of asenapine and desmethyl–asenapine after a single 5 mg sublingual dose of asenapine in 24 healthy, smoking male volunteers aged 18 - 45 years.

During the smoking phase of the study the subjects smoked from 5 minutes before to 10 minutes after asenapine administration.

Although asenapine is a CYP1A2 substrate the effect of smoking on the presumed product of this enzyme, 11-hydroxy-asenapine was not measured.

In addition to induction, smoking causes vasoconstriction and might be expected to decrease absorption acutely even in this population, however this was not seen, (see Figure 102, Figure 103, and Table 117).

In conclusion no effect of smoking was seen on the pharmacokinetics of asenapine or desmethyl-asenapine, although as the study was conducted in smokers no decrease in exposure is expected as subjects are already induced. In spite of this the presence of induction the low peak concentrations and AUCs seen in this study may be indirect evidence of induction (see Figure 102, Figure 103, and Table 117).

However, the effect of smoking in a non-induced population of non-smokers is still unknown. As schizophrenics tend to be heavy smokers the effect of smoking is more likely to be evident in patients with bipolar illness or if the drug is used off label for schizoaffective disorder where intermittent smoking may be more relevant.

Figure 102 Mean Concentration vs. Time Profiles of Asenapine in Chronic Smokers While Smoking and Not Smoking - Study 25545

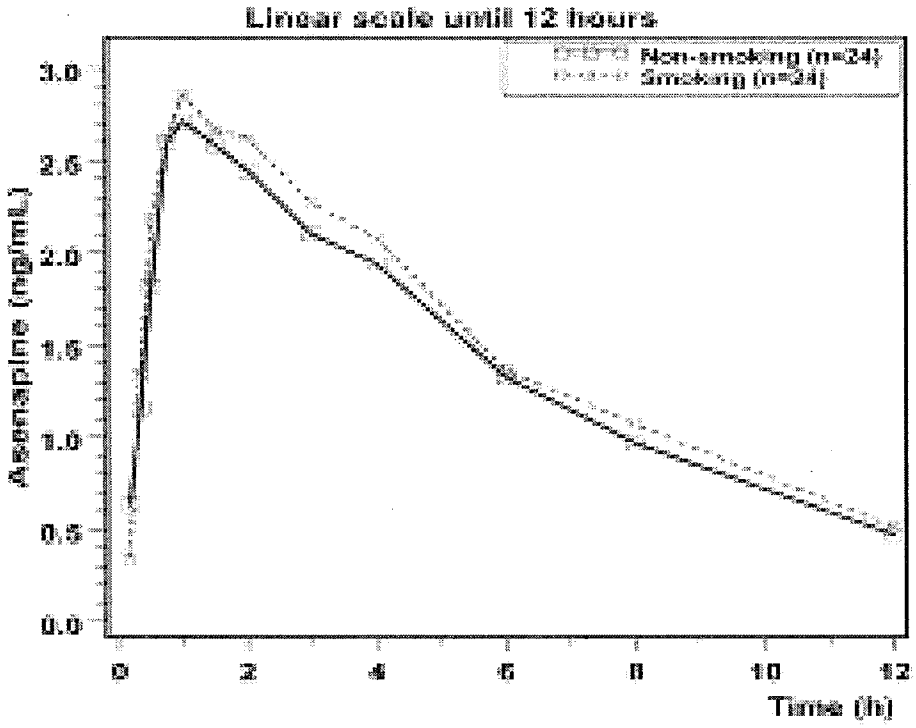


Figure 103 Mean Concentration vs. Time Profiles of Desmethyl-Asenapine in Chronic Smokers While Smoking and Not Smoking - Study 25545

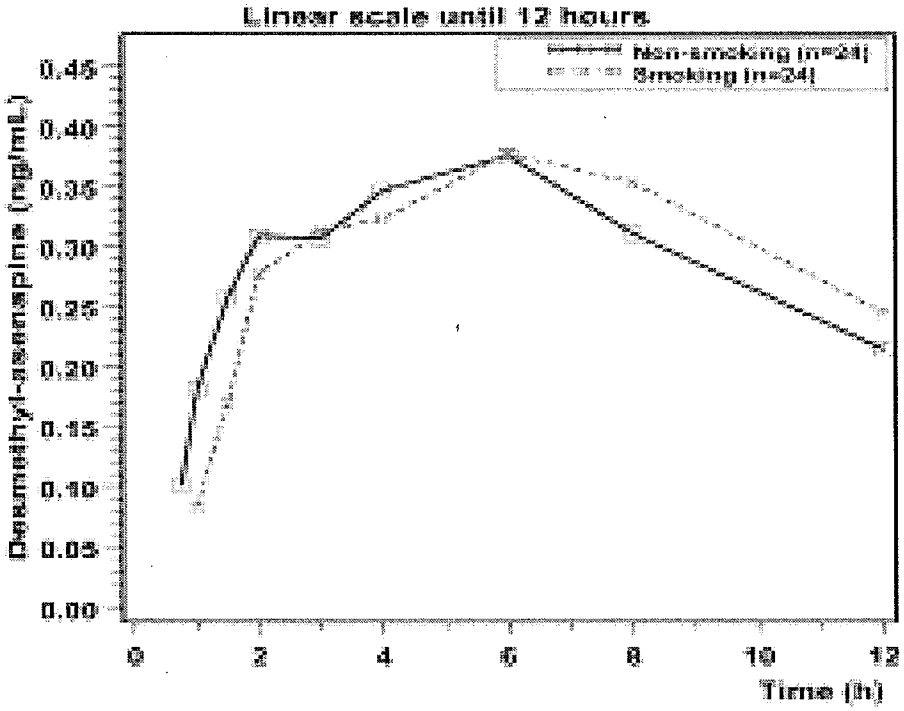


Table 117 Effect of Smoking a Cigarette on Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics in Chronic Smokers – Study 25545

	Asenapine			Desmethyl-Asenapine		
	Summary Statistics		GMR (90% CI)	Summary Statistics		GMR (90% CI)
	A: (+)-Cigarette	B: (-)-Cigarette	A:B With: Without Cigarette	A: (+)-Cigarette	B: (-)-Cigarette	A:B With: Without Cigarette
N	24	24	–	24	24	–
Tmax (h)	1.0 0.5 - 4.0	1.0 0.5 - 4.0	–	6.0 2.08 - 8.0	6.0 1.02 - 8.0	–
Cmax (ng/mL)	3.16 ± 1.73	3.00 ± 1.51	1.02 0.87 - 1.20	0.423 ± 0.153	0.427 ± 0.175	–
$AUC_{0-\infty}$ ($ng/mL \times hr^{-1}$)	25.6 ± 11.2	24.3 ± 10.1	1.06 0.91 - 1.24	7.33 ± 2.18 [a]	6.81 ± 2.01	–
CL/f (L/h)	237 ± 115	254 ± 139	–	n.c.	n.c.	–
wn - CL/f (L/h/kg)	3.16 ± 1.50	3.42 ± 1.95	–	n.c.	n.c.	–
$t_{1/2}$ (h)	15.8 ± 12.1	17.1 ± 10.7	–	10.91 ± 2.971	11.1 ± 3.76	–

Presented mean refers to arithmetic mean. n.c.= not calculated
a n=23
Source: Appendix BI, Table 5 - 2.1.

5.5.7.5 Drug - Drug Interactions

5.5.7.5.1 Effect of Imipramine and Asenapine on Each Other - CYP2D6 Competitive Inhibition – Study 25526

This was a single centre, open label, randomized, six-sequence, three-period cross-over study in 24 healthy male subjects aged 18 - 55 years of age, in which a single dose of asenapine 5mg SL or imipramine 75 mg po was each administered alone or simultaneously. Treatments were as follows:

Treatment A Asenapine 5 mg SL x 1 alone
Treatment B Imipramine 75 mg PO x 1 alone
Treatment C Combined treatment of Asenapine 5 mg SL x 1 and Imipramine 75 mg PO x 1

As per the protocol imipramine was dosed after asenapine:

During treatments B and C, 50 mL of water was given with the imipramine dose.
In the combination treatment arm [C] imipramine was administered immediately before the asenapine dose.
During treatment A, 50 mL of water was given prior to asenapine dosing."

There was a washout period of at least 1 week between successive drug administrations.

The pharmacokinetics of asenapine and N-desmethyl asenapine was assessed in absence and presence of imipramine and the pharmacokinetics of imipramine and desipramine assessed in absence and presence of asenapine. Plasma samples were obtained through 72 hours.

Demographic characteristics are shown in Table 118.

Table 118 Demographic Characteristics at Screening All Subjects - Treated Group – Study 25526

N	Age [years]	Body Weight [kg]	Height [cm]	Body Mass Index [kg/m^2]
25	35 ± 12 18 - 54 [37]	78.6 ± 9.5 59.7 - 96.9 [77.3]	181 ± 6.8 165 - 194 [181]	24.1 ± 2.7 19.1 - 29.8 [24.3]

No differences in pharmacokinetics were shown between groups, (see Table 119 and Table 120), although there was trend for higher asenapine concentrations (~10%) in the presence of imipramine. However this was a single dose study and asenapine is a mechanism based inhibitor. Consequently when the drugs are administered simultaneously there may not be time for inactivation of CYP2D6 by asenapine to occur. Although the rationale for dosing imipramine prior to asenapine is so that ingestion of water will not send asenapine to the stomach this is also likely to minimize inhibition because

a) Imipramine is administered first
b) Inhibition is more likely to occur with oral administration both due to the higher asenapine concentrations in the liver during first pass as well as the presentation of asenapine first if it were to be administered first.

Consequently, the multiple dose study with paroxetine, study 25525, is more applicable to the actual clinical dosing in practice.

In addition, the low dose of asenapine used, 5 mg will also minimize presentation to the GI tract and subsequent mechanism based inhibition.

One possibility that was considered was the possibility that any effect of asenapine that might be evident in a delay in Tlag for desipramine in the asenapine treated group. Such as effect is seen, however a delay in Tlag for imipramine is also evident, (see Table 120, Table 121, and Figure 104). Consequently there is no clear evidence for competitive inhibition from the present study, however this does not preclude mechanism based noncompetitive inhibition, (see §5.5.7.5.2).

It should be noted that subject 008 was discontinued from the study for smoking however approximately 48 hours after taking imipramine he was found unconscious. Although according to the records it appears the cause might have been drinking and cannabis use, as according to the records he remembered the following:

'passing out at the train station and waking up in the hospital. He could not recall how and when he left neither the hospital, nor a conversation with the physician about a diagnosis. He recalled walking around town in Nijmegen all day long, feeling "out off the world". He apparently spent the night in a nearby hotel." '

"Physical examination was performed; an agitated, drunk man with a few cuts and bruises. He smoked constantly; there were no signs of psychosis or neurologic abnormalities. ECG, standing and supine vital signs were normal, heart rate elevated (98 bpm).

Laboratory results were not clinically relevant abnormal, except for an alcohol promillage of 2.2%. Due to agitation, a urine drug screen was not performed."

Upon examination this subject had the 4th highest exposures to imipramine and desipramine both by Cmax and 24 hour concentrations. This raises the possibility that this was at least partially due to the imipramine.

Examination of AEs with structurally similar compounds, indicate that some cause extreme sedation and when used in combination with alcohol or other CNS depressants can cause varying degrees of coma. Asenapine in some studies was described as causing severe somnolence. Consequently, this might be a pharmacokinetic and / or pharmacodynamic interaction.

Table 119 Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics in the Presence and Absence of Imipramine - Study 25526

Analyte	Asenapine					Desmethyl-Asenapine				
Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)
Parameter (unit)	Asenapine	Asenapine + Imipramine	Asenapine	Asenapine + Imipramine		Asenapine	Asenapine + Imipramine	Asenapine	Asenapine + Imipramine	
n	24	24	–	–	23	24	24	23	–	–
Tmax (h)	0.75 0.50 - 3.0	0.875 0.50 - 2.0	–	–	–	6.00 2.00 - 8.05	3.0 1.5 - 12.0	–	–	–
Cmax (ng/mL)	4.87 (34.1) 2.67 - 9.01	5.39 (36.6) 0.874 - 10.5	4.56	5.33	1.17 1.05 - 1.30	0.490 (33.5) 0.313 - 1.08	0.541 (28.3) 0.299 - 0.881	0.476	0.521	1.09 1.03 - 1.17
AUCtlast (ng/mL x hr^{-1})	35.4 (27.3) 19.5 - 52.1	36.4 (24.6) 8.93 - 50.1	33.8	36.9	1.09 1.01 - 1.18	10.1 (37.7) 5.74 - 23.3	10.2 29.3 5.73 - 17.4	9.59	9.77	1.02 0.95 - 1.09
AUC∞ (ng/mL x hr^{-1})	38.1 (29.4) 21.9 - 63.8	39.2 (25.2) 10.3 - 54.6	36.1	39.7	1.10 1.01 - 1.20	11.7 (34.8) 7.04 - 25.2	12.1 (29.1) 7.13 - 20.0	11.1	11.6	1.04 0.98 - 1.11
CL/F (L/h)	143 (28.9) 78.3 - 228	144 (54.6) 91.5 - 488	–	–	–	445 (28.0) 188 - 675	427 (28.4) 238 - 667	–	–	–
Vz/F (L)	4934 (54.6) 1138 - 12392	5391 (48.1) 2186 - 10964	–	–	–	9085 (29.6) 3331 - 15967	9181 (45.6) 4338 - 26230	–	–	–
t½ (h)	25.5 (59.9) 8.13 - 66.8	28.7 (56.4) 9.94 - 83.0	–	–	–	14.6 (28.6) 9.29 - 24.3	15.4 (40.0) 9.07 - 34.2	–	–	–

Values are mean (%CV) range expect for Tmax where values are median and range.

Table 120 Imipramine and Desmethyl- Imipramine Pharmacokinetic Metrics in the Presence and Absence of Asenapine - Study 25526

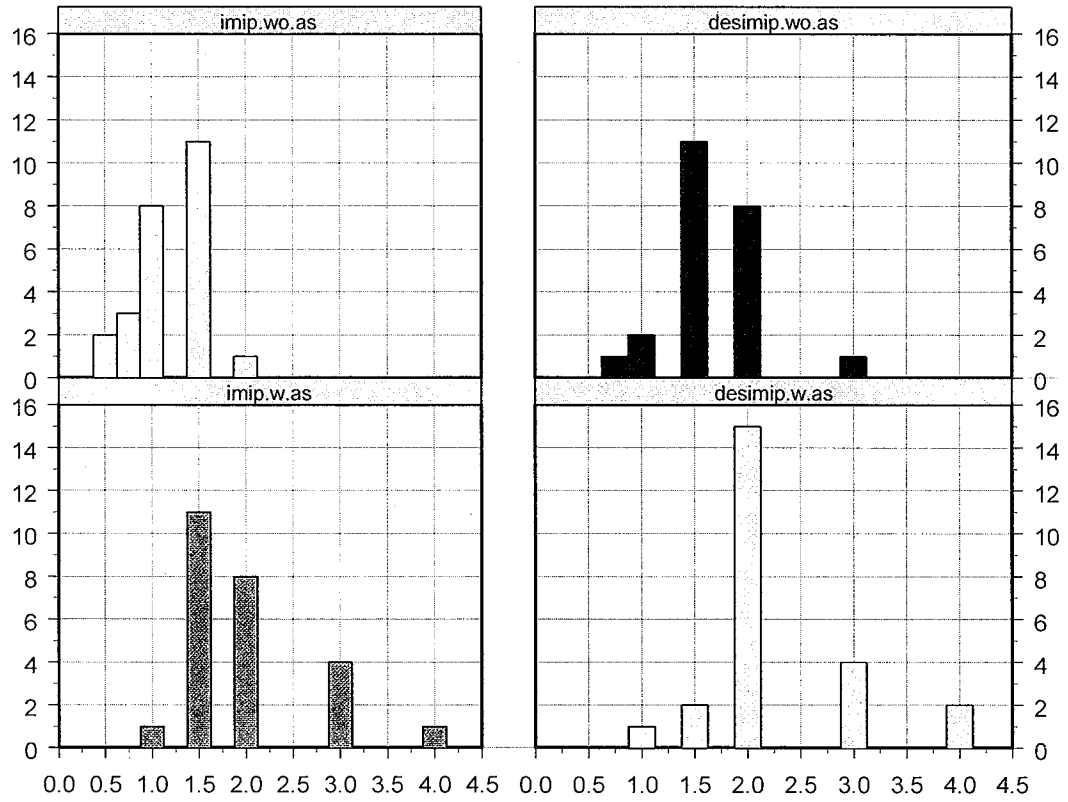
Analyte	Imipramine					Desipramine				
Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)
Parameter (unit)	Imipramine	Asenapine + Imipramine	Imipramine	Asenapine + Imipramine		Imipramine	Asenapine + Imipramine	Imipramine	Asenapine + Imipramine	
n	24	24				24	24			
Tlag (h)	1.0 0.5 – 2.0	2.0 1.0 – 4.0				1.5 0.75 – 3.0	2.0 1.0 – 4.0			
Tmax (h)	2.50 1.50 - 4.00	2.00 1.50 - 4.00				3.00 1.50 - 24.0	4.00 1.50 - 24.2			
Cmax (ng/mL)	44.6 (47.1) 10.4 - 98.7	45.0 (44.4) 17.7 - 83.8	41.9	42.0	1.00 0.91 - 1.11	12.8 (45.4) 3.45 - 25.3	13.4 (37.1) 6.22 - 23.4	12.2	12.7	1.04 0.98 - 1.11
AUCtlast (ng/mL x hr^{-1})	483 (60.5) 64.3 - 1060	505 (56.4) 164 - 1153	423	440	1.04 0.97 - 1.12	463 (87.0) 11.4 - 1390	466 (78.3) 78.8 - 1235	340	343	1.01 0.96 - 1.06
AUC∞ (ng/mL x hr^{-1})	542 (58.2) 91.4 - 1175	571 (56.7) 183 - 1364	483	501	1.04 0.97 - 1.10	801* (102) 154 - 3223	889 (105) 133 - 3461	521	560	1.08 0.99 - 1.17
CL/F (L/h)	210 83.1) 63.9 - 820	173 (52.5) 55.0 - 410				191* (71.3) 22.1 - 463	185 (74.9) 20.6 - 537			
Vz/F (L)	2956 (40.7) 1358 - 6788	2902 (30.4) 1175 - 4507				6334* (51.3) 2641 - 16095	6442 (45.3) 2687 - 14757			
t½ (h)	12.3 (37.7) 4.68 - 23.1	13.7 (44.5) 6.87 - 31.7				32.9* (58.1) 12.6 - 82.8	41.4 (96.1) 13.7 - 190			

Values are mean (%CV) range expect for Tmax where values are median and range.

Table 121 Runs Analysis for Lag Times for Imipramine and Desipramine in the Absence and Presence of Asenapine – Study 25526

	Asenapine	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Imipramine	-	2	1	1.5	0.75	1.5	1.5	1.5	1.5	1	1	1.5	0.5	1	1	0.75	1	1.5	0.75	1.5	1.5	1.5	1	0.5	1	1.5
	+	2	1	2	1.5	1.5	2	1.5	1.5	2	2	3	2	1.5	2	2	1.5	4	1.5	1.5	3	3	3	1.5	1.5	1.5
	Runs	*	*	+	+	*	+	*	*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*
Desipramine	-	3		2	1	1.5	2	2	1.5	1.5	2	2	2	1.5	1.5	1.5	1.5	2	1		1.5	1.5	1.5	0.75	1.5	2
	+	3		4	2	2	4	2	2	2	2	3	2	2	2	2	2	3	1.5	1	2	2	3	1.5	2	2
	Runs	*		+	+	+	+	*	+	+	*	+	*	+	+	+	+	+	+		+	+	+	+	+	+

Figure 104 Comparison of Tlags for Imipramine and Desipramine in the Absence and Presence of Asenapine – Study 25526[a]



a imip = imipramine; desimip = desipramine; as = asenapine; w = with; wo = without

5.5.7.5.2 CYP2D6 Interactions - Study 25525

Study 25525 was an open label, randomized, parallel group, pharmacokinetic interaction trial between asenapine, paroxetine and dextromethorphan in healthy male subjects aged 18 – 55 years of age.

Treatments were as follows:

Treatment Sequence A:	Day 1:	Paroxetine 20 mg PO x 1
	Days 4 - 16:	Asenapine 5 mg SL BID
	Day 12:	Dextromethorphan 30 mg x 1
	Day 14:	Paroxetine 20 mg PO x 1
Treatment Sequence B:	Day 2:	Asenapine 5 mg SL x 1
	Days 7 - 15:	Paroxetine 20 mg PO QD
	Day 11:	Dextromethorphan 30 mg x 1
	Day 13:	Asenapine 5 mg SL x 1

Seventeen subjects were included in sequence A and there were thirteen completers.

Thirty subjects were included in sequence B and there were twenty-six completers.

In both arms the 8 hour Urinary Metabolic Ratio of DX to DM was determined at screening and during treatment.

The single dose pharmacokinetics of paroxetine, asenapine, and desmethyl-asenapine were assessed.

The sponsor used inconsistent nomenclature throughout the report for the two sequences. Table 122 shows the study design and the nomenclatures used for this report.

Table 122 Study Design for Paroxetine / Asenapine Drug-Drug Interaction Study - Study 25525

Objective		Effect of Asenapine on Paroxetine & Dextromethorphan		Effect of Paroxetine on Asenapine & Dextromethorphan	
Nominal Designations Used	*Treatment Sequence*	A		B	
	CSR Statistical Analysis Arm[8]	B		A	
	PK Report SAS Analysis Arm	A		B	
	Treatment Arm	A		B	
	Pharmacokinetic Arm	A		B	
Treatments	*Screening*	DM 30 mg PO to determine 8 hour DX:DM UMR		DM 30 mg PO to determine 8 hour DX:DM UMR	
	Day 1		Paroxetine 20 mg SD		Placebo
	Day 2				Asenapine 5 mg SL
	Day 3		Placebo		
	Day 4	Asenapine 1 mg SL BID			
	Day 5	Asenapine 3 mg SL BID			
	Day 6	Asenapine 5 mg SL BID		Paroxetine 20 mg PO QD	
	Day 7				
	Day 8				
	Day 9				
	Day 10				
	Day 11				DM 30 mg PO to determine 8 hour DX:DM UMR
	Day 12		DM 30 mg PO to determine 8 hour DX:DM UMR		
	Day 13		Placebo Paroxetine		Placebo Asenapine
	Day 14		Paroxetine 20 mg SD		Asenapine 5 mg SL
	Day 15				
	Day 16				

[8] The reversal of the nominal designation was per the clinical study report. The statistical report and these nomenclature were used to assign the the precipitant to Table 127 and Figure 109 for the effect on dextromethorphan as the labeling that the sponsor used on tables was confusing. After the briefing on May 12, 2008 it was discovered that this reversal of the coding did not occur after all and the attribution of the effects of asenapine and paroxetine had been reversed. It has therefore been corrected in this final version.

5.5.7.5.2.1 *Evaluation of Asenapine as a CYP2D6 Inhibitor (Effect of Asenapine on Paroxetine)*

In sequence A (aka Arm B; aka Concentration Profile Arm A), the effect of multiple doses of asenapine on the (single dose) pharmacokinetics of paroxetine was studied. In addition, the effect of asenapine on the metabolic ratio of dextromethorphan as a probe substrate for CYP2D6 was investigated. The baseline Dextromethorphan : Dextorphan (DM/DX) ratio was determined at screening. Paroxetine 20 mg was administered as a single dose on day 1 and placebo on day 3. On Day 4 titration with asenapine SL BID was begun and 5 mg SL BID was administered from days 6 – 16. On Day 12, dextromethorphan (30 mg single dose) was co-administered, and on Day 13 and 14, single doses of placebo and paroxetine 20 mg PO were administered respectively.

As shown in Figure 105 and Table 123 asenapine 5 mg SL BID approximately doubles both the exposure and peak concentrations of paroxetine.

Figure 105 Single Dose Concentration vs. Time Profiles of Paroxetine 20 mg in the Absence of and Presence of Asenapine 5 mg BID in CYP2D6 Extensive Metabolizers – Study 25525

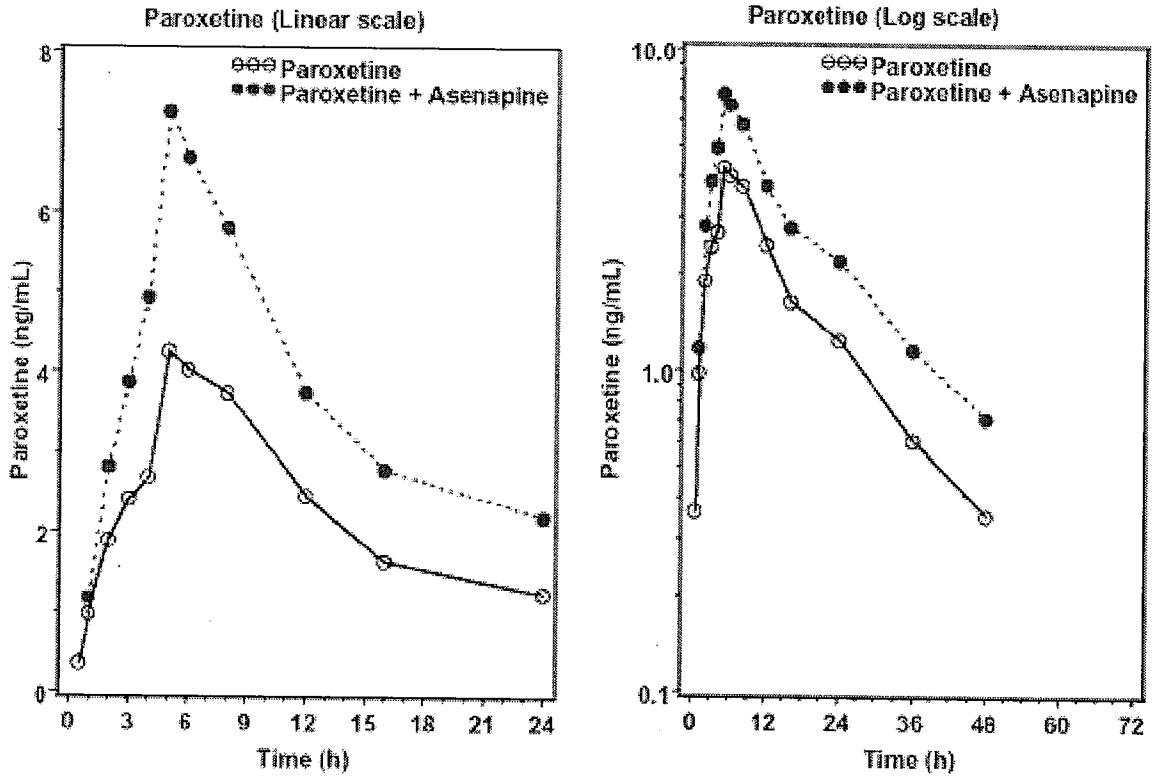


Table 123 Effect of Asenapine 5 mg SL BID on the Pharmacokinetics of Paroxetine 20 mg – Study 25525

	Summary Statistics		Geometric Means		Paroxetine +/- Asenapine Geometric Mean Ratio (90% CI)
	Paroxetine	Paroxetine & Asenapine	Paroxetine	Paroxetine & Asenapine	
N	15	15	15	15	–
Tmax (h)	5.6 ± 2.06 (36.8) 1.02 - 8 [6]	5.2 ± 1.08 (20.8) 3 - 8 [5]	5.03	5.1	–
Cmax (ng/mL)	4.46 ± 3.93 (88) 0.673 - 13.5 [2.72]	7.49 ± 5.83 (77.8) 1.93 - 21.9 [5.49]	3.15	5.73	1.82 1.59 - 2.09
AUCtlast (ng/mL x hr^{-1})	74.1 ± 79.2 (107) 7.65 - 241 [40.6]	128 ± 127 (99.5) 21.2 - 426 [86.4]	43.2	83.7	1.94 1.71 - 2.20
AUC∞ (ng/mL x hr^{-1})	77.7 ± 80.9 (104) 8.62 - 245 [42.9]	136 ± 137 (101) 23.7 - 470 [92.3]	46.9	90	1.92 1.70 - 2.17
AUCextrap (%)	7.71 ± 4.94 (64) 1.56 - 18.6 [5.38]	6.82 ± 5.07 (74.4) 1.77 - 22.7 [6.39]	6.41	5.54	–
Tlast (h)	47.2 ± 16 (33.9) 24 - 72 [48]	52.8 ± 15.6 (29.5) 24 - 72 [48]	44.5	50.5	–
CL/F (L/h)	708 ± 742 (105) 81.7 - 2319 [466]	321 ± 272 (84.8) 42.5 - 845 [217]	427	222	–
wn-CL/F (L/h/kg)	9.16 ± 10.7 (117) 1.05 - 37.5 [4.74]	4.08 ± 3.74 (91.6) 0.552 - 11.8 [2.56]	5.25	2.74	–
Vz/F (L)	10318 ± 8671 (84) 1385 - 28679 [7447]	5531 ± 4593 (83) 1230 - 15302 [3654]	7064	4025	–
wn-Vz/F (L/kg)	130 ± 115 (88.6) 18.3 - 357 [91.4]	71.4 ± 68 (95.3) 15.5 - 247 [42]	87	49.6	–
t½ (h)	12.9 ± 3.09 (24) 8.89 - 20 [12.8]	11.8 ± 2.69 (22.8) 6.12 - 16 [11.6]	12.6	11.5	–

5.5.7.5.2.2 Evaluation of CYP2D6 Inhibition on Asenapine (Effect of Paroxetine on Asenapine)

In sequence B (aka Arm A; aka Concentration Profile Arm B), the effect of multiple doses of paroxetine on the (single dose) pharmacokinetics of asenapine was studied. In addition, the effect of paroxetine on the metabolic ratio of dextromethorphan as a probe substrate for CYP2D6 was investigated. The baseline DM/DX ratio was determined at Screening. After a placebo dosing on Day 1, asenapine (5 mg) was given at Day 2. Paroxetine 20 mg once daily was given for 9 days (Day 7-15). On Day 11, dextromethorphan (30 mg single dose) was co-administered. On Days 12 and 13, placebo and asenapine (5 mg single dose) were co-administered, respectively.

The maximum usual starting dose for paroxetine is 20 mg QD and the maximum labeled dose is 60 mg QD for the IR formulation or 75 mg QD for the MR formulation.

There was a slightly lower exposure to asenapine in the presence of steady-state dosing of paroxetine but this was not significant, (see Figure 107 and Table 125).

In contrast, there was a 26% increase in exposure to desmethyl-asenapine (see Figure 108 and Table 125), presumably due to inhibition of CYP2D6 N-oxidation.

For desmethyl-asenapine, pre-dose concentrations above LLOQ, (0.05 ng/mL), were found for 8 of the 26 subjects during the second dosing period in arm B, (see Table 124).

Table 124 Predose Desmethyl-Asenapine Concentrations in Selected Subjects

Subject	Desmethyl-Asenapine C0 (ng/mL)	AUC_{0-72} correction
20	0.0537	3.87
24	0.133	9.58
28	0.0611	4.40
35	0.116	8.35
38	0.138	9.94
40	0.0789	5.68
122	0.121	8.71
129	0.0616	4.44

When these 8 subjects are excluded from the analysis as was done by the sponsor, or when the maximum possible AUCs attributable to these high baseline concentrations are subtracted as was done by this reviewer, the increase in exposures to desmethyl-asenapine are only around 10%, (see Table 126).

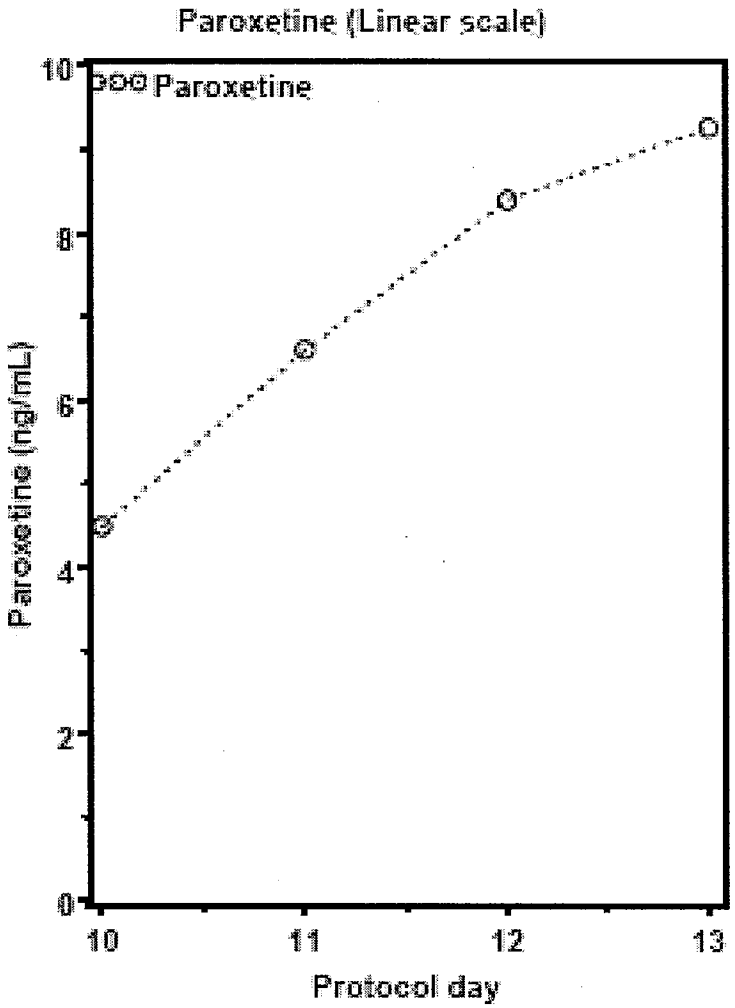
According to the sponsor,*"bioanalysis indicated that dextromethorphan interferes with the desmethyl-asenapine assay and as dextromethorphan was given 48 h before asenapine dosing in the second period this might be the explanation as washout from asenapine in first dosing period was long enough."*

The sponsor's claims were checked and there appears to be a 40% interference from DM and DX at 200 and 50 ng/mL respectively. Since concentrations of dextrorphan (DX) and dextromethorphan (DM) are typically less than 10 ng/ml at 48 hours post-dose, and since the amount of interference is on the order of 0.54 - 0.138 ng/ml it's uncertain if this is the true reason for the interference.

In contrast, Figure 106 shows that even after 7 days of dosing paroxetine trough concentrations are still increasing at a dose of 20 mg qd. Although paroxetine does exhibit nonlinear kinetics, even at a higher

dose of 30 mg mean half-life is 15 -22 hours with maximal half-lives of 65 hours. Conseqeuntly, steady-state should have already been reached (7 days = 156 hours). Instead it's likely that irreversible inhibition from the initial dose of asenapine 7 days before, was still inhibiting the elimination of paroxetine and this increased paroxetine resulting in the inhibition of CYP2D6 metabolism of N-desmethyl-asenapine, as well as the remaining inactivated CYP2D6 from the previouse dose of asenapine are acting together to increase the exposure to N-desmethyl-asenapine.

Figure 106 Mean Paroxetine Trough Concentrations vs. Time - Study 25525



Consequently, the degree of accumulation of desmethyl-asenapine and paroxetine when both are given in combination could be quite high under clinical dosing conditions and could result in an increased incidence of hepatotoxicity or other toxicities. Thus the present study clearly does not provide sufficient assurances of safety under clinical use.

Figure 107 Single Dose Concentration vs. Time Profiles of Asenapine 5 mg SL in the Absence and Presence of Paroxetine 20 mg qd in CYP2D6 EMs and PMs after a single 30 mg dose of Detromethorphan – Study 25525

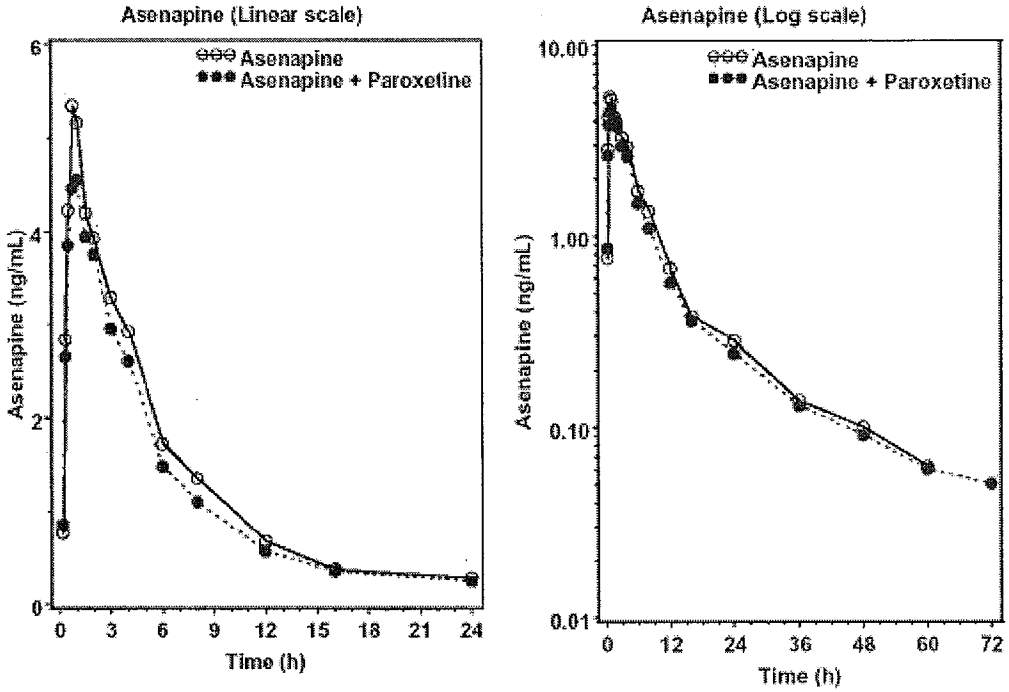


Figure 108 Single Dose Concentration vs. Time Profiles of Desmethyl-Asenapine after Asenapine 5 mg SL in the Absence and Presence of Paroxetine 20 mg qd in CYP2D6 EMs and PMs after a single 30 mg dose of Dextromethorphan – Study 25525

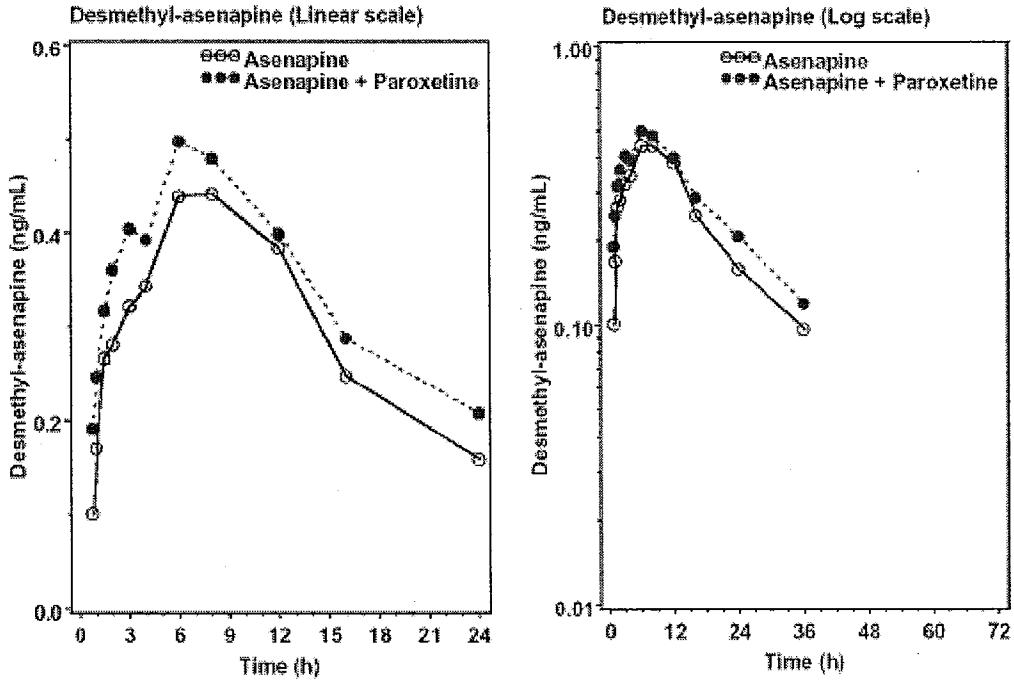


Table 125 Effect of Paroxetine 20 mg qd on the Pharmacokinetics of Asenapine 5 mg SL BID in Study 25525 Arm: [B] Asenapine vs. Asenapine + Paroxetine

	Summary Statistics		Geometric Means		Asenapine +/- Paroxetine Geometric Mean Ratio (90% CI)
	Asenapine	Asenapine & Paroxetine	Asenapine	Asenapine & Paroxetine	
N	26	26	26	26	
Tmax (h)	1.04 ± 0.63 (60.4) 0.5 - 3 0.875	1.07 ± 0.53 (49.2) 0.33-3 3 1	0.928	0.979	
Cmax (ng/mL)	5.7 ± 2.09 (36.6) 1.67 - 11.7 5.29	4.95 ± 1.8 (36.3) 2.49 - 9.02 4.52	5.33	4.66	0.87 0.80 - 0.96
AUCtlast (ng/mL x hr^{-1})	36.4 ± 10.9 (29.9) 19.5 - 65.9 34.5	32.6 ± 8.99 (27.6) 18.6 - 50.5 30.1	35	31.4	0.90 0.84 - 0.96
AUC∞ (ng/mL x hr^{-1})	38.4 ± 11.7 (30.5) 20.1 - 68.2 36.1	34.7 ± 9.62 (27.8) 19.3 - 55.4 32.4	36.8	33.4	0.91 0.85 - 0.97
AUCextrap (%)	4.91 ± 3.14 (63.9) 1.42 - 12.3 3.78	5.78 ± 4.13 (71.4) 1.09 - 23.1 4.81	4.14	4.89	
CL/f (L/h)	142 ± 42.3 (29.9) 73.3 - 249 139	156 ± 44.8 (28.8) 90.2 - 260 154	136	150	
wn-CL/f (L/h/kg)	1.77 ± 0.612 (34.5) 0.77 - 3.39 1.69	1.94 ± 0.616 (31.8) 1.01 - 3.47 1.83	1.67	1.85	
Vz/f (L)	4506 ± 1878 (41.7) 1979 - 8042 3884	5759 ± 3110 (54) 2040 - 17976 5228	4136	5182	
wn-Vz/f (L/kg)	55.9 ± 23.9 (42.9) 20.8 - 98.6 45.5	71.5 ± 40.2 (56.2) 26.5 - 225 65.2	51	63.9	
t½ (h)	22.6 ± 9.52 (42.2) 12.3 - 54.2 19	26.9 ± 16.3 (60.6) 8.74 - 96.4 23.3	21.1	24	

Table 126 Effect of Paroxetine 20 mg qd on the Pharmacokinetics of Desmethyl-Asenapine in Study 25525 Arm: [B] asenapine vs. asenapine + paroxetine

	Summary Statistics		All Subjects			Excluding Subjects with Baseline Values above LLOQ 0.05 ng/mL		
			Geometric Means		GMR (90% CI)	Geometric Means		GMR (90%)
	Asenapine	Asenapine + Paroxetine	Asenapine	Asenapine + Paroxetine	Asenapine + Paroxetine : Asenapine	Asenapine	Asenapine + Paroxetine	Asenapine + Paroxetine : Asenapine
n	26	26	26	26	26	18	18	18
Tmax (h)	7.1 ± 2.45 (34.5) 1.5 - 12 [7.02]	6.47 ± 2.49 (38.5) 2 - 12 [6]	6.6	5.91				
Cmax (ng/mL)	0.52 ± 0.31 (59.5) 0.18 - 1.43 [0.42]	0.55 ± 0.20 (37.2) 0.28 – 1.0 [0.52]	0.45	0.517	1.14 1.03 - 1.26	0.41	0.46	1.11 1.01 - 1.23
AUCtlast (72 hours) (ng/mL x hr^{-1})	9.1 ± 4.95 (54.5) 1.8 - 23.8 [8.29]	11.8 ± 6.12 (51.8) 5.64 - 26.2 [9.14]	7.96	10.6	1.33 1.18 - 1.49	7.36	8.73	1.18 1.05 - 1.34
						8.01	8.82[a]	1.10
AUC∞ (ng/mL x hr^{-1})	11.7 ± 5.58 (47.8) 2.59 - 26.6 [10.8]	14.2 ± 5.9 (41.7) 8 - 28.2 [11.3]	10.5	13.2	1.26 1.11 - 1.42	10.1	11.3	1.12 0.99 - 1.27
%extrap (%)	23.2 ± 12 (51.8) 5.42 - 48.4 [22.7]	18.7 ± 12.4 (66) 3.2 - 50.2 [13.7]	19.9	15.5				
CL/F (L/h)	514 ± 322 (62.6) 178 - 1835 [439]	383 ± 126 (32.8) 169 - 594 [420]	453	361				
wn-CL/F (L/h) / kg	6.25 ± 3.32 (53.1) 2.14 - 18.8 [5.72]	4.72 ± 1.55 (32.8) 2.11 - 8.21 [4.81]	5.58	4.44				
Vz/F (L)	13809 ± 7702 (55.8) 2694 - 30718 [11927]	11507 ± 6588 (57.2) 2546 - 27382 [9946]	11692	9915				
wn-Vz/F (L/kg)	166 ± 85.2 (51.2) 32.3 - 343 [151]	139 ± 72.6 (52.2) 30.5 - 317 [121]	144	122				
t½ (h)	20.5 ± 11.4 (55.4) 7.23 - 51.6 [19.2]	21.1 ± 9.97 (47.2) 6.91 - 48.7 [18.6]	17.9	19.1				

a GMR – Geometric Mean Ratio
b calculated by subtracting baseline

5.5.7.5.2.3 Comparative Evaluation of Asenapine and Paroxetine as CYP2D6 Inhibitors (Effects on Dextromethorphan)

Table 127 shows the comparative effects of asenapine and paroxetine on dextromethorphan.

The DX/DM ratio after paroxetine is about 7.5% of the DX/DM ratio after asenapine demonstrating that paroxetine is a more potent inhibitor. However the degree of effect on the DX/DM ratio is due to a combination of changes in both dextrorphan and dextromethorphan. Examination of the relative exposures to dextromethorphan is a better measure of the relative potency, and Table 127 shows dextromethorphan post dosing to pre-dosing GMRs of 13.1 for paroxetine compared with 1.55 for asenapine, however these are just means. When individual values are compared some subjects in the paroxetine group have exposures of nearly 45 times higher in the presence of paroxetine, whereas no one receiving asenapine had an increase of even 10 fold, (see Figure 109). However this was the low dose of asenapine and the effect would likely be greater with the 10 mg dose.

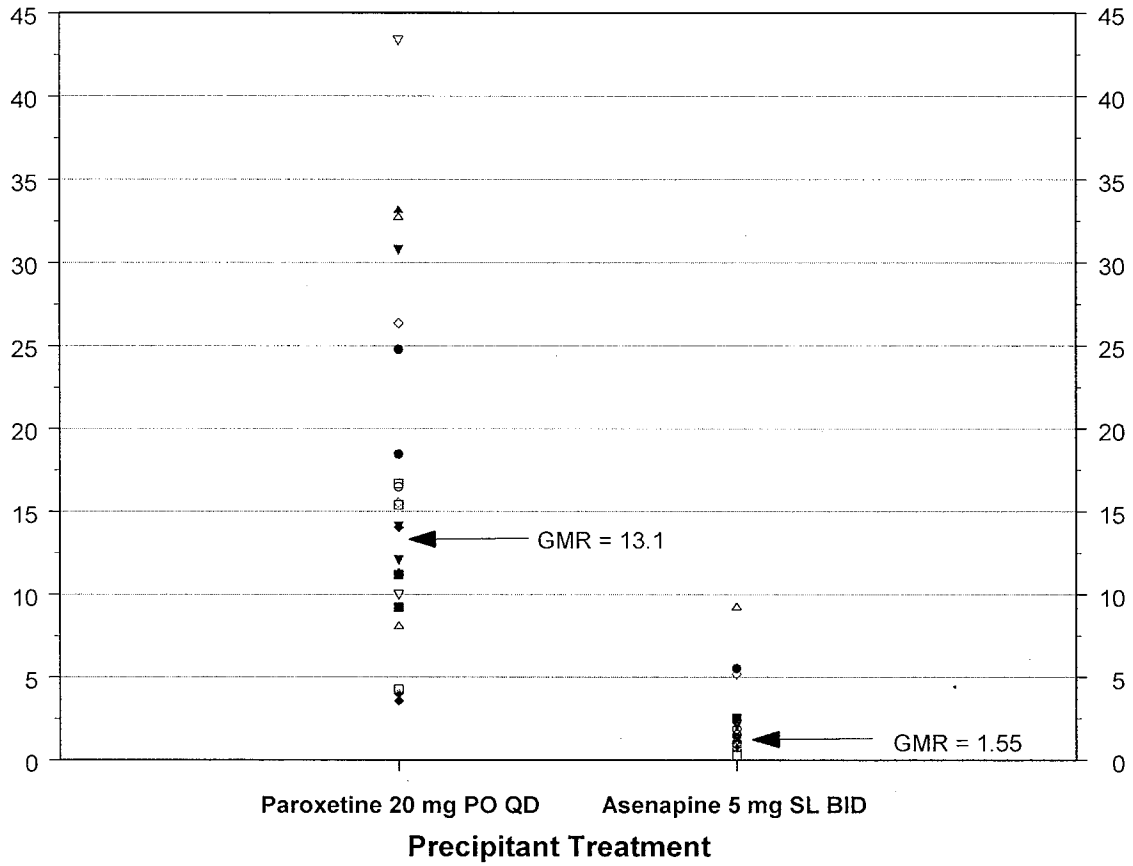
To demonstrate why comparing DX/DM ratios is flawed we need to remember that with inhibition the numerator DX will decrease and denominator DM will increase so the estimate of the degree of inhibition will be compounded consequently this is an invalid way of comparing the relative degree of inhibition with different compounds. Since the increased exposure to dextromethorphan is what is clinically important we need to compare the relative increases. Consequently the ratio of asenapine DX/DM / paroxetine DX/DM ratios is 13.44 (i.e. 0.43 / 0.032 or the inverse of 7.5%) whereas if we simply compare the GMRs of DM pre and post dosing for the two treatments we find that paroxetine has a 8.45 greater effect on dextromethorphan (i.e. 13.1 / 1.55).

Table 127 Summary of Dextromethorphan and Dextrorphan, and Dextrorphan/Dextromethorphan Ratio in Urine

Treatment Arm	Objective Substrate	Objective Substrate + Test Precipitant	N	Parameter (unit)	Summary Statistics of Individual Ratios of Dextromethorphan Recovery in Urine During – Treatment : Pre - Treatment[a]	Geometric Means		Geometric Mean Ratio During - Treatment : Pre – Treatment (95% CI)
						Pre - Treatment	During - Treatment	
Arm A (Effect of Asenapine on CYP2D6)	Paroxetine 20 mg	Paroxetine 20 mg + Asenapine 5 mg SL BID	15	Dextromethorphan (µg)	2.3 ± 2.5 (104.8) 0.3 - 9.2 [1.3]	43.6	67.7	1.55 0.93 - 2.59
				Dextrorphan (µg)		311	205	0.66 0.49 - 0.89
				Dextrorphan / Dextromethorphan ratio		7.14	3.03	0.43 0.32 - 0.56
				Approximate Amount Recovered (µg)		354.6	272.7	
				Recovery		1.18 %	0.91 %	Expected Direction
Arm B (Effect of Paroxetine on CYP2D6)	Asenapine 5 mg SL	Asenapine 5 mg SL + Paroxetine 20 mg QD	23	Dextromethorphan (µg)	16.2 ± 10.6 (65.4) 3.6 - 43.4 [14.1]	21.1	277	13.1 9.57 - 17.9
				Dextrorphan (µg)		250	104	0.41 0.29 - 0.60
				Dextrorphan / Dextromethorphan ratio		11.8	0.375	0.032 0.023 - 0.043
				Approximate Amount Recovered (µg)		271.1	381	
				Recovery		0.90 %	1.27 %	?

a Values are mean ± SD, (%CV), Range, [Median]

Figure 109 Ratio of Amount of Dextromethorphan Recovered in an 8 hour Urine Collection under Steady-State Dosing of Asenapine or Paroxetine as Compared to the Amount Recovered at Baseline – Study 25525



5.5.7.5.3 Effect of Valproate on Asenapine - Effect on 2C9, 3A4(?) and Glucuronidation - Study 25527

Study 25527 was an open-label, randomized, two-way cross-over study to investigate the effect of steady state valproate on the single dose pharmacokinetics of 5 mg asenapine in 24 healthy male subjects aged 18 – 55 years of age.

Treatment A:		Asenapine 5 mg SL x 1
Treatment B:	Days 1-9:	Valproate (Depakine® enteric tablet): 500 mg, PO BID
	Day 6:	Asenapine (Org 5222) placebo: SL
	Day 7:	Asenapine (Org 5222) 5 mg SL

There was a washout of at least 2 weeks between successive treatment periods.

The pharmacokinetics of asenapine, N-desmethyl asenapine, and asenapine N-glucuronide were measured in absence and presence of valproate. The pharmacokinetics of valproate and its metabolites were not assessed.

Subject demographics are shown in Table 128, and pharmacokinetic metrics are shown in Table 129.

Table 128 Demographic Characteristics by Treated Group – Study 25527

Sequence	N	Age [years]	Weight [kg]	Height [cm]	Body Mass Index [kg/m^2]
AB	24	30 ± 7.7 19 - 41 [29]	79.3 ± 10.4 69.1 - 106.5 [77.0]	183 ± 7.5 172 - 196 [184]	23.5 ± 2.2 20.7 - 27.7 [23.1]
BA	24	33 ± 11.3 19 - 53 [32]	77.8 ± 9.6 62.6 - 91.8 [76.3]	179 ± 7.0 171 - 193 [178]	24.2 ± 2.2 20.8 - 27.4 [24.7]

There was no clear effect of valproate on total asenapine Cmax or AUC, (seeTable 129 and Figure 110).

The extent of exposure for desmethyl - asenapine as expressed by AUC∞ was on average 30% lower in the presence of valproate whereas no effect was seen on Cmax, (see Table 129 and Figure 111). This may indicate decreased formation of desmethyl–asenapine by inhibition of CYP2C9, which is polymorphic.

The effect of valproate on the pharmacokinetics of asenapine–glucuronide was to decrease both AUC∞ and Cmax on average by 85%, meaning exposure in the presence of valproate was 1/7 the exposure in the absence of valproate, (see Table 129 and Figure 112). This appears to indicate that Valproate competes with glucuronidation by UDPGT1A4 with not much effect on active secretion.

Regarding side effects there were more side effects for asenapine when given in combination with valproate as compared to when given alone. The greater values are as follows:

Fatigue	6 (25%) vs. 2 (8%)
Headache	6 (25%) vs. 1 (4%)

Unfortunately the effect of asenapine on valproate was not examined. In addition, there still exists the possibility of a pharmacodynamic intereaction via mitochondrial metabolism that this study was not designed to detect.

Table 129 Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide 5 mg SL Single Dose PK Parameters in the Absence and Presence of Valproate 500 mg PO BID – Study 25527

Parameter (unit)	Asenapine			Desmethyl-Asenapine			Asenapine-Glucuronide		
	Asenapine	Asenapine + Valproate	GMR (90% CI)	Asenapine	Asenapine + Valproate	GMR (90% CI)	Asenapine	Asenapine + Valproate	GMR (90% CI)
N	24	24	—	24	24	—	24	24	—
Tmax (h)	0.875 0.333 - 1.50	0.750 0.333 - 1.50	—	6.00 1.50 - 12.0	3.50 1.50 - 12.0	—	4.00 3.00 - 6.02	3.03 2.00 - 6.05	—
Cmax (ng/mL)	5.74 (50.5) 2.38 - 15.9	5.79 (46.2) 1.64 - 15.5	1.02 0.91 - 1.15	0.409 (32.5) 0.252 - 0.791	0.399 (42.7) 0.149 - 0.943	0.94 0.85 - 1.04	6.01 (48.9) 2.21 - 12.7	0.987 (64.9) 0.250 - 2.58	0.15 0.13 - 0.18
	5.18 [a]	5.30 [a]		0.39 [a]	0.37 [a]		5.34 [a]	0.81 [a]	
AUCtlast (ng/mL x hr^{-1})	34.3 (29.5) 16.6 - 56.7	33.2 (26.8) 16.2 - 53.0	0.98 0.90 - 1.06	8.19 (41.0) 4.48 - 19.1	5.74 (57.7) 0.829 - 18.1	0.65 0.55 - 0.76	70.9 (49.6) 18.0 - 152	6.50 (74.2) 0.125 - 18.4	0.06 0.04 - 0.10
	32.7 [a]	32.0 [a]		7.69 [a]	4.96 [a]		62.1 [a]	3.92 [a]	
AUCtlast (ng/mL x hr^{-1})	35.9 (29.8) 17.1 - 58.3	35.3 (27.4) 17.5 - 55.4	0.99 0.91 - 1.08	9.70 (36.9) 5.54 - 21.2	7.14 (44.4) 3.65 - 19.1	0.70 0.64 - 0.77	76.2 (46.8) 25.3 - 159	10.4 (40.5) 4.93 - 21.8	0.14 0.12 - 0.16
	34.2 [a]	33.9 [a]		9.52 [a]	6.67 [a]		72.3 [a]	9.82 [a]	
CL/f (L/h)	154 (36.2) 85.8 - 293	154 (31.7) 90.3 - 286	—	541 (29.0) 224 - 859	752 (31.5) 249 - 1304	—	133 (51.2) 51.0 - 321	905 (39.7) 372 - 1644	—
t½ (h)	22.9 (37.9) 8.27 - 38.8	27.6 (37.8) 9.24 - 57.4	—	14.2 (28.0) 7.72 - 24.2	10.3 (21.0) 6.74 - 14.7	—	9.36 (74.0) 4.53 - 33.8	5.08 (33.7) 2.86 - 9.25	—

a Geometric Mean

Figure 110 Mean Asenapine Concentration vs. Time Profiles in the Absence and Presence of Valproate – Study 25527

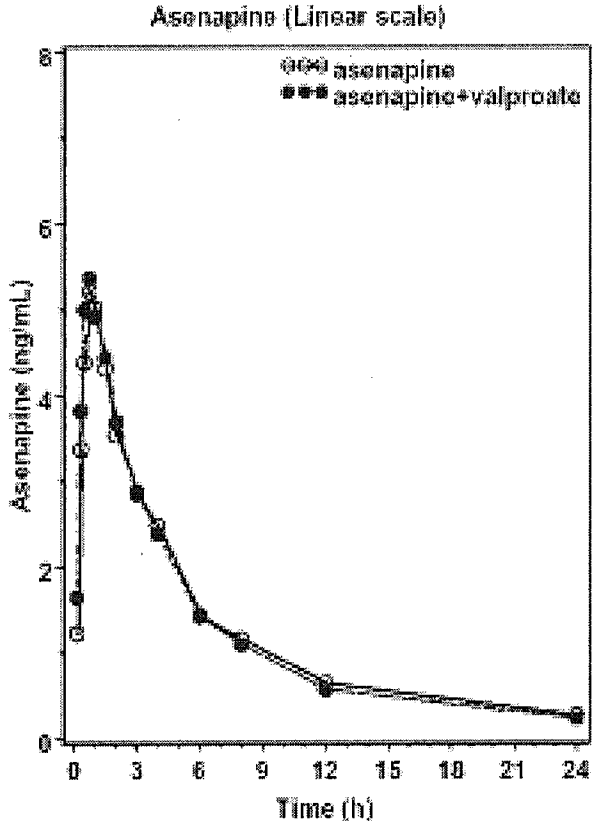


Figure 111 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Valproate – Study 25527

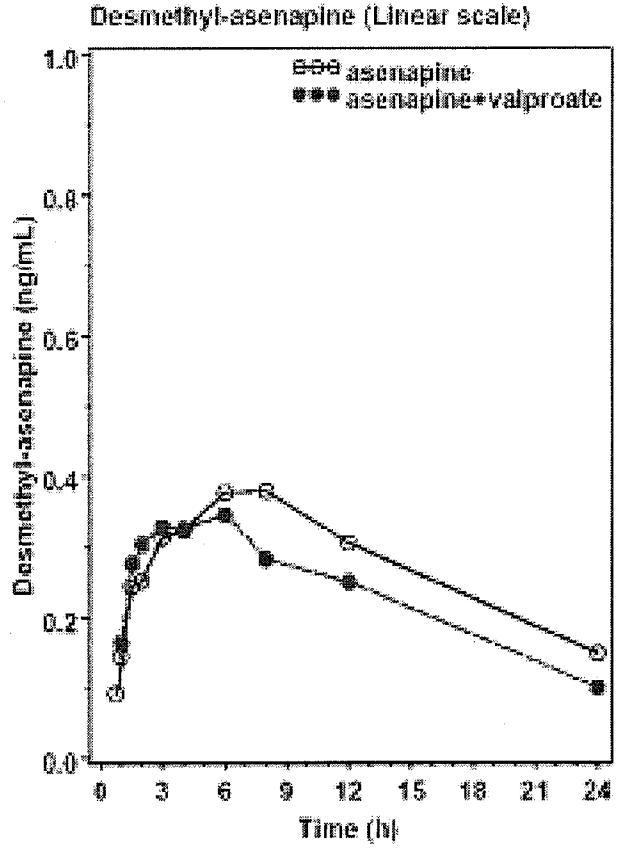
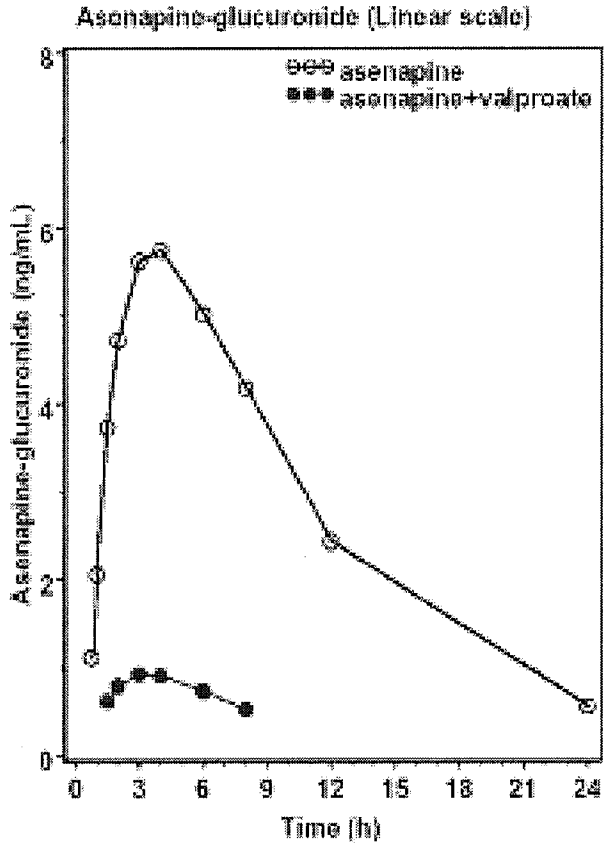


Figure 112 Mean Asenapine Glucuronide Concentration vs. Time Profiles in the Absence and Presence of Valproate – Study 25527



5.5.7.5.4 Effect of Carbamazepine on Asenapine - Study 25528

Study 25528 was a single center, open label, single arm study in 24 healthy male subjects 18 - 45 years of age. A single dose of asenapine was administered sublingually before and during treatment with carbamazepine.

Treatments consisted of the following:

Day 1 and Day 20: Asenapine 5 mg SL once on each day

Days 4-7: Carbamazepine 200 mg PO BID
Days 8-22: Carbamazepine 200 mg PO BID

The pharmacokinetics of asenapine, N-desmethyl asenapine, asenapine N-oxide, and asenapine N-glucuronide were assessed after dosing on Day 1 (without carbamazepine) and on Day 20 (with carbamazepine).

The CYP3A4 inducing effect of carbamazepine was measured by determining the ratio of 6β-OH cortisol/cortisol in urine collected prior to and during carbamazepine treatment.

Subject demographics are shown in Table 130, and pharmacokinetic metrics are shown in Table 134.

Table 130 Subject Demographics - Study 25528

N	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)
29	31.3 + 8.0 18 - 45 [31.0]	78.0 + 10.7 58.5 - 97.0 [79.0]	179.7 + 6.3 168 - 198 [180.0]	24.07 + 2.42 18.9 - 28.4 [24.1]

Carbamazepine induces both CYP3As and CYP2C19, and Table 131 demonstrates that at least cortisol 6- β–hydroxylation by CYP3A4 was induced.

Table 131 Effect of Carbamazepine on 6β–Hydroxy-Cortisol Urine Excretion Evidencing CYP3A4 Induction - Study 25528

Parameter (unit)	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 19 / Day -1 [95% CI]
	Day -1	Day 19	Day -1	Day 19	
Free cortisol (µg)	48.4 (59.2) 15.0 - 131	32.8 (50.5) 8.54 - 70.0	41.6	28.7	0.69 [0.55 - 0.87]
6β–hydroxy-cortisol (µg)	254 (36.2) 117 - 521	702 (36.8) 184 - 1252	239	651	2.73 [2.32 - 3.20]
6β–hydroxy-cortisol / free cortisol	6.25 (39.5) 2.03 - 12.2	24.4 (38.6) 11.0 - 46.0	5.75	22.7	3.95 [3.26 - 4.78]

Results are shown in Figure 110 to Figure 112 and Table 134. Results indicate that carbamazepine induces the elimination of asenapine resulting in a secondary decrease in glucuronidation. In addition, the lower concentrations early on in both of their concentration vs. time profiles with more similar concentration vs. time curves later on indicates that elimination is driving the earlier phase of the declining

profile while redistribution may be driving the later phase. In addition, there is a much greater percentage decrease in N-desmethyl-asenapine exposure (30%) compared with the decreases in asenapine and asenapine glucuronide exposures (i.e. 15% for each). This may indicate that elimination of both asenapine and N-desmethyl-asenapine is mediated by CYP3A4, and for both of them the most likely reaction induced is 11-hydroxylation.

Table 132 shows the sponsor's summary of the categorical incidence AEs. The text in red highlights a possible increase in severe AEs when the drugs are taken in combination. When examined these severe AEs were somnolence.

Table 132 Sponsor's Summary of the Categorical Incidence AEs – Study 25528

Incidence of AEs	Placebo	Asenapine	Carbamazepine		Asenapine + Carbamazepine 400 mg
			200 mg	400 mg	
	N=29	N=27	N=26	N=26	N=24
	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	2 (6.9%)	25 (92.6%)	16 (61.5%)	24 (92.3%)	23 (95.8%)
Without any AE	27 (93.1%)	2 (7.4%)	10 (38.5%)	2 (7.7%)	1 (4.2%)
Any drug related AE	0 (0.0%)	25 (92.6%)	16 (61.5%)	24 (92.3%)	23 (95.8%)
Severe AEs	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.8%)	3 (12.5%)
Subjects with any SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discontinations due to AEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.7%)	0 (0.0%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

When AEs are examined by Treatment what jumps out is that fatigue is also much greater when the drugs are combined, (see Table 133).

Table 133 Selected Adverse Events by Treatment – Study 25528[a]

	Placebo	Asenanpine	Carbamazepine		Asenapine + Carbamazepine 400mg	Overall
			200 mg	400 mg		
Administration site conditions						
Asthenia	–	–	1 (1, 3.8%)	–	1 (1, 4.2%)	2 (2, 6.9%)
Miscellaneous						
Drug Withdrawal Syndrome	–	–	–	–	1 (1, 4.2%)	1 (1, 3.4%)
Fatigue	–	3 (2, 7.4%)	6 (6, 23.1%)	5 (5, 19.2%)	11 (11, 45.8%)	25 (17, 58.6%)
Thoracic and mediastinal disorders						
Respiratory, Total	–	–	–	4 (3, 11.5%)	5 (2, 8.3%)	9 (5, 17.2%)
Cough	–	–	–	–	1 (1, 4.2%)	1 (1, 3.4%)
Nasal Congestion	–	–	–	1 (1, 3.8%)	1 (1, 4.2%)	2 (2, 6.9%)
Pharyngolaryngeal Pain	–	–	–	2 (2, 7.7%)	2 (2, 8.3%)	4 (4, 13.8%)
Rhinorrea	–	–	–	1 (1, 3.8%)	1 (1, 4.2%)	2 (2,6.9%)

a n (y, z %): n = number of incidences of particular adverse event
y = number of subjects with particular adverse event
z = percentage of subjects with particular adverse event (refer to the number of subjects treated)
Note: Percentages refer to the number of subjects received the respective treatment at least once.

Figure 113 Mean Asenapine Concentration vs. Time Profiles in the Absence and Presence of Carbamazepine – Study 25528

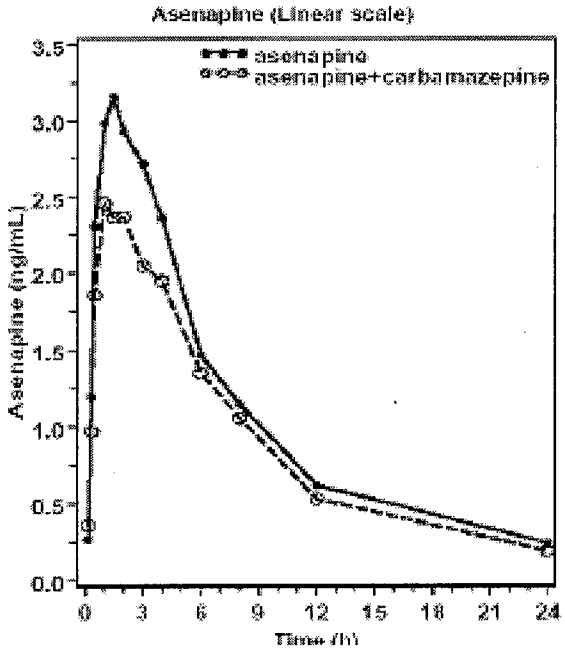


Figure 114 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Carbamazepine – Study 25528

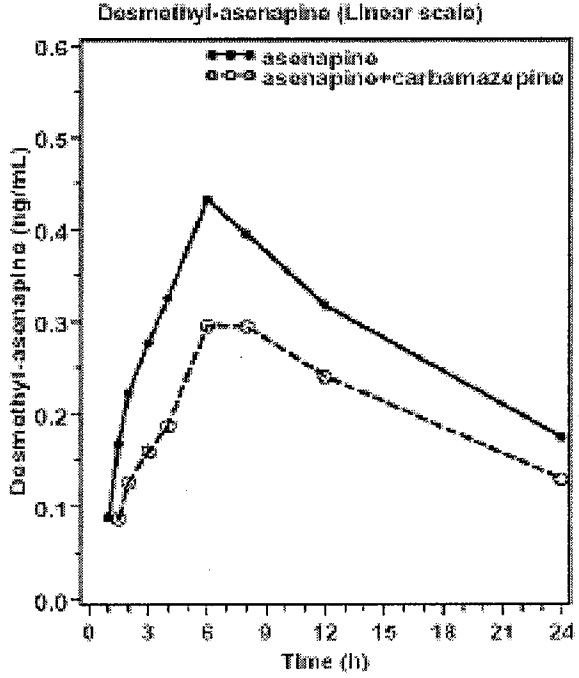


Figure 115 Mean Asenapine Glucuronide Concentration vs. Time Profiles in the Absence and Presence of Carbamazepine – Study 25528

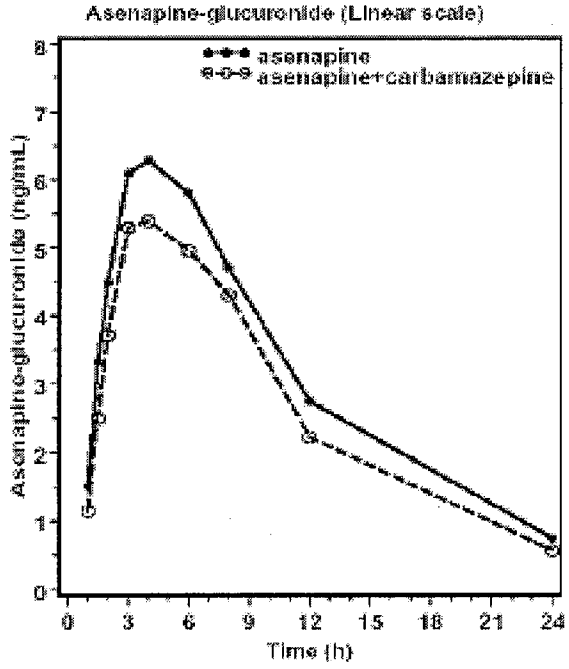


Table 134 Asenapine, Desmethyl-Asenapine, & Asenapine Glucuronide 5 mg SL SD PK Parameters in the Absence and Presence of Carbamazepine 400 mg PO BID – Study 25527

Parameter (unit)	Asenapine			Desmethyl-Asenapine			Asenapine-Glucuronide		
	Asenapine	Asenapine + Carbamazepine	GMR (90% CI)	Asenapine (n=24)	Asenapine + Carbamazepine	GMR (90% CI)	Asenapine (n=23)	Asenapine + Carbamazepine	GMR (90% CI)
N	24	24	—	24	24	—	23	23	—
Tmax (h)	1.25 0.50 - 2.0	1.00 0.50 - 4.0	—	6.00 3.00-12.0	6.00 6.00-12.0	—	4.00 3.00 - 8.00	4.00 3.00 - 8.02	—
Cmax (ng/mL)	3.46 (26.3) 1.67 - 5.76	2.94 (32.7) 1.44 - 5.27	0.84 0.74 - 0.95	0.447 (23.1) 0.245 - 0.617	0.314 (25.1) 0.140 - 0.474	0.70 0.66 - 0.74	6.54 (36.5) 2.12 - 10.7	5.80 (33.8) 2.69 - 9.90	0.90 0.82 - 0.99
AUCtlast (ng/mL x hr^{-1})	29.7 (28.4) 14.3 - 45.9	24.3 (24.1) 15.0 - 35.5	0.83 0.76 - 0.90	9.01 (30.0) 3.65 - 13.9	6.05 (35.3) 2.40 - 10.5	0.66 0.61 - 0.71	84.2 (45.8) 22.4 - 160	67.6 (36.0) 24.1 - 126	0.84 0.75 - 0.94
AUC∞ (ng/mL x hr^{-1})	31.0 (27.5) 14.8 - 47.1	25.6 (22.2) 15.6 - 36.1	0.84 0.77 - 0.91	11.0 (29.8) 4.28 - 16.8	7.72 (29.8) 4.00 - 13.2	0.70 0.65 - 0.76	93.2 (44.9) 34.0 - 175	75.4 (33.9) 33.0 - 132	0.84 0.74 - 0.96
CL/F (L/h)	175 (31.9) 106 - 338	206 (23.7) 139 - 321	—	478 (37.8) 283 - 1110	675 (32.7) 361 - 1190	—	107 (48.4) 46.2 - 238	123 (40.7) 61.2 - 245	—
Vz/F (L)	5167 (57.9) 1403 - 12437	5729 (63.1) 1853 - 15200	—	11296 (46.1) 4965 - 25844	14475 (34.4) 8417 - 27983	—	1597 (55.8) 579 - 4699	1887 (81.4) 758 - 6191	—
t½ (h)	20.6 (47.8) 6.45 - 46.1	19.4 (61.6) 7.29 - 49.8	—	18.3 (67.0) 8.35 - 63.3	15.7 (37.4) 9.86 - 33.6	—	12.7 (73.7) 4.12 - 40.2	12.4 (103) 3.71 - 51.6	—

a Values are Mean (CV %) range; Median range

5.5.7.5.5 Effect of Cimetidine on Asenapine - Study 25529

Study 25529 was an open-label, randomized, two-way cross-over study to investigate the effect of cimetidine at steady state on the single dose pharmacokinetics of 5 mg asenapine in 12 healthy male subjects aged 18 – 45 years of age.

Treatments were as follows:

Treatment A: Asenapine 5 mg SL x 1
Treatment B: Days 1-7 Cimetidine 800 mg b.i.d. with a single Asenapine 5 mg sublingual dose on Day 5.

During treatment with cimetidine the inhibitory effects of cimetidine on CYPs 1A2, 2D6, and 3A4 were assessed as follows:

- **CYP1A2:** Plasma 6 hour paraxanthine/caffeine ratio during treatment (Day 3) to pre-treatment (Day - 1) (Caffeine 100 mg)
- **CYP2D6:** Urine 8 hour dextrorphan/dextromethorphan ratio during treatment (Day 3) to pre-treatment (Day - 1) (Dextromethorphan 30 mg)
- **CYP3A4:** Urine 24 hour 6β–OH cortisol/cortisol ratio during treatment (Day 3) to pre-treatment (Day - 1)

There was a washout period of at least 2 weeks between successive treatment periods.

The pharmacokinetics of asenapine, N-demethyl-asenapine, asenapine N-oxide, and asenapine N-glucuronide were measured in the absence and presence of cimetidine.

Results:

Demographics

Subject demographics are shown in Table 135.

Table 135 Subject Demographics - Study 25529

N	Age (years)	Height (cm)	Weight (kg)	BMI (kg / m^2)
29	32.8 18 - 43 [33.0]	180.2 163 - 195 [180.0]	77.90 57.0 - 90.0 [80.0]	23.95 19.8 - 27.5 [24.03]

Controls for P450 CYP Inhibition

Cimetidine is an imidazole that binds directly to the heme of certain P450s accounting for its ability to inhibit multiple isozymes.

Figure 116 Structure Cimetidine

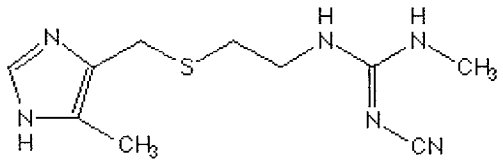


Table 136 to Table 138 show the effect of cimetidine on positive controls for P450 isozyme activity, there is a mean 34% decrease in CYP1A2 activity, a mean 75% decrease in CYP2D6 activity, and a mean 25% decrease in CYP3A4 activity.

Effect of Cimetidine on Plasma Paraxanthine/Caffeine Ratio (CYP1A2 Inhibition)

Table 136 6 Hour Plasma Caffeine and Paraxanthine Concentrations and Ratios in the Absence and Presence of Cimetidine – Study 25529

Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 3/Day -1 [95% CI]
	Pre-Cimetidine	With Cimetidine	Pre-Cimetidine	With Cimetidine	
	Day -1	Day 3	Day -1	Day 3	
Caffeine (ng/mL)	1144 (27.5) 604 - 1930	2103 (50.9) 1150 - 6030	–	–	–
Paraxanthine (ng /mL)	673[a] (33.9) 436 - 1370	963 (85.9) 365 - 3200	–	–	–
Paraxanthine / Caffeine Ratio	0.621 (30.8) 0.267 - 1.10	0.422 (48.2) 0.181 - 0.953	0.59	0.38	0.64 0.56 - 0.73

a Estimates based on n=23 subjects (Caffeine: n=24)
For Subject 12, Day - 1, an exceptionally low paraxanthine concentration was measured (129 ng/mL). The outlier resulted from a bioanalytical rerun as the original run did not meet the acceptance criteria. In the non - accepted run the paraxanthine concentration was much higher than 129 ng/mL. So it was decided to exclude this outlier from further calculations.

Effect of Cimetidine on Urine Dextrorphan/Dextromethorphan Ratio (CYP2D6 Inhibition)

Table 137 8 Hour Urine Dextromethorphan and Dextrorphan Concentrations and Ratios in the Absence and Presence of Cimetidine – Study 25529

Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 3/Day -1 [95% CI]
	Pre-Cimetidine	With Cimetidine	Pre-Cimetidine	With Cimetidine	
	Day -1	Day 3	Day -1	Day 3	
Dextromethorphan (µg)	81.6 (185) 2.29 - 586	136 (164) 3.98 - 934	–	–	–
Dextrorphan (µg)	127 (72.5) 13.7 - 343	73.1 (63.2) 9.29 - 165	–	–	–
Dextrorphan / Dextromethorphan Ratio	9.11 (98.5) 0.0234 - 32.8	2.05 (110) 0.0206 - 8.81	4.35	1.07	0.25 0.17 - 0.36

a For subject 108, the urine sample of Day 3 was lost and consequently no assessments on dextromethorphan and cortisol were available during treatment. Estimates based on n=23 (#: n=22) subjects

Effect of Cimetidine on Urine Cortisol and 6β–Hydroxycortisol Ratio (CYP3A4 Inhibition)

Table 138 24 Hour Urine Cortisol and 6β–Hydroxycortisol Excretion and Ratios in the Absence and Presence of Cimetidine – Study 25529

Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 3/Day -1 [95% CI]
	Pre-Cimetidine	With Cimetidine	Pre-Cimetidine	With Cimetidine	
	Day -1	Day 3	Day -1	Day 3	
Free cortisol (µg)	34.4 (47.2) 17.9 - 91.7	21.8 (36.5) 6.58 - 37.1	31.7	20.2	0.64 [0.52 - 0.78]
6β–hydroxy–cortisol (µg)	197 (39.0) 65.9 - 341	100 (53.8) 33.6 - 286	182	89.4	0.49 [0.43 - 0.57]
6β–hydroxy-cortisol / free cortisol	6.19 (39.5) 2.78 - 12.5	4.63 (30.2) 2.23 - 7.80	5.74	4.42	0.77 [0.68 - 0.87]

Estimates based on n=23 subjects

Effect of Cimetidine on Asenapine

Figure 117 to Figure 119 demonstrate the effect of cimetidine on asenapine, desmethyl-asenapine, and asenapine-glucuronide.

Table 139 on the following page also shows that the exposure to asenapine, desmethyl-asenapine, and asenapine glucuronide in the absence and presence of cimitidine. Exposure to asenapine doesn't change, although the exposure to asenapine glucuronide increases slightly, (~22% on average), whereas the exposure to desmethyl-asenapine approximately doubles.

Figure 117 Mean Asenapine Concentration vs. Time Profiles in the Absence and Presence of Cimetidine – Study 25529

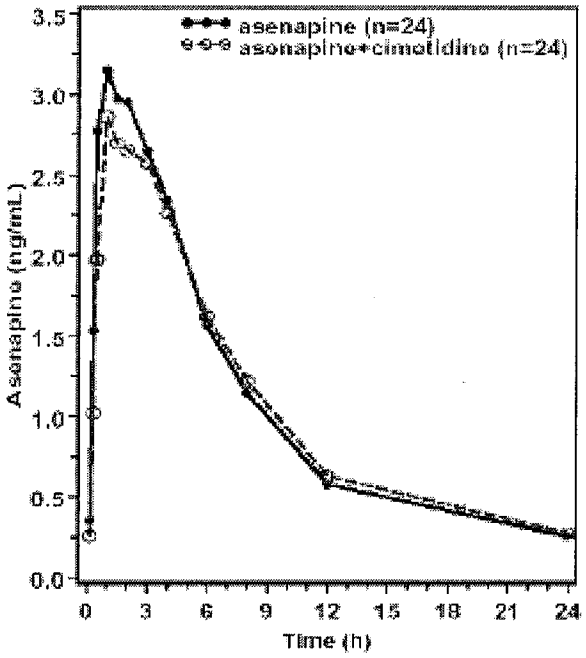


Figure 118 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Cimetidine – Study 25529

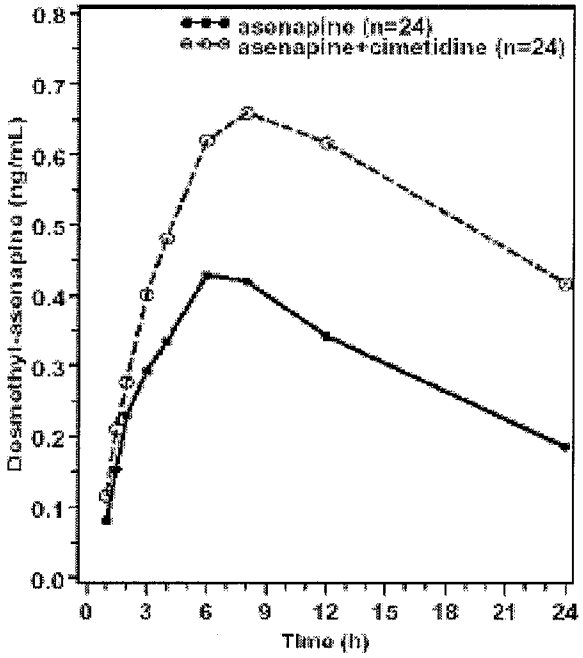


Figure 119 Mean Asenapine Glucuronide Concentration vs. Time Profiles in the Absence and Presence of Cimetidine – Study 25529

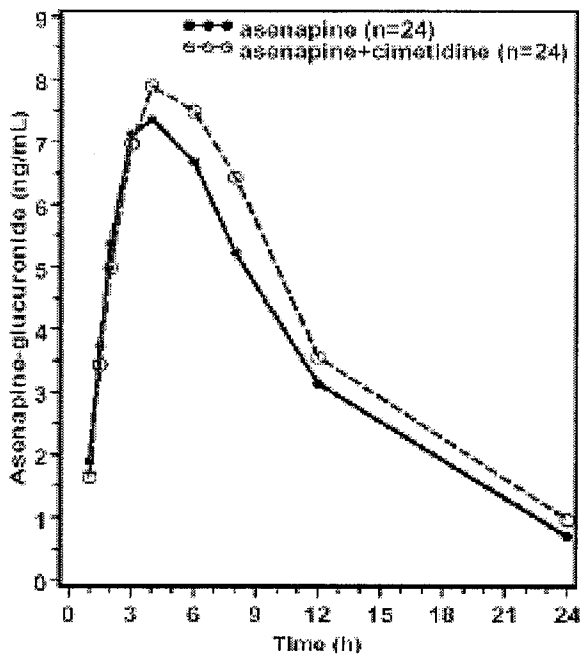


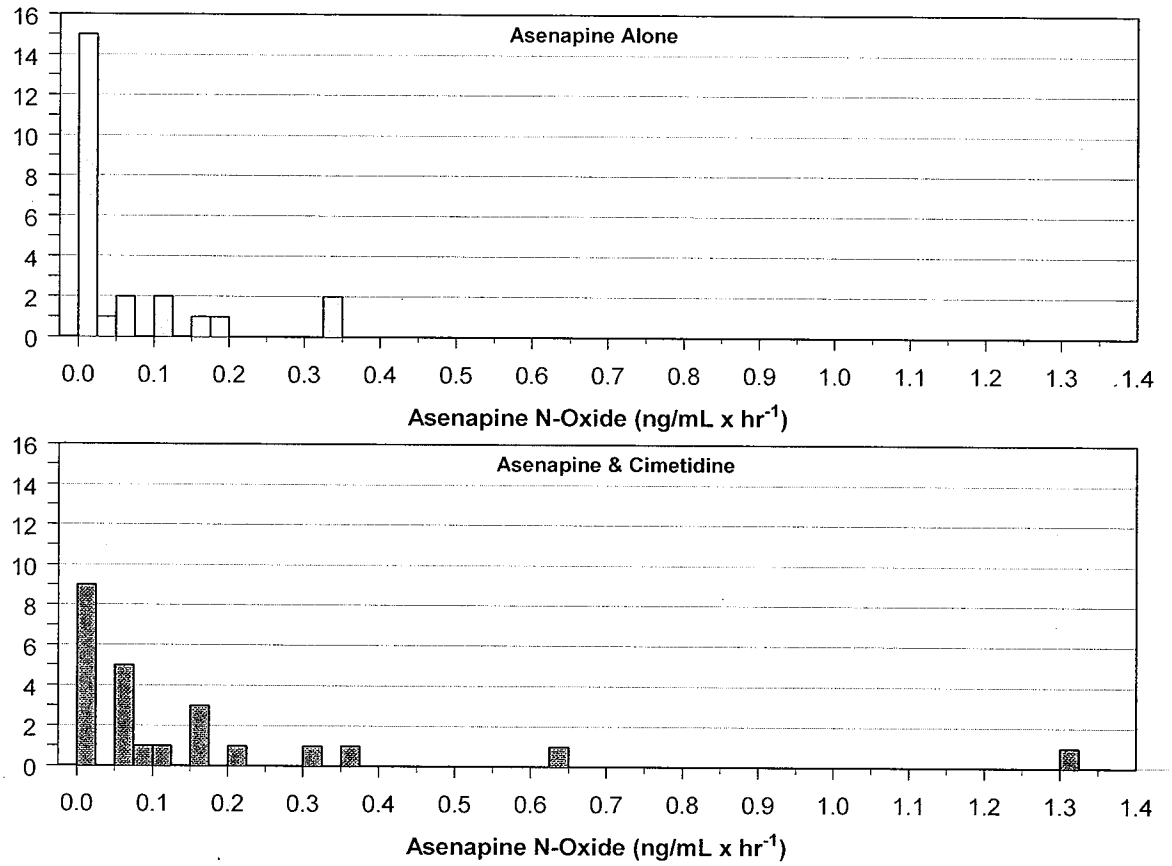
Table 139 Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide 5 mg SL Single Dose PK Parameters in the Absence and Presence of Cimeitdine 800 mg PO BID – Study 25527

Parameter (unit)	Asenapine			Desmethyl-Asenapine			Asenapine-Glucuronide		
	Asenapine	Asenapine + Cimetidine	Geometric Mean Ratio (90% CI)	Asenapine	Asenapine + Cimetidine	Geometric Mean Ratio (90% CI)	Asenapine	Asenapine + Cimetidine	Geometric Mean Ratio (90% CI)
N	24	24	—	24	24	—	24	24	—
Tmax (h)	1.0 0.5 - 3.0	1.0 0.5 - 3.0	—	6.00 3.00 - 12.0	8.00 4.00 - 24.0	—	4.0 3.0 - 8.0	4.0 3.0 - 8.0	—
Cmax (ng/mL)	3.80 (51.4) 1.75 - 11.1	3.20 (38.2) 1.66 - 6.76	0.87 0.77 - 0.98	0.458 (33.0) 0.238 - 0.826	0.697 (32.4) 0.163 - 1.14	1.50 1.32 - 1.70	7.79 (40.8) 3.96 - 17.4	8.29 (32.4) 2.42 - 13.4	1.07 0.95 - 1.21
$AUC_{0-tlast}$ (ng·h/mL)	30.4 (29.1) 17.7 - 53.9	30.6 (32.3 16.8 - 51.3	0.99 0.90 - 1.10	9.79 (34.4) 3.17 - 16.1	21.6 (29.8) 4.92 - 31.9	2.22 1.90 - 2.58	92.8 (37.8) 32.4 - 163	107 (32.6) 16.4 - 157	1.15 0.97 - 1.36
AUC_{0-inf} (ng·h/mL)	33.0 (31.4) 18.1 - 58.4	33.7 (32.1) 18.1 - 56.3	1.01 0.91 - 1.13	11.4 (32.2) 3.91 - 18.0	25.1 (28.1) 6.25 - 43.5	2.22 1.91 - 2.58	99.2 (35.6) 43.5 - 168	119 # (26.6) 46.7 - 169	1.22 1.11 - 1.34
CL/f (L/h)	166 (30.4) 85.6 - 277	165 (34.3) 88.8 - 276	—	472 (43.1) 264 - 1217	215 (56.7) 109 - 761	—	93.4 (39.6) 48.2 - 186	74.9 # (39.2) 47.9 - 173	—
Vz/f (L)	6250 (47.9) 1798 - 15702	7648 (57.2) 2835 - 18716	—	10302 (34.3) 5233 - 17401	6516 (57.4) 3000 - 20360	—	1376 (48.8) 482 - 3975	1362 # (53.3) 667 - 3650	—
$t_{1/2}$ (h)	29.1 (62.0) 7.19 – 93.1	33.9 (55.7) 14.1 - 86.5	—	16.3 (40.4) 8.96 - 37.7	21.5 (37.8) 10.7 - 43.9	—	11.7 (60.8) 4.81 - 34.5	13.7 # (56.9) 4.17 - 36.0	—

a Values are Mean (CV %) min – max; except for Tmax where values are median, min – max

Although the sponsor claimed that asenapine N-oxide metrics weren't reported as it was largely undetectable, this reviewer was still able to calculate AUCs and compare them between treatments. As descriptive statistics were not helpful comparative histograms are plotted and show in Figure 120. Figure 120 indicates that there may be a slight trend for slightly higher N-oxide AUCs in the presence of cimetidine.

Figure 120 Histograms of Asenapine N-Oxide AUC_{0-72} in the Absence and Presence of Cimetidine –Study 25529



However the pharmacokinetics dosn't quite make sense, (see metabolic scheme, and indicates decreased elimination of N-desmethyl-asenapine by CYP2D6. In addition other pathways that might be affected include 11- hydroxylation, due to CYP3A4 or possible inhibition of 1A2.

Correlation between Phenotyping Assessments and Asenapine Pharmacokinetics might be helpful but were not done even though samples were collected.

"Correlation analyses (including scatter plots) of AUC versus the paraxanthine/caffeine ratio are presented in Appendix BI, Figures 10 - 1 and Analyses 10 - 1. None of the plots nor the correlation analyses indicated a correlation between exposure to asenapine and metabolites and the paraxanthine/caffeine ratio. The strongest correlation observed was with AUC0 - inf of asenapine - glucuronide on Day 5 of treatment B (administration of asenapine during cimetidine treatment) with the paraxanthine/caffeine ratio on Day 3 (r= - 0.31, p>0.05).
The results are somewhat confusing.

Correlation analyses (including scatter plots) of AUC versus the dextrorphan / dextromethorphan ratio are presented in Appendix BI, Figures 10 - 2 and Analyses 10 - 2. Neither any of the plots nor the correlation analyses indicated a relevant correlation between exposure to asenapine or metabolites and the dextrorphan/ dextromethorphan ratio except an incidental significant correlation for AUC0 - inf of asenapine - glucuronide on Day 5 (administration of asenapine during cimetidine treatment) with the ratio Day 3/Day - 1 of the dextrorphan/dextromethorphan ratio (r=0.51, p=0.022).

Results of correlation analyses (including scatter plots) of the PK parameters AUC0 - tlast and AUC0 - ∞ of asenapine and metabolites with the urinary 6β–hydroxycortisol/free cortisol ratio are given in Appendix BI, Figures 10 - 3 and Analyses 10 - 3. Neither any of the plots nor the correlation analyses indicated a relevant correlation between exposure to asenapine or metabolites and the 6β–hydroxycortisol/free cortisol ratio except an incidental significant correlation for AUC0 - tlast of asenapine - glucuronide on Day 5 of treatment B (administration of asenapine during cimetidine treatment) with the Day 3/Day - 1 ratio of the 6β–hydroxycortisol/free cortisol ratio (r= - 0.47, p=0.022)."

Safety

Mainly mild dizziness was reported for one subject after asenapine alone and for five subjects after administration of asenapine plus cimetidine. Dizziness started between 0.5 and 4.5 hours after dosing, the duration varied between one and 30 minutes, only Subject 19 reported mild dizziness for about eight hours.

Incidence of AEs	Treatment A		Treatment B			
	Placebo (N=29) n (%)	Asenapine (N=25) n (%)	Caffeine/ Dextro-methorphan (N=24) n (%)	Cimetidine (N=24) n (%)	Cimetidine+Caffeine/ Dextromethorphan (N=24) n (%)	Cimetidine+ Asenapine (N=24) n (%)
Subjects with any AE	1 (3.4%)	20 (80.0%)	0 (0.0%)	4 (16.7%)	1 (4.2%)	22 (91.7%)
Subjects without any AE	28 (96.6%)	5 (20.0%)	24 (100.0%)	20 (83.3%)	23 (95.8%)	2 (8.3%)
Subjects with any drug related AE*	1 (3.4%)	20 (80.0%)	0 (0.0%)	4 (16.7%)	0 (0.0%)	22 (91.7%)
Subjects with any severe AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (25.0%)
Subjects with any SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects discontinued due to an AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

* Relationship specified as 'definite', 'probable', 'possible'

N = number of subjects receiving the respective treatment at least once, n = number of subjects with at least one AE in the respective category

Source: Appendix F4, Table 4.1.1

"asenapine. Mainly mild dizziness was reported for one subject after asenapine alone and for five subjects after administration of asenapine plus cimetidine. Dizziness started between 0.5 and 4.5 hours after dosing, the duration varied between one and 30 minutes, only Subject 19 reported mild dizziness for about eight hours. Subject 14 had a syncope on his way back from the toilet (the subject had difficulties to urinate in the study room, therefore he was allowed to go to the toilet under supervision of the investigator), the syncope occurred at about three hours after dosing of asenapine during treatment with cimetidine and lasted for two minutes; the first available blood pressure value was recorded at the end of the syncope, the value was still low (84/53 mmHg, pulse rate 44 bpm), but increased in the next minutes (six minutes later: 110/64 mmHg, pulse rate 48 bpm). The systolic blood pressure remained below 110 mmHg for the next hour and increased thereafter. Twenty minutes after the syncope the subject reported moderate dizziness. Fifteen minutes after the start of this event the subject received an infusion with 5% glucose solution. (see Section 8.1.4). The event resolved immediately. For three other subjects blood pressure was measured at the time of the occurrence of dizziness (always at the end of the event), the measurements revealed a decreased blood pressure in Subject 17 (92/58 mmHg, pulse rate 44 bpm), a slightly decreased blood pressure in Subject 16 (108/72 mmHg, pulse rate 56 bpm) and an increased blood pressure in Subject 111 (147/88 mmHg, pulse rate 65 bpm, see Appendix G, Listing 12.1)."

Listing 12.2 **Listing of Clinically Relevant Abnormal Vital Signs Values.**

Vital sign parameter	Subject number	Treatment	Assessment Name	Day (*)	Actual date	Relative time	Actual time	Baseline (*)	Value	Absolute change (*)
Supine systolic blood pressure (mmHg)	14	B	Unplanned	5 #	05JUL2005	AFTER 10 MIN	12:40	117	84 L	-33 L
	21	A	P2 Day 1	1	22JUL2005	+01:00	10:55	113	78 L	-35 L
Supine diastolic blood pressure (mmHg)	15	B	Unplanned	4 #	04JUL2005	AFTER 10 MIN	08:28	64	46 L	-18 L
Supine pulse rate (bpm)	14	B	Unplanned	5 #	05JUL2005	AFTER 10 MIN	12:40	60	44 L	-16 L
							14:02	60	44 L	-16 L
	17	B	Unplanned	5 #	05JUL2005	AFTER 10 MIN	14:10	74	44 L	-30 L
							14:12	74	49 L	-25 L

5.5.7.5.6 Effect of Fluvoxamine on Asenapine - Study 41033

Study 41033 was an open-label, randomized, two-way crossover study to assess the effect of fluvoxamine on asenapine in 26 healthy non-smoking male subjects between 18 and 55 years of age

Treatments were as follows:

Treatment A (asenapine alone):	Day 1: Asenapine 5 mg SL x 1.
Treatment B (asenapine + fluvoxamine):	Days 1-7: Fluvoxamine 25 mg po BID Day 5: Asenapine 5 mg SL x 1

There was a minimum 1 week interperiod washout.

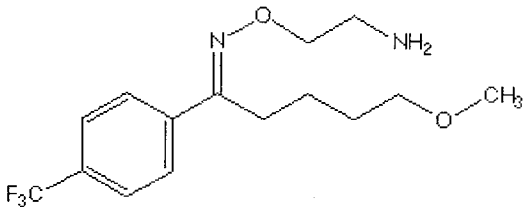
The inhibitory effect of fluvoxamine on CYP1A2 during treatment was assessed as follows:

Caffeine 100 mg po x 1 on Days -1 and 3 of the asenapine and fluvoxamine treatment with the paraxanthine/caffeine ratio determined at 6 hours post-dose and compared with the pre-dose ratio.

The pharmacokinetics of asenapine, N-demethyl-asenapine, and asenapine 11-O-sulfate were measured in the absence and presence of fluvoxamine.

The structure of fluvoxamine is shown in Figure 121 for information.

Figure 121 Fluvoxamine Structure



Results:

Demographics

Subject demographics are shown in Table 140.

Table 140 Subject Demographics - Study 41033

N	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
26	33.6 ± 10.8 21–53 [31.5]	183.4 ± 8.5 161.5-201.0 [184.0]	85.8 ± 10.3 68.4-106.7 [86.6]	25.45 ± 1.91 22.7-29.3 [25.25]

Effect of Fluvoxamine on Plasma Paraxanthine/Caffeine Ratio (CYP1A2 Inhibition)

Table 141 shows that fluvoxamine affects the probe compound.

Decrease in 6 hour caffeine concentrations by half and a 3 fold increase in paraxanthine concentrations.

Table 141 6 Hour Plasma Caffeine and Paraxanthine Concentrations and Ratios in the Absence and Presence of Fluvoxamine 25 mg PO BID – Study 41033

Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 3/Day -1 [95% CI]
	Pre-Fluvoxamine	With Fluvoxamine	Pre-Fluvoxamine	With Fluvoxamine	
	Day -1	Day 3	Day - 1	Day 3	
Caffeine (ng/mL)	691 (29.5) 368 - 1160	438 (71.4) 97.0 - 1320	666	349	0.52 [0.39 - 0.70]
Paraxanthine (ng/mL)	999 (46.9) 286 - 2590	2735 (36.1) 1570 - 5900	903	2593	2.87 [2.41 - 3.43]
Paraxanthine / Caffeine Ratio	0.781 (33.6) 0.437 - 1.29	0.163 (72.1) 0.0437 - 0.61	0.740	0.136	0.18 [0.15 - 0.22]

Effect of Fluvoxamine on Asenapine and Metabolites (CYP1A2 Inhibition)

Figure 122 to Figure 124 and Table 142 show that fluvoxamine increases the exposure to asenapine by 30%, decreases exposure to asenapine 11-O-sulfate by 30%, and increases exposure to desmethyl-asenapine by 2 fold. The metabolic scheme, (Figure 15), shows that the increase in exposure to desmethyl-asenapine is likely due to inhibition of 11-hydroxylation of desmethyl-asenapine. This will result in shunting to N-oxidation, although increased formylation is also a possibility. The shunting to N-oxidation will result in greater inhibition of CYP2D6 and as a suicide substrate result in even greater inhibition and thus result in nonlinear accumulation of desmethyl-asenapine upon multiple dosing. It's also possible that the increased inhibition of CYP2D6 with result in increased hepatotoxicity.

Figure 122 Mean Asenapine Concentration vs. Time Profiles in the Absence and Presence of Fluvoxamine – Study 41033

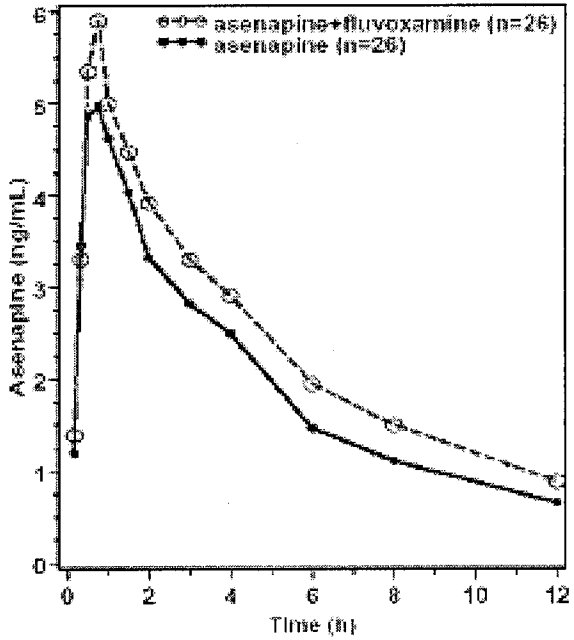


Figure 123 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Fluvoxamine – Study 41033

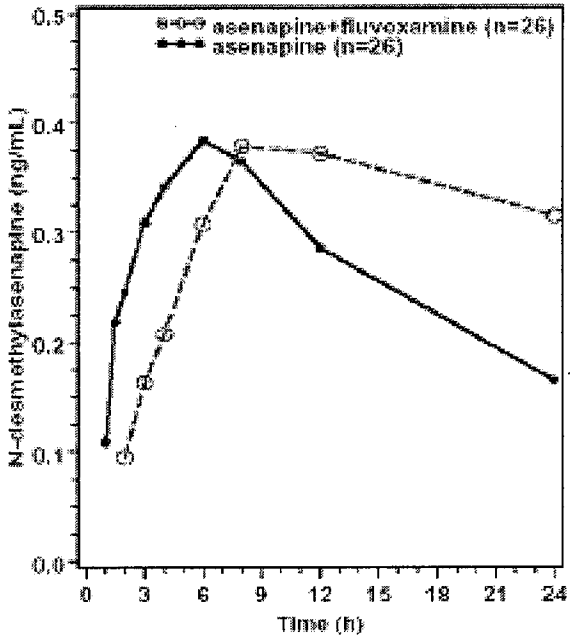


Figure 124 Mean Asenapine 11-O-Sulfate Concentration vs. Time Profiles in the Absence and Presence of Fluvoxamine – Study 41033

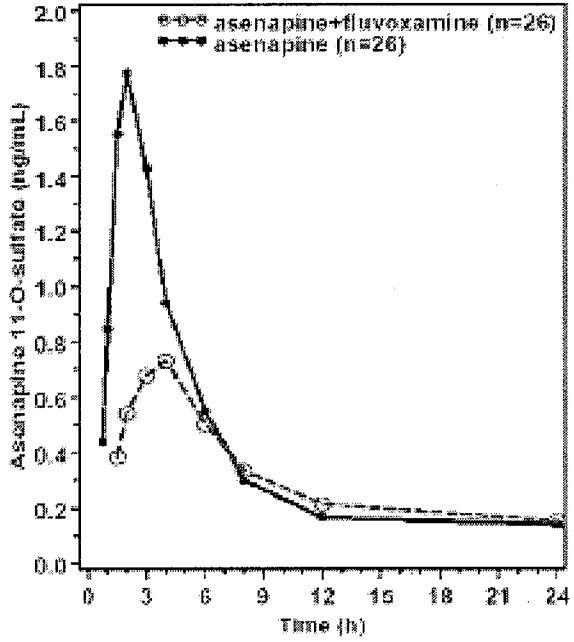


Table 142 Asenapine, Desmethyl-Asenapine, and Asenapine 11-O-sulfate 5 mg SL Single Dose PK Parameters in the Absence and Presence of Fluvoxamine 25 mg PO BID – Study 41033

Parameter (unit)	Asenapine			N – Desmethyl-Asenapine			Asenapine 11 - O - Sulfate		
	Asenapine	Asenapine + Fluvoxamine	GMR (90% CI)	Asenapine	Asenapine + Fluvoxamine	GMR (90% CI)	Asenapine	Asenapine + Fluvoxamine	GMR (90% CI)
N	26	26		26	26		26	26	
Tmax (h)	0.75 0.33 - 1.52	0.75 0.50 - 2.00		6.00 3.00 - 12.0	12.0 6.00 - 24.0		2.00 1.00 - 3.02	4.00 1.50 - 8.00	
Cmax (ng/mL)	5.40 (40.2) 2.67 - 10.9	6.11 (42.8) 1.64 - 13.9	1.13 0.99 - 1.30	0.413 (34.6) 0.109 - 0.650	0.415 (42.3) 0.107 - 0.770	0.99 0.83 - 1.18	1.95 (75.6) 0.115 - 7.17	0.784 (78.9) 0.052 - 2.69	0.40 0.30 - 0.52
AUC_{tlast} ($ng/mL \times hr^{-1}$)	34.5 (32.1) 18.8 - 69.9	44.9 (38.6) 20.0 - 106	1.29 1.15 - 1.45	8.34 (43.6) 1.67 - 15.9	16.1 (43.3) 3.54 - 30.7	1.97 1.66 - 2.35	10.6 (82.2) 0.621 - 34.8	8.80 (88.2) 0.203 - 30.3	0.71 0.52 - 0.98
AUCinf ($ng/mL \times hr^{-1}$)	37.6 (34.2) 21.1 - 78.0	49.0 (40.9) 22.3 - 121	1.29 1.14 - 1.46	10.4 (37.6) 3.33 - 18.7	22.0 (44.2) 6.25 - 54.2	2.10 1.82 - 2.43			
CL/F (L/h)	147 (32.2) 64.1 - 237	117 (37.3) 41.3 - 224		536 (47.0) 255 - 1429	259 (50.8) 87.8 - 761				
Vz/F (L)	5417 (58.2) 1620 - 15166	4429 (45.2) 2062 - 9336		11833 (64.8) 5529 - 44366	10644 (55.9) 3561 - 33529				
$t_{1/2}$ (h)	27.6 (61.9) 9.33 - 69.1	27.8 (42.8) 12.5 - 64.0		15.7 (38.7) 8.65 - 39.2	29.5 (38.9) 17.6 - 63.9		20.5# (38.2) 9.54 - 36.7	26.7## (93.8) 8.95 - 102	

Values are Mean, CV (%), min – max

5.5.8 Population Pharmacokinetics

The sponsor conducted two sets of population pharmacokinetic analyses that were reported in the following reports:

- INT00036661 Phase I and Phase II Safety Studies
- INT00036719 Phase II and Phase III Efficacy Studies in Acute Excerbations of Schizophrenia and Mania

The population PK model was developed using the phase I and II study data from single and multiple dose data with intensive PK sampling in healthy subjects and some patients with schizophrenia.

The data from the Phase II and III studies were then used to validate the population PK model previously developed, see Table 151 for these studies.

The purpose of this exercise appears to be two-fold: to make a decision on risks associated with design of Phase III studies and to develop drug-disease models for future modeling and stimulation.

5.5.8.1 Population Pharmacokinetic Modeling of Phase I and Phase II Safety Studies

The phase I and II studies used to develop the population pharmacokinetic mode are shown in Table 143 on the following page. Dosages with PK data range from 0.8 mg BID to 20 mg BID for up to 16 days.

All of the phase I and II studies utilized intense pharmacokinetic sampling, although the studies in healthy volunteers collected from 4 – 6 samples in the first hour post dosing with the first sample typically collected at 10 minutes (0.17 hours) and as early as 6 minutes post dosing. In contrast sampling in the studies in patients typically obtained the first sample at 1 hour post-dose although in one study the first sample was obtained at 0.5 hours, (see Table 143).

Table 143 Phase I/II Studies included in the Development of the Population Pharmacokinetic Model

Study # (Phase)	SD / MD	Study Design	Subjects	Dose	Use IOV[a]	Fed/ Fasted	Analytic Method	LLOQ (ng/mL)	Sampling Days	PK Sampling Times (hr postdose)	Data to be Used
25537 (1)	MD	Effect of water	Vols	1, 3, 5 mg once daily (3- day titration) followed by 10 mg once daily for 28 days.	Yes	Fasted	LC-MS	0.025	Days 10, 17, 24 and 31	Predose, 0.1, 0.18, 0.25, 0.52, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24.	Water 10 and 30 min after dosing
25542 (1)	MD	S/T	Male Vols	Titrated up (over 3 or 4 days) to 3, 5, 10, or 15 mg BID and remaining at that dose for 6 or 7 days; 2 mg SD; 5 mg SD	Yes	No food 0.5 h after dosing	LC-MS	0.100, Or 0.025 (Group 5)	Groups 1-3: Day 9: Group 4: Day 11: same as Groups 1-3; Group 5: Days 1 and 8:	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 20, 24, 30, 36, 48 and 72; Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48, and 72.	Asenapine
25545 (1)	SD	2-way crossover study in smokers	Male Vol Smokers	5 mg	Yes	Fasted	LC-MS	0.025	Days 1 and 8:	Predose, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 60.	All
25546 (1)	SD then MD	S/T PK	Japanese and Caucasian Vols	1, 3, 5 mg SD 1, 3, 5, 10 mg BID up to 9 days	Yes	No food 0.5 hours before or after dosing	LC-MS	0.025	SD period: Day 1: MD period: Last day of dosing:	Predose, 0.17, 0.33, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48 and 72. same timepoints.	Asenapine
A7501001 (1)	MD	Parallel, study of effect of asenapine, quetiapine, and placebo on QTc	Pxts with Schizo-phrenia	5-10 and 15-20 mg BID up to 16 days	Yes	Fed	LC-MS	0.100	Days 1, 10, and 16 (pAM dose): Day 16:	Predose, Predose, 1, 2, 3, 4, 6, 8, and 12 16, 24, 36 and 48.	Asenapine
A7501015 (1)	SD	3-treatment, 3-way crossover, BE Study	Vols	5 mg	Yes	Fasted	LC-MS	0.025	Days 1, 8 and 15:	Predose, 0.17, 0.33, 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48.	All
A7501016 (1)	SD	2-way X-over, BE study	Vols	5 mg	Yes	Fasted	LC-MS	0.025	Days 1 and 8:	Predose, 0.17, 0.33, 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48.	All
041001 (2)	MD	Dose- titration MTD study	Pxts	0.2 - 0.8 mg BID up to 17 days	Yes	Fasted	GC-MS	0.020	At screening. Then at each day of up-titration 1-2 hours prior to the morning dose. Then at 2 days after attainment of the maximum dose at 1.5 hours after the morning dose. Then at final dose:	Predose, 1, 1.5, 2, 10, 24, 36, and 48.	Asenapine
041007 (2)	MD	Dose- titration MTD study	Pxts	0.2 – 4.8 mg BID up to 18 days	Yes	Fasted	GC-MS	0.020	Block 1: Predose on Days 2-5, 8, 11, 14 and 15. Blocks 2 and 3: Each day of up-titration following the morning dose. All Blocks: At final dose,	Predose, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72.	Asenapine
041012 (2)	MD	Dose- titration MTD study	Pxts	2 to 20 mg BID up to 10 days	Yes	Fasted	GC-MS	0.020	Each titration day: Predose. Endpoint day:	Predose, 1.0, 1.5, 2, 4, 8, and 12.	Asenapine
041014 (2)	MD	2-way X-over relative BE S/T	Pxts	3x5, and 15 mg BID for 7 days	Yes	Fed	GC-MS	0.020 ng/	At screening. Days 5 and 7	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12. Day 7: 24.	All

a IOV – Inter-occasion variability

The sponsor's description of their Pop PK model development follows:

"Base Model Development

A 2-compartment model with first-order absorption (nonlinear mixed effects modeling [NONMEM] subroutine ADVAN4) was fit to the <natural log of the> *asenapine concentrations. The dependent variable was log-transformed concentration. An apparent first order absorption rate constant (ka) and a lag-time parameter (Tlag) were used to characterize the absorption process. The disposition kinetics were modeled using a parameterization involving apparent oral clearance (CL/F), apparent central volume (V2), apparent intercompartmental clearance (Q), and apparent peripheral volume (V3). Although CL, V2, Q, and V3 are typical for NONMEM subroutine TRANS4 parameterizations, TRANS1 was utilized whereby the TRANS4 parameterization was retained and intersubject random effects were added to the TRANS1 parameters such as ka, k23, and k32, to increase the computational stability. The parameter k represented the elimination rate constant and the parameters k23 and k32 were used to represent the inter-compartmental transfer rate constants. The FOCE interaction estimation method of NONMEM was employed. The within-subject variability was modeled with an additive error on the log-transformed concentration and reported as the approximate coefficient of variation (CV [%]).*

Prior knowledge of nonlinear PK, and inspection of diagnostic plots by dose, suggested the need for incorporating parameters to account for the dose dependency of apparent bioavailability (F1).

A linear model with respect to logarithmic dose, normalized by the approximate mean dose of 10 mg, was used to describe nonlinear F1 dependent on dose.

$$F_1 = 1 - Slope \cdot \log\left(\frac{Dose}{10}\right)$$

where F1 represents apparent bioavailability in the model, slope is a constant to describe the linear relationship between F1 and logarithmic dose. A positive quantity of slope represents decreased bioavailability with increasing dose."

Random Effects Model Development

Interindividual variability (IIV) and interoccasion variability (IOV) in the pharmacokinetic parameters (ie, k, V2, k23, k32, ka, and F1) were modeled using multiplicative exponential random effects of the form:

$$\theta_{ij} = \theta \cdot \exp(\eta_i + k_{ij})$$

where θij represents the value of the PK parameter (eg, V2) for individual i during occasion j, θ is the typical individual (population mean) value of the parameter, ηi denotes the interindividual random deviation from θ for patient i, and kij denotes the random deviation from individual i's prediction for occasion j. The values for ηi and kij are assumed to have zero means and covariance matrices of Ω and Ψ. The square roots of the diagonal elements of Ω and Ψ can be interpreted as approximate coefficients of variation (CVs). A full block (unstructured) Ω was attempted to be estimated. Alternative reduced structures for Ω were also evaluated to obtain a stable and parsimonious covariance structure. Residual variability was modeled using the log-transformed error model:

ln(Yij) = ln(Fij) + εij

where Yij denotes the observed concentration for the ith individual at time tj, Fij denotes the corresponding predicted concentration based on the PK model, and εij denotes the intraindividual (residual) random effect assumed to have zero mean and variance σ2. Other residual error models were explored when heterogeneity was observed in the WRES versus PRED or IWRES versus IPRED plots.

Full Model Development

Covariates were added to the base model simultaneously to form the full model. Continuous covariates examined in this analysis include age and weight. Continuous covariates were modeled as multiplicative effects of the form:

$\theta = \theta_0 \bullet (x / x_{norm})^{\theta x}$

where θ_0 denotes the population value of the parameter when $x = x_{norm}$ (eg, x_{norm}= 40 years for age and x_{norm} = 70 kg for weight). The parameter θ denotes the population value conditional on the value of x, which is proportional to the power θx. When θx = 1, θ is directly proportional to x.

Dichotomous covariates examined were:

- *Gender (0 for females, 1 for males);*
- *Race (indicator variables for white, black, or Asian for which 1 is for yes and 0 is for no.)*
- *Smoking use (0 for nonsmokers (includes former smokers), 1 for smokers);*
- *Alcohol use (0 for no alcohol consumption, 1 if one or more drinks/week were consumed); and*
- *Patient status (0 for patients, 1 for healthy volunteers).*

The effect of a dichotomous covariate x was modeled as:

$\theta = \theta_0 \bullet (1 + \theta_x \bullet x)$

where θ_0 denotes the population value of the parameter for the null value of the covariate x (ie, x = 0). The parameter θ_x denotes the fractional change in θ_0 when x = 1.

For Tlag, a high correlation (-0.999) between θ_0 and θ_x was observed, which caused instability in the full model. Since the effect of patient status on lag time was highly significant (OFV decreased by 420.8 with its inclusion to the base model), the effect of patient status was incorporated as structural differences in further covariate testing procedures as follows:

$\theta = \theta_0$ *(for healthy volunteers)*

$\theta = \theta_x$ *(for patients)*

The covariates included in the full model are listed in Table 144.

Table 144 Covariates Included in the Full Model

PK Parameter	Covariates
CL/F (ke)	Age, Gender, Weight, Race, Smoking , Alcohol Use
F1	Patient Status
Ka	Patient Status
Tlag	Patient Status

When a covariate value was missing for a given visit, the missing value was replaced using a prior reported value, or the average value of all visits for that subject. This was done for all studies.

A full list of the covariates examined is shown in Table 145 on the following page.

Table 145 Covariates Examined

Variable	Definition	Categories / Units
ID	NONMEM Identification Number (unique for the entire dataset)	NA
STUD	Study Number	NA
DOSE	Dose Administered for the dosing period	Mg
AMT	Amount (Dose) for Dosing Event	µg
TIME	Relative Time Since the Very First Dose Within Subject	Hours
RLTM	Relative Time Since the Most Recent Dose	Hours
DV	Dependent Variable: log (asenapine conc)	ng/mL
MDV	Missing Data Value	0 = asenapine observation; 1 = other
EVID	Event Identification Data Item	0 = observation; 1 = dose
HV	Patient Status	0 = patients; 1 = healthy
AGE	Age	Years
WGT	Weight	Kg
SEX	Sex	1 = male; 0 = female
RACE	Race	1=White, Non-Hispanic; 2=Black, Non-Hispanic; 3=Hispanic (White or Black); 4=Asian or Pacific Islander; 6=Other
CLCR	Creatinine Clearance Derived using the following equations: Males: CLcr = (((140-age)*weight)/(72*scr)) Females: CLcr = (((140-age)*weight)/(72*scr))*0.85	mL/min
SMOK	Smoking (Daily Use)	0=no, 1=<1 pack per day, 2=1 to 2 packs per day, 3=>2 packs a day, 4, smoker, but the quantity unknown, 5=unknown
HORM	Hormonal status	2=unknown, 0=pre-menopausal 1=post-menopausal, 3=male
ETH	Ethanol consumption (Past 1 month)	0=none 1= <1 drink per week 2= 1 - 6 drinks per week 3= 7 - 12 drinks per week 4= 13 - 18 drinks per week 5= 19 - 24 drinks per week 6= 25 - 35 drinks per week 7= 36+ drinks per week 8=unknown
ALBU	Albumin concentration	g/dL
BILI	Bilirubin concentration	mg/dL

The characteristics of continuous demographic variables from the phase I/II population PK studies are shown in Table 146.

Table 146 Phase I/II Pop PK Studies Population Characteristics for Continuous Demographic Variables[a] [Mean ± SD]

Treatment	SD / MD	Study Objective	Subjs	Dosage	Duration (days)	N	Age (yr)	Weight (kg)	CLcr[b] (mL/min)	Albumin (g/dL)	Bilirubin (mg/dL)
25537	MD	BE H20	Vol	10 mg qd	28	23	34.3 ± 6.63	78.8 ± 7.97	104 ± 13.3	4.78 ± 0.274	0.701 ± 0.258
25542	MD	MTD	Vol	15 mg	6 - 7	30	23.9 ± 6.91	75.6 ± 9.29	110 ± 16.4	4.82 ± 0.284	0.745 ± 0.461
25545	SD	Smokers	Vol	5 mg		24	32.6 ± 7.86	75.3 ± 6.38	107 ± 14.1	4.81 ± 0.275	0.595 ± 0.241
25546	SD/MD	Race	Vol	10 mg	9	49	24.4 ± 3.39	67.7 ± 7.68	102 ± 15	4.82 ± 0.205	1.03 ± 0.414
A7501001	MD	QTc	Vol	**20 mg**	**16**	76	43 ± 8.63	84.2 ± 15.8	104 ± 43.2	7.21 ± 10.1	**1.26 ± 2.64**
A7501015	SD	BE	Vol	5 mg		38	24.7 ± 6.53	74.5 ± 14.9	118 ± 28	4.51 ± 0.341	0.737 ± 0.331
A7501016	SD	BE	Vol	5 mg		36	26.7 ± 9.08	74.4 ± 11.2	119 ± 22	4.33 ± 0.341	0.833 ± 0.379
041001	MD	MTD	Pxt	0.8 mg	17	24	38.5 ± 6.9	82.5 ± 13	120 ± 16	4.3 ± 0.303	0.717 ± 0.232
041007	MD	MTD	Pxt	4.8 mg	18	20	36.7 ± 7.66	83.7 ± 13.2	140 ± 41.7	4.11 ± 0.335	0.415 ± 0.15
041012	MD	MTD	Pxt	20 mg	10	18	44.3 ± 8.19	87.8 ± 20.8	119 ± 43.2	4.14 ± 0.299	0.5 ± 0.228
041014	MD	MTD	Pxt	15 mg	7	8	39.6 ± 8.16	87.5 ± 19.1	147 ± 40.1	4.3 ± 0.283	0.438 ± 0.16
All Studies (Range)						346	33.0 ± 10.7 (18 - 57)	78.2 ± 14.2 (44.7 - 134.5)	111.9 ± 31.8 (0.78 - 233.8)	5.18 ± 4.99 (1.6 - 50)	0.860 ± 1.32 (0.1 - 11)

a Based on data at screening
b MD is BID unless otherwise noted
c CLcr = Creatinine clearance.

What was noteworthy to this reviewer was that the mean bilirubin and albumin concentrations were elevated and the variability was increased in the thorough QTc study which employed the highest dose for the longest duration. This reviewer then performed identified all bilirubin values in the pop PK dataset that were listed as greater than 1 mg/dL. This resulted in identification of 24 elevated values in 22 individuals. Of these elevated values 6 were 10 or greater and came from the thorough QT study which employed the largest doses for the longest duration in 76 subjects (6/76 = 7.9%). There were also two other bilirubins from other studies listed as > 2X ULN.

Upon checking, this reviewer found that the clinical study report for the thorough QTc study did not include laboratory values. Mean values were reported in the text of the clinical study report, however they were only for pre- and post-treatment values, and the mean and variabilities reported do not indicate any elevated values of bilirubin. In contrast laboratory chemistry values were deteremined during drug adminisation on day 9 per the protocol, however there is no indication that these were reported. Since the bilirubin and other laboratory values could not be checked, it cannot be ascertained whether the elevations are due to hepatic impairment or other mechanisms such as acute hemolytic anemia, and the implication of these values for the pop PK analysis is uncertain. It's also noteworthy that there was a high participation rate of women, blacks, and smokers in this study. Concentrations are expected to be higher in women and blacks, and smaller in smokers. The implications of each of these factors on exposure to asenapine itself and on metabolic shunting is unclear, however they might respectively either increase or decrease risk in a nonadditive manner. In checking other studies this reviewer found that bilirubin values were reported in SI units however, on conversion the values did not match the values in mg/dL reported in the pop PK database. Lastly this reviewer also noted that in the study report for PET study xxx, that

The totality of the information suggests that a dose and treatment duration hepatotoxicity is of real concern with asenapine and there may be greater risk if the drug is swallowed or if children should take an adult dose. Due to these concerns this reviewer requested that the sponsor be asked to provide complete laboratory information and informed the medical reviewer so that this concern could be fully evaluated. A meeting was held with the medical division where the medical division dismissed the concern of hepatotoxcicity. However, this reviewer has been unable to find where the information request for laboratory information was ever forwarded to the sponsor or where it was ever received.

Table 147 shows the number of missing values by study. It's noteworthy that information on alcohol use and smoking is not available from most studies and in particular the degree of tobacco use was not quantified in the smoking study, and was greatest in the thorough QTc study which might skew both the pop PK and the safety results.

Table 148 shows the distribution of categorical variables in the phase I/II pop PK studies. Again it's noteworthy that tobacco use was highest in the patient studies, which is to be expected, however the lack of smokers in other studies may bias the model.

Finally Table 149 shows the degree of tobacco use is highest in the thorough QTc study. Consequently, this may again bias the results resulting in lower exposures with the higher doses used in this study. Although 8 nonsmokers are listed there were only 3 nonsmokers in the highest asenapine dose group.

Table 147 Phase I/II Pop PK Number of Missing Variables by Study

Study	SD / MD[a]	Study Obj	Subjs	Dosage[a]	N	Age (yrs)	Gender	Hormonal Status	Race	Weight (kg)	CLcr (mL/min)	Albumin (g/dL)	Bilirubin (mg/dL)	EtOH	Smoking
25537	MD	BE H20	Vol	10 mg qd	23	0	0	0	0	0	0	0	0	23	23
25542	MD	MTD	Vol	15 mg	30	0	0	0	0	0	0	0	0	30	30
25545	SD	Smokers	Vol	5 mg	24	0	0	0	0	0	0	0	0	24	24
25546	SD/MD	Race	Vol	10 mg	49	0	0	0	0	0	0	0	0	49	49
A7501001	MD	QTc	Vol	20 mg	76	0	0	0	0	0	0	0	0	0	0
A7501015	SD	BE	Vol	5 mg	38	0	0	0	0	0	0	0	0	0	0
A7501016	SD	BE	Vol	5 mg	36	0	0	0	0	0	0	0	0	0	0
041001	MD	MTD	Pxt	0.8 mg	24	0	0	24	0	0	18	18	18	24	24
041007	MD	MTD	Pxt	4.8 mg	20	0	0	20	0	1	1	0	0	20	0
041012	MD	MTD	Pxt	20 mg	18	0	0	18	0	0	0	0	0	18	0
041014	MD	MTD	Pxt	15 mg	8	0	0	8	0	0	0	0	0	8	0
Total (%)					346	0 (0)	0 (0)	70 (20.2)	0 (0)	1 (0.29)	19 (5.5)	18 (5.2)	18 (5.2)	196 (56.6)	150 (43.4)

a MD is BID unless otherwise noted

Table 148 Phase I/II Pop PK Population Characteristics for Categorical Variables by Study[a] [N (%)]

Study	SD / MD[b]	Study Obj	Subjs	Dosage[b]	N	Gender		Race				EtOH Use		Smoking Status	
						Male	Female	White	Black	Asian	Other	Yes	No[c]	Yes	No[c]
25537	MD	BE H20	Vol	10 mg qd	23	23 (100)	0 (0)	23 (100)	0 (0)	0 (0)	0 (0)	0 (0)	23 (100)	0 (0)	23 (100)
25542	MD	MTD	Vol	15 mg	30	30 (100)	0 (0)	28 (93.3)	1 (3.33)	1 (3.33)	0 (0)	0 (0)	30 (100)	0 (0)	30 (100)
25545	SD	Smokers	Vol	5 mg	24	24 (100)	0 (0)	24 (100)	0 (0)	0 (0)	0 (0)	0 (0)	20 (100)	0 (0)	**24 (100)**
25546	SD/MD	Race	Vol	10 mg	49	49 (100)	0 (0)	25 (51)	0 (0)	24 (49)	0 (0)	0 (0)	49 (100)	0 (0)	49 (100)
A7501001	MD	QTc	Vol	20 mg	76	59 (77.6)	**17 (22.4)**	30 (39.5)	37 (48.7)	1 (1.32)	8 (10.5)	**16 (21.1)**	60 (78.9)	**68 (89.5)**	8 (10.5)
A7501015	SD	BE	Vol	5 mg	38	27 (71.1)	11 (28.9)	0 (0)	8 (21.1)	3 (7.89)	27 (71.1)	17 (44.7)	21 (55.3)	13 (34.2)	25 (65.8)
A7501016	SD	BE	Vol	5 mg	36	22 (61.1)	14 (38.9)	0 (0)	4 (11.1)	0 (0)	32 (88.9)	16 (44.4)	20 (55.6)	13 (36.1)	23 (63.9)
041001	MD	MTD	Pxt	0.8 mg	24	21 (87.5)	3 (12.5)	18 (75)	1 (4.17)	0 (0)	5 (20.8)	0 (0)	24 (100)	0 (0)	24 (100)
041007	MD	MTD	Pxt	4.8 mg	20	16 (80)	4 (20)	13 (65)	4 (20)	1 (5)	2 (10)	0 (0)	20 (100)	16 (80)	4 (20)
041012	MD	MTD	Pxt	20 mg	18	17 (94.4)	1 (5.56)	3 (16.7)	15 (83.3)	0 (0)	0 (0)	0 (0)	18 (100)	17 (94.4)	1 (5.56)
041014	MD	MTD	Pxt	15 mg	8	6 (75)	2 (25)	5 (62.5)	1 (12.5)	0 (0)	2 (25)	0 (0)	8 (100)	8 (100)	0 (0)
Total					346	294 (85.0)	52 (15.0)	169 (48.8)	71 (20.5)	30 (8.67)	76 (22.0)	49 (14.2)	297 (85.5)	135 (39.0)	211 (61.0)

a Based on data at screening
b MD is BID unless otherwise noted
c including missing values

Table 149 Smoking Status by Study in Studies used in Phase I/II Pop PK Analyses

Study Number	NONMEM Study Code	N	SD / MD	Study Objective	Subjs	Dosage[a]	Smoking Status Group					
							0	1	2	3	4	5
							Nonsmoker	< 1 PPD	1 - 2 PPD	> 2 PPD	Smoker Unknown Qty	Status Unknown
25537	37	23	MD	BE H_2O	Vol	10 mg qd	0	0	0	0	—	23
25542	42	30	MD	MTD	Vol	15 mg	0	0	0	0	—	30
25545	**45**	**24**	**SD**	**Smokers**	**Vol**	**5 mg**	**0**	**0**	**0**	**0**		**24**
25546	46	49	SD/MD	Race	Vol	10 mg	0	0	0	0	—	49
A7501001	**1**	**76**	**MD**	**QTc**	**Vol**	**20 mg**	**8**	**32**	**35**	**1**		**0**
A751015	15	38	SD	BE	Vol	5 mg	25	11	2	0	—	0
A751016	16	36	SD	BE	Vol	5 mg	23	6	7	0	—	0
041001	41	24	MD	MTD	Pxt	0.8 mg	0	0	0	0	—	24
041007	47	20	MD	MTD	Pxt	4.8 mg	4	13	2	1	—	0
041012	12	18	MD	MTD	Pxt	20 mg	1	14	2	1	—	0
041014	44	8	MD	MTD	Pxt	15 mg	0	8	0	0	—	0
Total		**346**					**61**	**84**	**48**	**3**		**150**

a MD is BID unless otherwise noted

The following pages show the sponsor's figures of typical semi-log concentration vs. time profiles predicted using the base structural model, (i.e. a 2 compartment open model with a lag phase and nonlinear first order absorption), developed from the phase I and II data overlaid with observed single dose concentration data in Figure 125 and multiple dose data in Figure 126. Data from healthy volunteers are indicated by red circles and from patients with gray asterixes in these figures.

Figure 127 shows the same data overlaid on the expected typical semi-log concentration vs. time profile with the 95% confidence interval for the population.

Figure 128 shows a QQ plot for observed vs. simulated asenapine concentrations it's clear from this plot that the model begins to break down at concentrations above approximately 11 ng/ml. At the other end of the concentration spectrum examination of Figure 125 shows that at concentrations of around 0.02 ng/ml the concentration vs. profiles indicate a deviation from the model that may be indicative of either a third compartment or cross-over interference in the assay from a metabolite.

Figure 125 and Figure 126 show maximally achieved peak concentrations of around 10 ng/ml after single and multiple 5 mg doses respectively. Figure 126 shows maximally achieved peak concentrations of upwards of 20 ng/ml at multiple dosing of 20 mg, and Figure 127 clearly shows a maximal peak concentration of around 16 ng/ml after multiple dosing of 10 mg. However when the pop PK datafile was checked to determine the actual maximal peak concentrations at various dosages the highest concentration listed at any dose was only 9.58 ng/ml.

This reviewer attempted to double-check the Cmax ranges reported in the individual studies that used the larger doses by examining the summary tables already included in this review, this reviewer noted that ranges were not reported for these studies but only measures of central tendency. Since these reports were done by Pfizer and utilize the type of methodology that is being presently implemented in the FDA, this raises concerns that FDA will not be able to detect problems in the future.

Table 150 Attempt to Verify Cmax Range Across Studies

Study	SD / MD[a]	Study Objective	Subjs	Dosage[a]	Study Report	Data Files with Original Submission	Data Files Provided in Response to OCP Request	Upper Reported Range of Cmax (ng/ml)	Comment
25537	MD	BE H20	Vol	10 mg qd	No	No	Yes[b]		Can't open hyperlink does not work in EDR.
25542	MD	MTD	Vol	15 mg	No	No	Yes[c]		Can't open. Missing header in file.
25545	SD	Smokers	Vol	5 mg	No	No	Yes[b]		Can't open hyperlink does not work in EDR.
25546	SD /MD	Race	Vol	10 mg	Yes	No	Yes[b]	13.3	Can't open hyperlink does not work in EDR. Also receive error message in JMP Can't open. Missing header in file.
A7501001	MD	QTc	Vol	20 mg	Yes	No	Yes[c]	15 mg 8.05 (0.672 – 18.0) [d] 20 mg 10.6 (1.58 - 19.8) [d]	Told not to Review Can't open missing header in file. Followup submission of data to QT team. Max reported Conc in datafile was 9.949 ng/ml BP Oct 3, 2007 SN 0004. In addition nearly 1000 samples are listed as But when try to reopen get error msg 25512 then won't even open JMP
A7501015	SD	BE	Vol	5 mg					Told not to Reveiw
A7501016	SD	BE	Vol	5 mg					Told not to Reveiw
041001	MD	MTD	Pxt	0.8 mg		No		Dose normalilzed to 1 mg	
041007	MD	MTD	Pxt	4.8 mg	Yes	No	Yes	5.3	
041012	MD	MTD	Pxt	20 mg	Yes	No	Yes	10 mg 15.5 15 mg 11.8 20 mg 11.4	Can't open missing header in file.
041014	MD	MTD	Pxt	15 mg	Yes	No	Yesb, [c]	13.4	Told not to Review Can't open missing header in file.

a except where noted multiple dosing is BID
b Although data files were submitted in SN 0006 submitted Nov 19, 2007. On March 17, 2009 found that EDR http link does not work. Receive error message that can't find file.

Information for OCP included in Supplement 0006

25545

22 listed as NSR on 15. 20 mg

Information for OCP included in 4month Safety Update

A7501021 PK but what

011

All indiv sub listings

Exploratory Exposure Response to EPS

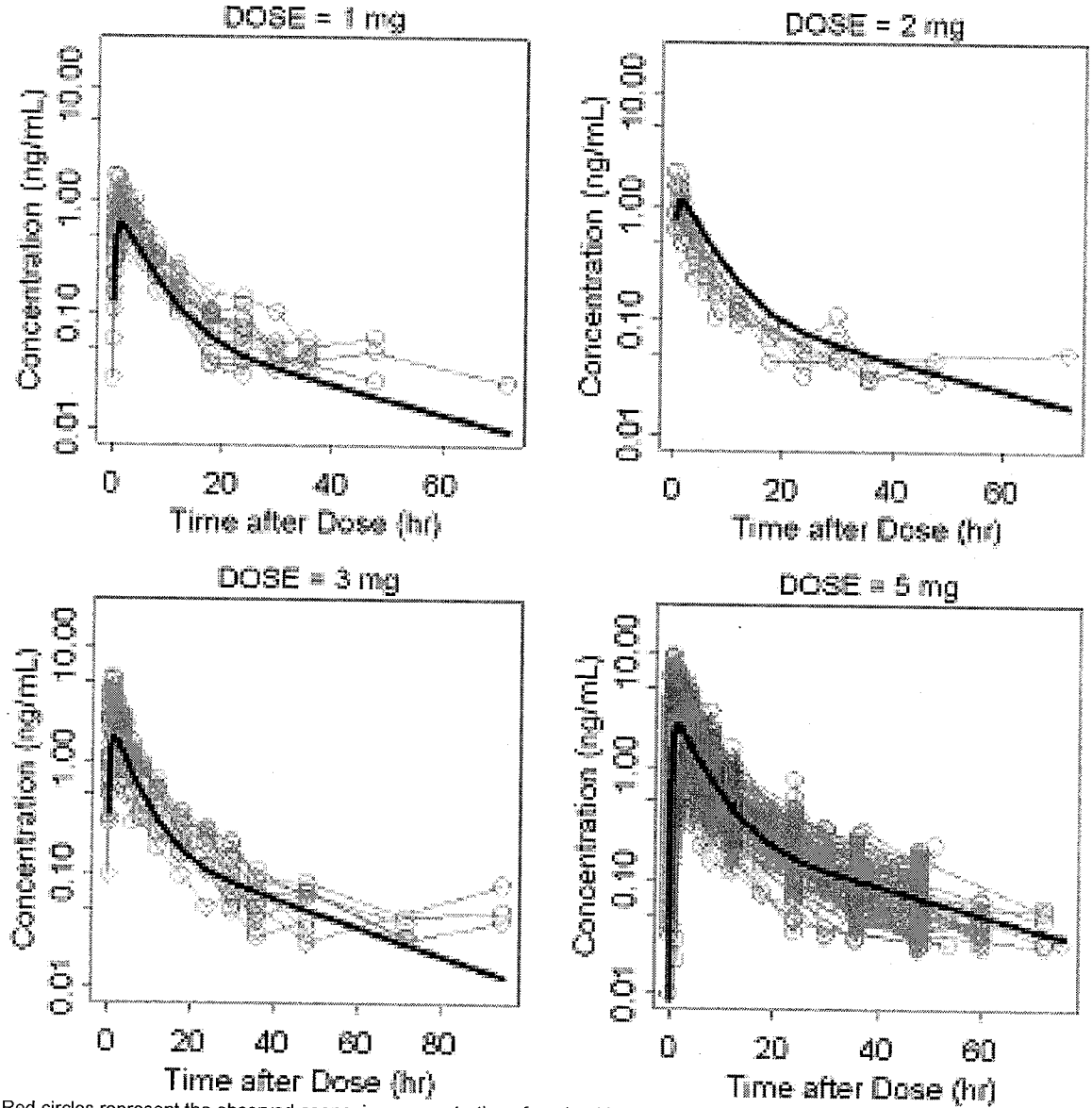
INT000656682

Model Codes

Study 1, the thorough QT study, (i.e. study A7501001), in addition to listing several subjects with bilirubins of 10 and 11 in the pop PK datafile also lists several subjects with albumin concentrations and creatinine clearances that are inconsistent with the units given in the pop PK study report and with the values from all other subjects. For albumin the concentrations listed are 30, 38, 40, 44, and 50 gm/dL and the creatinine clearances are 0.87, 0.96, 0.99, 1.23, 0.78, and 1.25 ml/min. It's possible that the reported values for these measures as well as for bilirubin may be due to misplacement of the decimal point, however this needs to be clarified with the sponsor.[9]

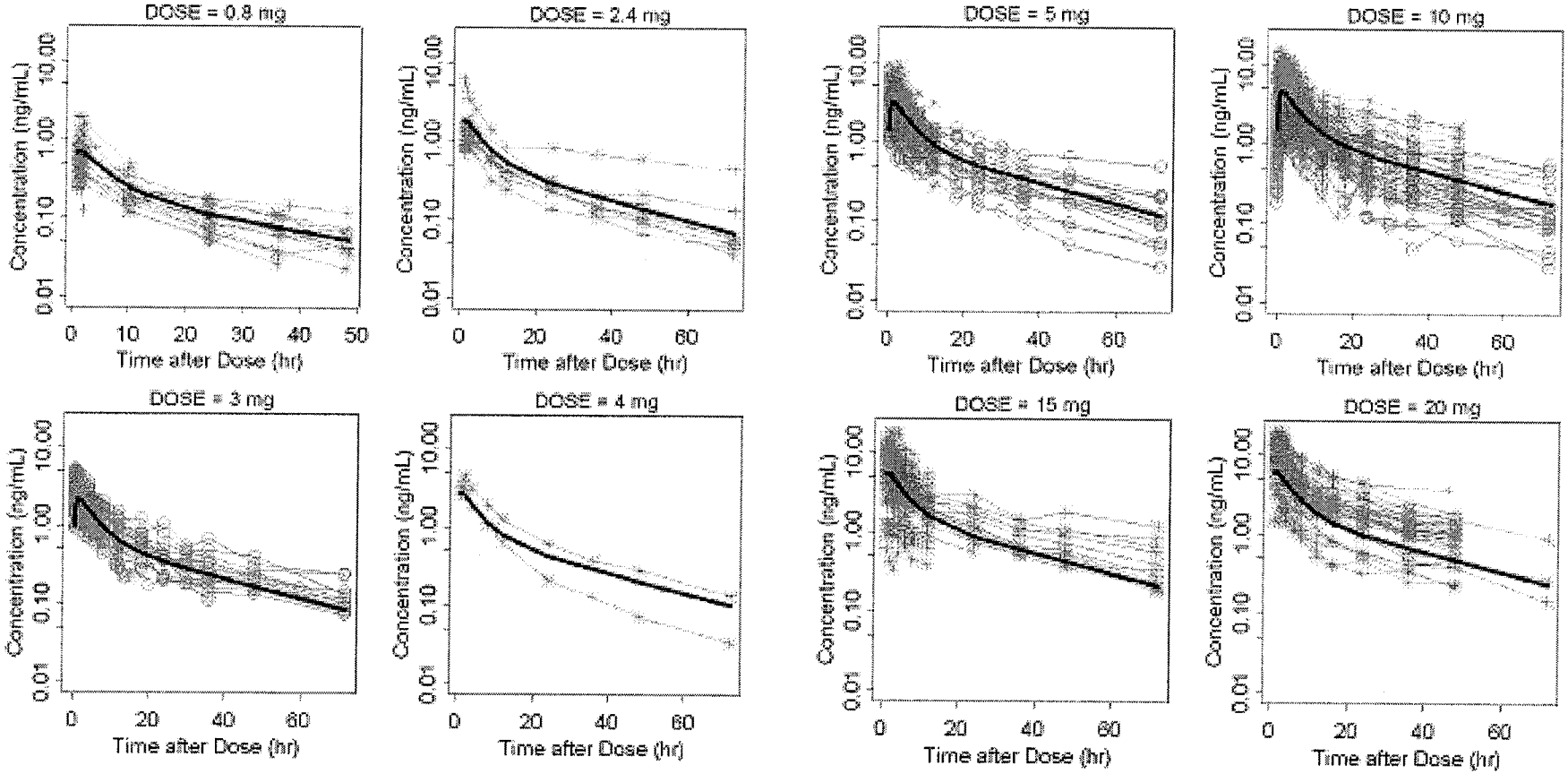
[9] Potential followup issue to be discussed with medical division as necessary.

Figure 125 Single Dose Phase I/II Pop PK Predicted Asenapine Concentration-Time Profile (Base Model) for Selected Doses versus Observed Concentrations



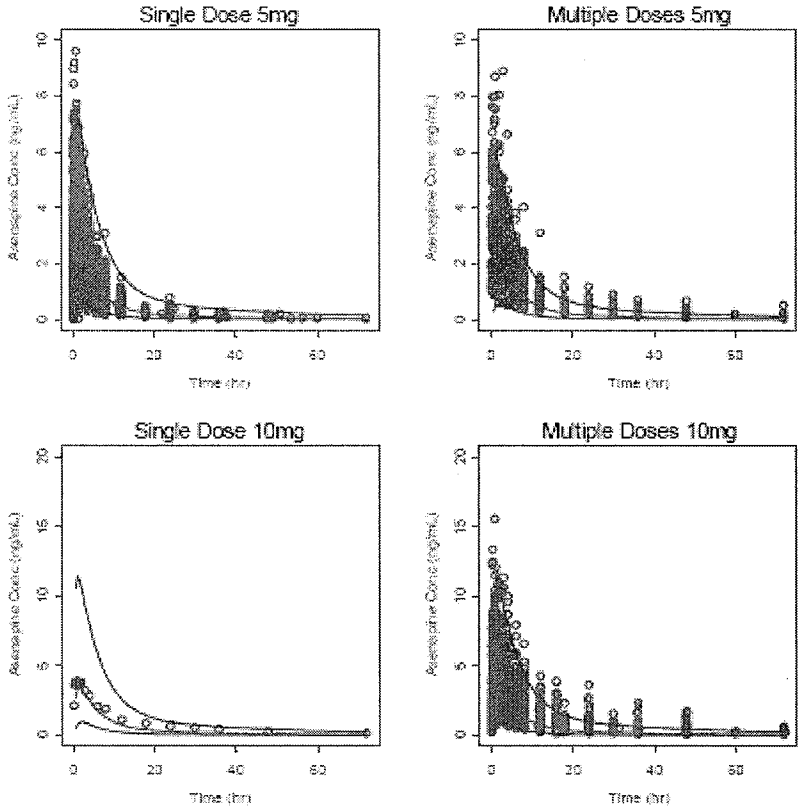
Red circles represent the observed asenapine concentrations from healthy volunteers; gray asterisks represent the observed asenapine concentrations from patients with schizophrenia. Solid lines represent the typical individual (population) predictions obtained from the final base model.

Figure 126 Phase I/II Pop PK Predicted Asenapine Multiple Dose Steady State Concentration-Time Profiles (Base Model) for Selected Doses with Overlaid Observed Concentrations



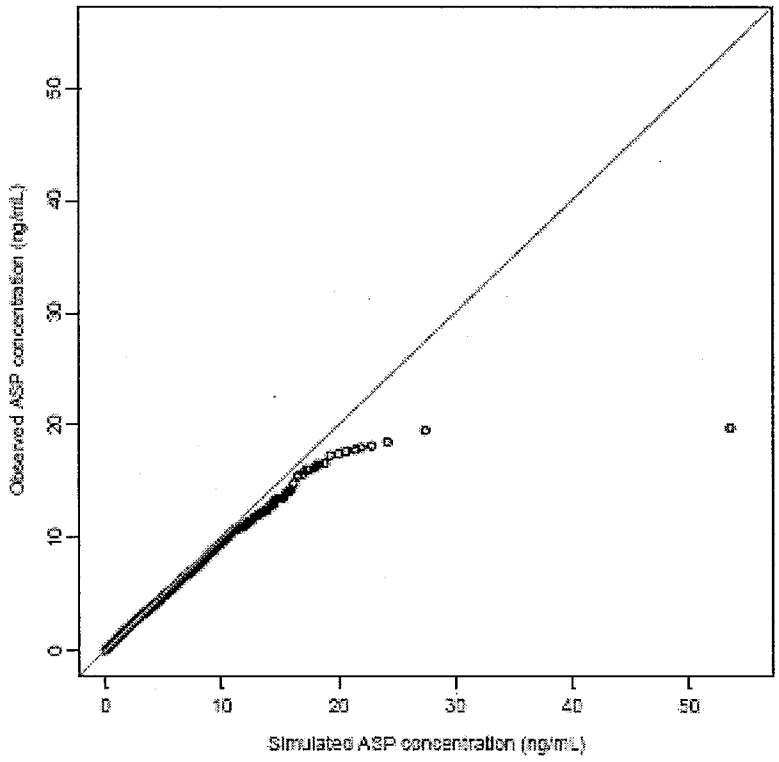
Red circles represent the observed asenapine concentrations from healthy volunteers; gray asterisks represent the observed asenapine concentrations from patients with schizophrenia. Solid lines represent the typical individual (population) predictions obtained from the base model.

Figure 127 Sponsor's Plot of Phase I/II Pop PK Unconditional 95% Prediction Interval with Overlaid Observations



Gray circles represent the observed asenapine concentrations; red lines represent the 0.975th and 0.025th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

Figure 128 QQ Plot of Observed vs. Phase I/II Pop PK Simulated Asenapine Concentrations



The sponsor makes the following statements in the phase I/II pop PK study report:

'RESULTS:

Asenapine pharmacokinetics both after single dose and at steady state of BID dosing were adequately described by a 2-compartment model with first-order absorption and a lag time on the absorption. The dose-dependent decrease in relative bioavailability was described by a linear function of the logarithm of dose. Inter-individual variability was modeled on the elimination rate constant ke, the apparent central volume of distribution (V2/F), the inter-compartmental transfer rate constants k23 and k32 and the absorption rate constant ka. In the final model for the inter-individual random effects all covariances were fixed to zero to obtain the most parsimonious model. Inter-occasion variability was modeled on ka and relative bioavailability Frel. In the final model apparent clearance estimate was 288 L/h and the overall apparent volume of distribution was 4840 L.

The following covariates were included in the final model: race (Black) on clearance (elimination rate), patient status on ka and patient status on lag time tlag. For black subjects, the estimated elimination rate was 13.8 % smaller than that of other races. In patients, a shorter tlag (0.025 h vs 0.125 h in healthy volunteers) and a lower absorption rate constant (50% of that in healthy volunteers) indicated a different absorption pattern. Most likely these differences can be attributed to the less dense pharmacokinetic sampling scheme in the patient studies. None of the other covariates were found to have an effect.

DISCUSSION

Asenapine is a high extraction ratio drug; therefore elimination may also be dependent on hepatic blood flow. Asenapine is highly protein bound and is widely distributed. As expected with such compounds, no major covariates were identified in this population PK analysis that may warrant dose adjustments.

Large inter-subject and inter-occasion variability was seen in the absorption. Asenapine shows unique characteristics of absorption kinetics for a sublingual formulation. Its individual Tmax values range 0.3 to 4 hours. Nonlinear bioavailability may be due to the solubility limit of asenapine in the mouth. The relationship between relative bioavailability and dose appears to be log-linear rather than an Emax type of relationship.

The different lag times estimated for patients and healthy volunteers as well as the effect on the absorption rate constant between the two groups would indicate a different absorption pattern of sublingual asenapine in patients and healthy volunteers. Most likely these differences can be attributed to the less dense sampling scheme in the patient studies. Race (Black) was identified as a statistically significant covariate on clearance (elimination rate). However, the magnitude of the covariate effect is relatively small compared to intersubject and inter-occasion variability seen with this compound.

CONCLUSION(S)

Asenapine pharmacokinetics after single dose and during BID dosing can be modeled adequately with a 2-compartment model with first order absorption, a lag time on absorption and a dose dependent decrease in relative bioavailability. No clinically meaningful covariates were identified that may warrant dose adjustments.'

Reviewer Comments

Most of the conclusions qualitatively reflect the conclusions drawn from the individual studies themselves. However, the sponsor's statement regarding Tlag is opposite what was reported in the body of the report

where a 1.5 minute Tlag was reported for healthy volunteers and a 7.5 minute Tlag was reported for patients. This degree of difference especially as the sampling schemes would be unable to measure Tlags of these magnitudes, for either population, clearly demonstrate the inappropriateness of the structural model.

The claim regarding the lack of expected effects due to asenapine being a high intrinsic clearance drug is not correct, with the clearest example being the effect of food, as seen in study 41029, which was not even included as acovariate used in this analysis. In addition, the age range was insufficient to detect an effect of age in the elderly or the pediatric populations, and lastly covariates such as smoking were not adequately documented to determine an effect, plus the use of laboratory values obtained prior to dosing may also bias the evaluation of these covariates, if they should change with dosing, e.g. in hepatotoxicity.