5.5 Pharmacokinetics - Sublingual

5.5.1 Single Dose Pharmacokinetics - Dose Linearity

Two studies in young healthy males were dedicated to examining sublingual single rising dose (SRD) pharmacokinetics of asenapine. Study 25509 used subtherapeutic doses of up to 0.3 mg and study 25542 used doses of 2 mg and 5 mg. Due to the limited amount of data that this provided this reviewer also looked at the first and single dose data from several other studies shown below.

Study No.	Design	Population	Doses Studied
25509	SRD S/T Study	young healthy males	10 – 300 mcg, (0.01 – 0.3 mg)
25514	First Dose (MD)	young healthy males	200 mcg
25542	SRD & MD S/T	young healthy males	2 mg, 5 mg
25533	SD Absolute Bioavailability	young healthy males	5 mg
25540	SD w/wo charcoal	young healthy males	5 mg

Study 25509 was a single rising dose study of sublingual asenapine in young healthy male volunteers over a dose range of 10 – 100 mcg, (0.01 – 0.1 mg),

In addition mean single dose Cmax and AUC data for healthy volunteers from an additional number of studies (but not all studies) were examined.

Plots of single dose mean concentration vs. time profiles both of raw and dose normalized concentrations on linear and semi-log scales for doses of 2 mg and 5 mg from study 25542 show that sublingual asenapine exhibits linear 2-compartment pharmacokinetics over this dose range, (see Figure 35 to Figure 38).

When administered sublingually, linearity over the range of 0.02 mg to 5 mg is confirmed by the mean Cmax and AUC data from a number of other studies, (see Figure 39 and Figure 40).

Asenapine pharmacokinetic metrics from the five studies listed above are shown in Figure 41, Table 46 and Table 47. These metrics indicate that asenapine is a high intrinsic clearance drug with an intrinsic clearance that is likely equal to hepatic blood flow when bioavailability is considered, has an extremely large volume of distribution of roughly 100 L/kg, and an initial phase half-life of around 5 hours with a terminal phase half-life of around 24 hours.

For desmethyl-asenapine the reported Cmaxs are around 20% those of asenapine and the reported AUCs are around 40% of the parent, (see Table 47). Desmethyl-asenapine's shorter reported half-life doesn't make sense and is most likely due to lack of assay sensitivity. Based on this single dose data desmethyl-asenapine likely has formation-rate-limited pharmacokinetics. Thus the estimated clearances, volumes, and half-lives for desmethyl-asenapine are likely in error.

Figure 35 Mean Single Dose Asenapine Concentration vs. Time Profiles – Study 25542

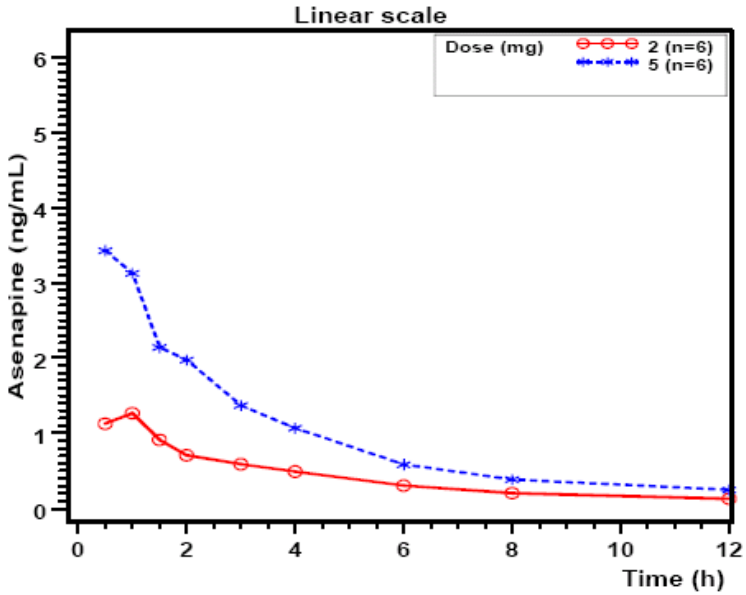


Figure 36 Mean Single Dose Asenapine Dose-Normalized Concentration vs. Time Profiles – Study 25542

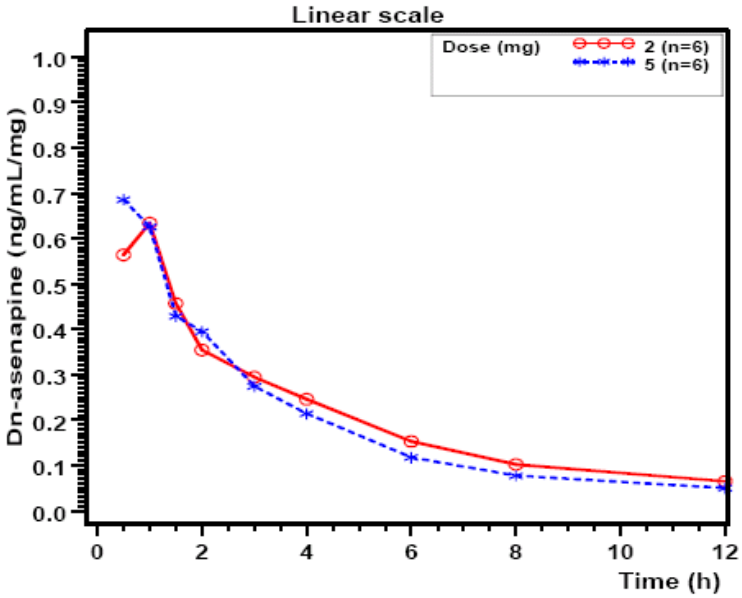


Figure 37 Mean Single Dose Asenapine Semi-log Concentration vs. Time Profiles – Study 25542

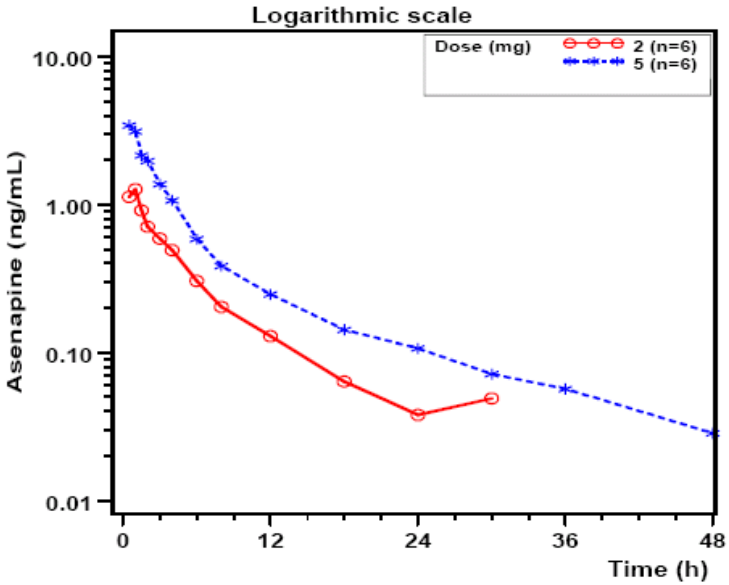


Figure 38 Mean Single Dose Asenapine Semi-log Dose-Normalized Concentration vs. Time Profiles – Study 25542

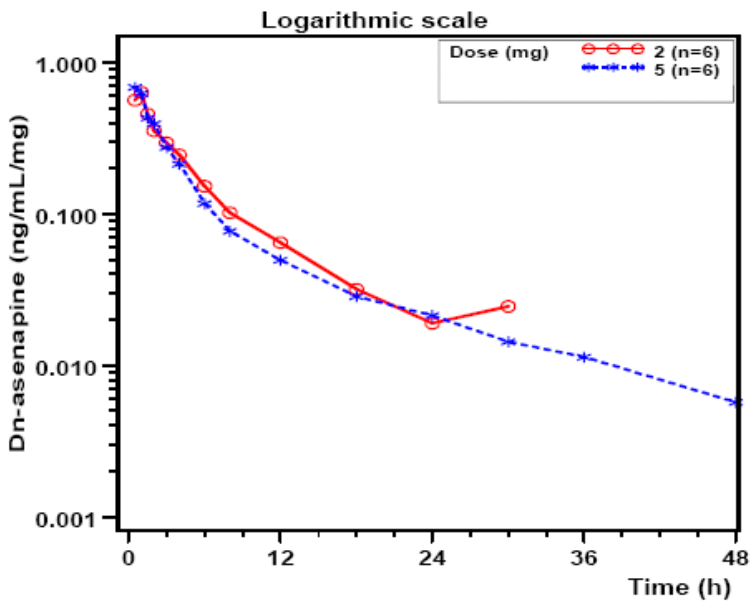

Logarithmic scale
Dose (mg)
2 (n=6)
5 (n=6)
1.000
0.100
0.010
0.001
Dn-asenapine (ng/mL/mg)
0
12
24
36
48
Time (h)

Figure 39 Asenapine Single Dose Mean Cmax vs. Dose from Multiple Studies

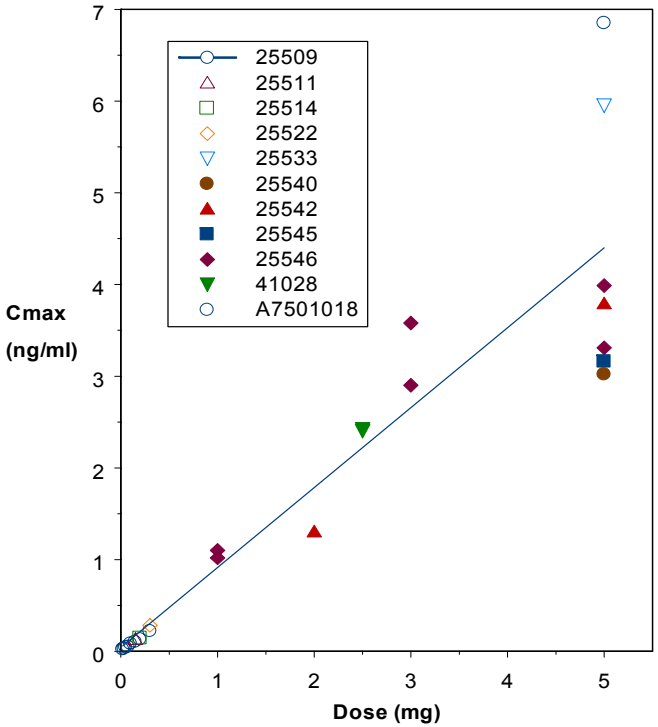


Figure 40 Asenapine Single Dose Mean AUC vs. Dose from Multiple Studies

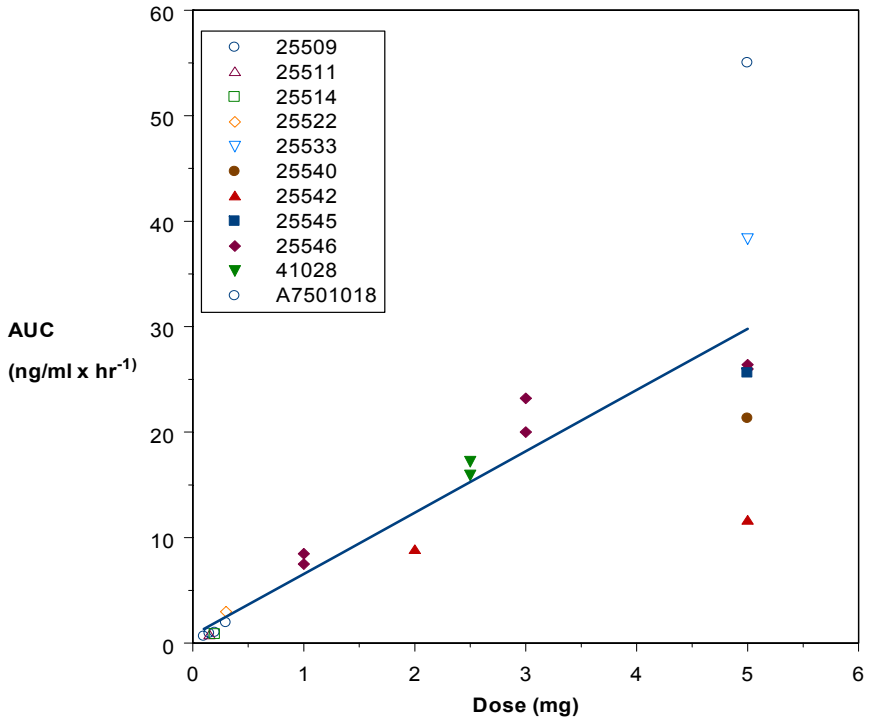


Figure 41 Pharmacokinetic Metrics (Mean ± SD) for Single Rising Doses of Sublingual Asenapine in Healthy Young Males - Study 25509

Dose group (µg)	C_{max} (pg/ml)	t_{max} (h)	$AUC_{0-\infty}$ (pg·h/ml)	AUC_{0-tfix} (pg·h/ml)	CL_{app} (l/h/kg)	$t_{½}$ (h)
10*	-	-	-	-	-	-
20**	21.37	1	-	-	-	-
35***	28.47±5.60	2.00±0.91	-	-	-	-
50	40.85±9.75	1.70±0.25	-	-	-	-
75	47.73±18.14	2.25±1.00	-	217±78	-	-
100	84.26±11.11	1.63±0.92	635±73	413±52	1.9±0.3	5.0±1.1
150	103.10±16.49	2.13±0.83	916±131***	533±108	2.2±0.2***	5.7±1.1***
200	129.32±37.59	1.69±0.65	1023±358	639±220	2.9±1.0	5.1±1.0
300	220.16±75.42	1.75±0.96	1932±651	1031±297	2.2±0.4	7.9±3.6

* N=0 (all levels below the lower limit of quantification) ** N=1 *** N=7 All other groups N=8

Table 46 Asenapine Pharmacokinetic Metrics after the First 200 mcg SL Dose – Study 25514[a]

N	Tmax (hrs)	Cmax (pg/mL)	AUC_{0-12} (pg/mL x hr^{-1})	Clapp (L/hr/kg)	dn-Cmax (pg/mL x hr^{-1})	dn-AUC_{0-12} (pg/mL x hr^{-1})	t½ (hrs)
12	1.67 ± 0.81 0.5 - 4.0	142.2 ± 49.3 62.5 - 220.6	848.4 ± 189.2 542.0 - 1127.9	3.33 ± 0.99 2.1 - 5.5	0.71 ± 0.25 0.31 - 1.1	4.24 ± 0.95 2.71 - 5.64	4.3 ± 0.9 2.7 - 5.6

a Values are mean ± SD and range.

Table 47 Asenapine and Desmethyl-Asenapine Sublingual Pharmacokinetic Single Dose Metrics – Studies 25542 and 25533[a]

Analyte	Asenapine				Desmethyl-Asenapine			
Study	25542		25533	25540	25542		25533	25540
Asenapine Dosage	2 mg	5 mg	5 mg	5 mg	2 mg	5 mg	5 mg	5 mg
N	6	6	8	7	6	6	8	7
Tmax (h)	[1.0] 0.50 - 1.0	[0.78] 0.5 - 1.0	[1.0] (0.5 - 3.0)	1.0 (0.5 - 2.0)	[5.0] 1.5 - 8.0	[3.0] 3.0 - 6.0	[6.0] (2.0 - 12.0)	6.0 (4.0 - 8.0)
Cmax (ng/mL)	1.30 ± 0.459	3.79 ± 1.21	5.95 (40.7) 2.05 - 8.64	3.02 (1.38)	0.237 ± 0.0485	0.571 ± 0.076	0.463 (14.0) 0.321 - 0.532	0.428 (0.210)
dn - Cmax (ng/mL/mg)	0.648 ± 0.229	0.758 ± 0.242			0.119 ± 0.0242	0.114 ± 0.015		
$AUC_{0-12\ (t)}$ (ng /mL x hr^{-1})	4.99 ± 1.48	11.6 ± 2.94	37.0 (24.2) 19.6 - 44.6	20.3 (5.75)	1.98 ± 0.472	4.74 ± 0.68	7.76 (21.70 6.08 - 11.0	7.59 (4.13)
dn – AUC_{0-12} (ng /mL x hr^{-1} / mg)	2.49 ± 0.742	2.32 ± 0.587			0.990 ± 0.236	0.949 ± 0.136		
$AUC_{0-\infty}$ (ng /mL x hr^{-1})	8.82* ± 2.51*	16.9 ± 4.35	38.3 (24.1) 19.9 - 46.6	21.3 (6.11)	4.01* ± 1.43*	11.5** ± 3.18**	8.85 (22.5) 6.99 - 12.7	10.3 (3.34†
dn - $AUC_{0-\infty}$ (ng /mL x hr^{-1} / mg)	4.41* ± 1.25*	3.38 ± 0.870			2.01* ± 0.715*	2.30** ± 0.636**		
CLapp (L/h)	241* ± 71.0*	316 ± 101	141 (34.6) 107 - 251		—	—	559 (19.9) 374 - 681	
wn - CLapp (L/h/kg)	3.27* ± 1.09*	4.24 ± 1.38			—	—		
Vz,app (L)	7180* ± 4874*	13689 ± 9438	3713 (42.7) 2070 - 6847		—	—	8311 (31.1) 5918 - 13941	
wn - Vz,app (L/kg)	95.6* ± 65.1*	182 ± 124			—	—		
t½ (h)	24.8* ± 23.8*	29.6 ± 15.9	19.7 (44.2) 7.68 - 31.0	15.9 (5.04)	7.97* ± 2.58*	17.1** ± 8.69**	10.7 (38.8) 6.34 - 20.2	15.1 (4.32)†

a Values are [Median] range, mean ± SD, mean (%CV) and range, or mean (%CV); * n = 4; ** n =5; † n = 6

5.5.2 Multiple Dose Pharmacokinetics - Dose Linearity, Time Invariance, Diurnal Variation, Dose Titration and Maximally Tolerated Dose Evaluation

Six studies were conducted that evaluated multiple dose pharmacokinetics. These included studies to evaluate the multiple dose pharmacokinetics, various dose titration regimens, and the maximally tolerated dose after sublingual administration, as-well-as proof of concept and PK/P. Descriptions of the study populations, study designs, and maximum dosages examined are shown in Table 48.

Studies 41001, 41007, 25542, and 41012 examined various titration schedules and dosages up to 20 mg BID and the titration schedules and study cohorts for these studies are shown in Table 49 to Table 52.

Studies 25511 and 25514 used subtherapeutic doses of 0.15 – 0.3 mcg BID and the metrics are included only for completeness in the last table in this section, Table 56.

Study 41001 also used a subtherapeutic dose of 0.8 mg BID and the sponsor only reported pharmacokinetic metrics dose normalized to 1 mg. Thus the results of this study are not reported or reviewed here. This was also a proof-of-concept study in patients with schizophrenia or schizoaffective disorder, however as the dose was subtherapeutic no evidence of efficacy was observed.

Studies 41007 and 25542 examined multiple doses in the range of 4.8 – 10 mg BID, as well as higher. As the proposed therapeutic dose range is 5 mg to 10 mg BID the focus of this review section will be on these studies. Study 41007 also included a PET sub-study in healthy volunteers at a dose of 4.8 mg and study 25542 also examined diurnal variation. Asenapine pharmacokinetic summary metrics from these studies are shown in Table 53.

The pharmacokinetic metrics from these studies reveal the following:

a) absorption is rapid with a median Tmax of 0.5 – 1.0 hours

b) Dose normalized Cmaxs at 5 mg BID and below are around 0.8 ng/ml per mg (~ 4 ng/ml total) with lower Cmaxs and delayed Tmaxs at higher doses (10 mg BID) probably due to swallowing

c) High intrinsic clearances approximating hepatic blood flow

d) Large volumes of distribution averaging 150 – 200 L/kg

e) Long terminal half-lives averaging around 1 day in one study and 1 – 1½ in others and ranging up to 2½ days in the PET study.

f) No significant diurnal variation in the overall profile however predose concentrations show clear diurnal variation when dose normalized.

Desmethyl-asenapine pharmacokinetics from study 25542 are shown in Table 54 and show Cmaxs around 30% of asenapine's at 5 mg BID and below, and around 60% of asenapine's at 10 mg BID. AUCs of desmethyl-asenapine average 85% of asenapine's at doses of 5 mg BID, and 110% at 10 mg BID. Although the half-lives for desmethyl-asenapine are shorter than asenapine's, this is probably due to assay insensitivity and most likely desmethyl-asenapine has formation rate limited kinetics.

Figure 42 and Figure 44 show steady-state asenapine mean concentration vs. time profiles after morning and evening doses. When the concentrations are transformed to the log scale they demonstrate biphasic kinetics during a single dosage interval, (see Figure 43 and Figure 45), and if the dose is high enough and sampling is sufficiently long a triphasic elimination profile indicating 3 compartment pharmacokinetics is observed, (see Figure 45).

For desmethyl-asenapine, Figure 46 and Figure 48 reveal monoexponential decline during a single dosage interval. However when dose-normalized concentration vs. time profiles are examined there is clear nonlinearity indicating saturable absorption, (see Figure 47 and Figure 49).

In addition, dose normalized pre-dose concentrations for asenapine reveal a degree of diurnal variation, (see Figure 50), although examination of Figure 47 and Figure 49 reveal that this is mainly in the 2nd phase kinetics and that the amount of diurnal variation is small and thus does not raise any obvious concerns especially as dosing is BID.

Asenapine and desmethyl-asenapine pharmacokinetics at doses of 10 – 20 mg BID from study 41012 are shown in Table 55. Asenapine's Cmax again appears to plateau, but only above 10 mg BID and there is a decrease in dose normalized AUC. The ratio of desmethyl-asenapine to asenapine in this study and study 25532 (Table 22) is also similar but somewhat lower than the ratios in study 25542, (see Table 54). The most likely explanations are the small number of subjects in these studies and whether subjects swallowed drug or not. In study 41012 there were also cases of severe oral dystonia at the 15 mg BID dose.

Plots of Cmax's and AUC's vs. dose from a number of multiple dose studies also appear to show possible plateauing at doses above 5 mg BID, (see Figure 51 and Figure 52), and plots of dose normalized values versus dose confirm this, although the cutoff for linearity is not clear, (see Figure 53).

As mentioned earlier, studies 25511 and 25514 used subtherapeutic doses of 0.15 – 0.3 mcg BID and are included in Table 56 on the last page in this section simply for completeness,

Table 48 Study Populations, Designs, and Maximum Dosages Examined in Phase I Multiple Dose Clinical Pharmacology Studies

No.	Nominal Design	Population	Design	Cohort	N	Maximum Dosage
25511	MD	Young healthy male volunteers	Rand, DB, PBO controlled, parallel grp, MD study	1	6	150 mcg SL BID x 6.5 days
				2	12	or 150 mcg SL BID x 13.5 days
25514	MD	Young healthy male volunteers	Rand, DB, PBO controlled, parallel grp, MRD study	1	12	200 mcg SL BID x 2 days then 300 mcg SL BID x 4.5 day
41001	MRD	M/F patients with schizophrenia or schizoaffective disorder	Rand, DB PBO controlled 3-way sequential design S/T MTD PK proof of concept study	1	10	up to 0.8 mg BID over 5 days
				2	10	up to 0.8 mg BID over 6 days
				3	10	up to 0.8 mg BID over 9 days
41007	MRD	Young otherwise healthy subjects with schizophrenia or schizoaffective disorder (PET substudy also included healthy subjects)	Rand, DB, PBO controlled, sequential design, MRD, S/T MTD PK study with PK/PD PET sub-study	Grp 1	6	2.4 mg BID x 5 days
				Grp 2	6	2.4 mg BID x 5 days
				Grp 3A	3	4.8 mg BID x 5 days
				Grp 3B	3	4.8 mg BID x 5 days
25542	MRD	Young healthy male volunteers	Rand, DB, PBO controlled, 5-way parallel design MRD study	1	6	up to 3 mg BID x 6 days
				2	6	up to 5 mg BID x 6 days
				3	6	up to 10 mg BID x 6 days
				4	6	up to 15 mg BID x 6 days
	SRD			5	6	2 mg and 5 mg SD
41012	MRD	M/F patients with schizophrenia or schizoaffective disorder	S/T MTD titration study in Rand DB PBO controlled 3-way sequential design	1	6	up to 15 mg BID x 5 days
				2	6	up to 15 mg BID x 5 days
				3	6	up to 20 mg BID x 5 days

Table 49 Dose Titration Schedules - Study 41001

Grp	N	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	total # days
1	10	0.2 mg BID x 3 days			0.3 mg BID x 3 days			0.4 mg BID x 3 days			0.6 mg BID x 3 days			0.8 mg BID x 5 days					17
2	10	0.2 mg BID x 2 days		0.3 mg BID x 2 days		0.4 mg BID x 2 days		0.6 mg BID x 2 days		0.8 mg BID x 6 days									14
3	10	0.2 mg BID x 1 day	0.3 mg BID x 1 day	0.4 mg BID x 1 day	0.6 mg BID x 1 day	0.8 mg BID x 9 days													13

Table 50 Dose Titration Schedules - Study 25542

Group	Day 1	2	3	4	5	6	7	8	9	10	11	total # days
1	0.3 mg BID x 1 day	0.6 mg BID x 1 day	1 mg BID x 1 day	3 mg BID x 6 days								9
2	0.3 mg BID x 1 day	1 mg BID x 1 day	3 mg BID x 1 day	5 mg BID x 6 days								9
3	1 mg BID x 1 day	3 mg BID x 1 day	5 mg BID x 1 day	10 mg BID x 6 days								9
4	1 mg BID x 1 day	3 mg BID x 1 day	5 mg BID x 1 day	10 mg BID x 1 day	15 mg BID x 6 days							11
5	2 mg SD							5 mg SD				

Table 51 Dose Titration Schedules - Study 41007

Grp	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17 18	total # days
1	0.2 mg BID x 1 day	0.4 mg BID x 1 day	0.6 mg BID x 1 day	0.8 mg BID x 1 day	1.2 mg BID x 3 days			1.6 mg BID x 3 days			2.0 mg BID x 3 days			2.4 mg BID x 5 days				18
2	0.3 mg BID x 1 day	0.6 mg BID x 1 day	0.8 mg BID x 1 day	1.2 mg BID x 1 day	1.6 mg BID x 1 day	2.0 mg BID x 1 day	2.4 mg BID x 5 days											11
3A	0.4 mg BID x 1 day	0.8 mg BID x 1 day	1.2 mg BID x 1 day	1.6 mg BID x 1 day	2.0 mg BID x 1 day	2.4 mg BIDx 2 days		3.2 mg BID x 2 days		4.0 mg BID x 2 days		4.8 mg BID x 5 days						16
3B	0.6 mg BID x 1 day	1.2 mg BID x 1 day	1.6 mg BID x 1 day	2.0 mg BID x 1 day	2.4 mg BID x 1 day	3.2 mg BID x 1 day	4.0 mg BID x 1 day	4.8 mg BID x 5 days										12

Table 52 Dose Titration Schedules – Study 41012

Grp	Day 1	2	3	4	5	6	7	8	9	10	total # days
1	2 mg BID x 1 day	3 mg BID x 1 day	5 mg BID x 1 day	8 mg BID x 1 day	10 mg BID x 1 day	15 mg BID x 5 days					10
2	3 mg BID x 1 day	5 mg BID x 1 day	8 mg BID x 1 day	10 mg BID x 1 day	15 mg BID x 5 days						9
3	5 mg BID x 1 day	10 mg BID x 1 day	15 mg BID x 1 day	20 mg BID x 5 days							8

Table 53 Asenapine Steady-State Pharmacokinetic Metrics – Studies 41007 and 25542

Study	41007	25542		41007	25542			
Dosage	2.4 mg	3 mg		4.8 mg	5 mg		10 mg	
Dose	Morning	Morning	Evening	Morning	Morning	Evening	Morning	Evening
N	8	5	5	4	6	6	5	5
Tmax[a] (h)	1.6 ± 0.4 (26.7) 1 - 2 [1.5]	[0.5] 0.5 - 1.0	[1.0] 0.5 - 1.0	2.0 ± 1.4 (67.7) 1.0 - 4.0 [1.5]	[0.5] 0.5 - 1.5	[0.5] 0.5 - 1.0	[1.0] 0.52 - 1.5	[0.5] 0.5 - 0.5
Cmax (ng/mL)	2.0 ± 1.7 (88.6) 0.9 - 6.2 [1.4]	2.76 ± 1.48	2.95 ± 1.76	3.6 ± 1.8 (50.8) 1.0 - 5.3 [4.1]	3.59 ± 1.27	3.46 ± 1.62	4.9 ± 1.9	5.57 ± 2.36
dn - Cmax (ng/mL/mg)	0.8 ± 0.7 (88.5) 0.4 - 2.6 [0.6]	0.92 ± 0.49	0.98 ± 0.58	0.8 ± 0.4 (50.9) 0.2 - 1.1 [0.9]	0.72 ± 0.26	0.69 ± 0.32	0.49 ± 0.19	0.557 ± 0.236
AUC0 - 12 (ng/mL *hr^{-1})	11.5 ± 7.1 (61.4) 6.1 - 27.2 [9.6]	11.0 ± 2.91	12.8 ± 4.75	22.4 ± 10.0 (44.6) 8.1 - 30.9 [25.3]	15.5 ± 5.47	14.6 ± 5.42	24.4 ± 13.0	28.2 ± 16.0
dn - AUC0 - 12 (ng/mL *hr^{-1} / mg)	4.8 ± 2.9 (61.20 2.6 - 11.3 [4.0]	3.68 ± 0.97	4.27 ± 1.58	4.7 ± 2.1 (44.7) 1.7 - 6.4 [5.3]	3.11 ± 1.09	2.92 ± 1.08	2.4 ± 1.3	2.82 ± 1.60
Clapp (L/h)	251 ± 89 (35.6) 88.3 - 392 [251]	284 ± 61.2	261 ± 92.0	283 ± 209 (73.8) 155.0 - 595.0 [191]	349 ± 94.4	405 ± 218	485 ± 187	449 ± 223
wn - CLapp (L/h/kg)		3.71 ± 0.76	3.42 ± 1.26		5.02 ± 1.28	5.84 ± 3.02	6.20 ± 2.68	5.80 ± 3.19
Vz,app (L)	10830 ± 3710 (34.3) 7410 - 16560 [9900]			14515 ± 10679 (74) 7265 - 30355 [10219]				
dn - Cmin,av (ng/mL/mg)		0.188 ± 0.017	0.115 ± 0.02		0.151 ± 0.045	0.096 ± 0.024	0.136 ± 0.101	0.084 ± 0.056
t½ (hr)	30.9 ± 12.5 (40.4) 20.3 - 58.2 [27.1]	—	18.2 ± 6.98	36.2 ± 8.3 (23.0) 24.8 - 43.3 [38.4]	—	18.8 ± 10.6	—	20.4 ± 6.70
Tss(protocol day)		6	6		5	4	5	4

a Mean ± SD, except, Median and range for Tmax, and Mean for Tss (Time to steady - state).

Table 54 Desmethyl-Asenapine Steady-State Pharmacokinetic Metrics – Study 25542

		Asenapine 3 mg		Asenapine 5 mg		Asenapine 10 mg	
		Morning (n=5)	Evening (n=5)	Morning (n=6)	Evening (n=6)	Morning (n=5)	Evening (n=5)
Tmax (h)		[6.0] 3.0 - 6.0	[3.0] 1.0 - 12.0	[2.0] 1.50 - 4.0	[1.75] 1.07 - 6.0	[4.0] 1.50 - 4.0	[3.0] 1.0 - 8.0
Cmax (ng/mL)		0.805 ± 0.312	0.701 ± 0.317	1.49 ± 0.312	1.16 ± 0.346	3.41 ± 1.18	2.59 ± 0.874
dn - Cmax (ng/mL/mg)		0.268 ± 0.104	0.234 ± 0.106	0.297 ± 0.0625	0.233 ± 0.0693	0.341 ± 0.118	0.259 ± 0.0874
AUC_{0-12} (ng*h/mL)		7.63 ± 3.24	6.77 ± 2.94	14.0 ± 3.58	11.6 ± 3.38	31.8 ± 14.3	25.7 ± 11.4
dn - AUC_{0-12} (ng*h/mL/mg)		2.5 ± 1.08	2.26 ± 0.982	2.79 ± 0.715	2.32 ± 0.675	3.18 ± 1.43	2.57 ± 1.14
dn - Cmin,av (ng/mL/mg)		0.150 ± 0.0742	0.168 ± 0.0780	0.168 ± 0.0383	0.180 ± 0.0516	0.191 ± 0.102	0.193 ± 0.105
t½ (h)		—	17.2 ± 8.51	—	15.0 ± 3.68	—	14.9 ± 4.80
Tss (Day)		6	6	5	4	7	5
Ratio DesMe-Asenapine: Asenapine	**Cmaxs**	0.29	0.24	0.41	0.34	0.70	0.46
	AUCs	0.69	0.53	0.9	0.79	1.3	0.91

Figure 42 Mean Steady-State Asenapine Concentration vs. Time Profiles after a Morning Dose – Study 25542

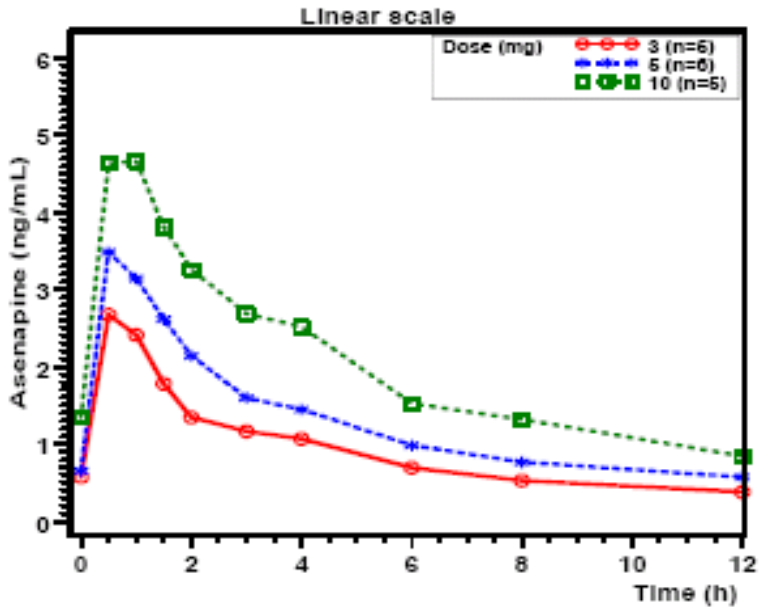


Figure 43 Mean Steady-State Asenapine Semi-log Concentration vs. Time Profiles after a Morning Dose – Study 25542

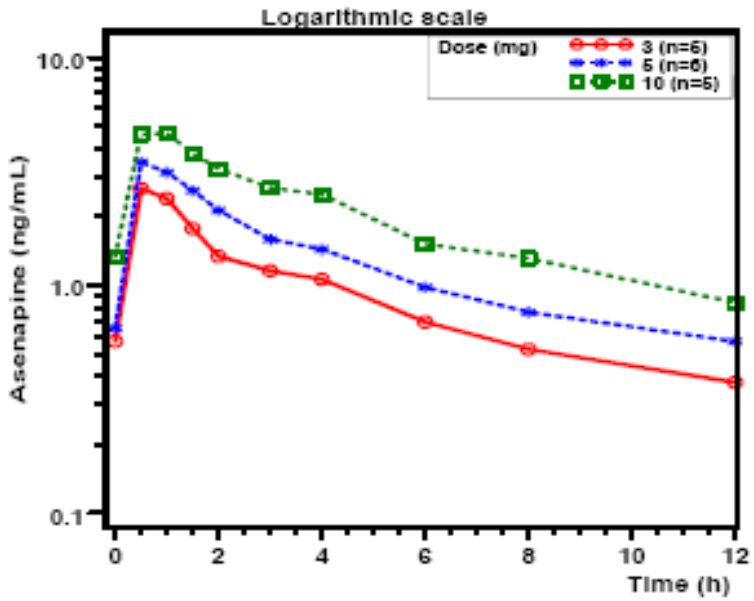


Figure 44 Mean Steady-State Asenapine Concentration vs. Time Profiles after an Evening Dose – Study 25542

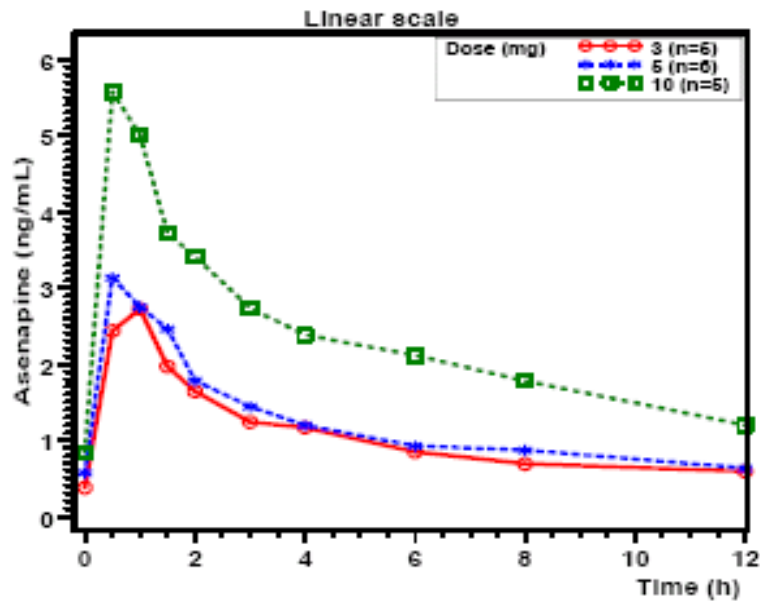


Figure 45 Mean Steady-State Asenapine Semi-log Concentration vs. Time Profiles after an Evening Dose – Study 25542

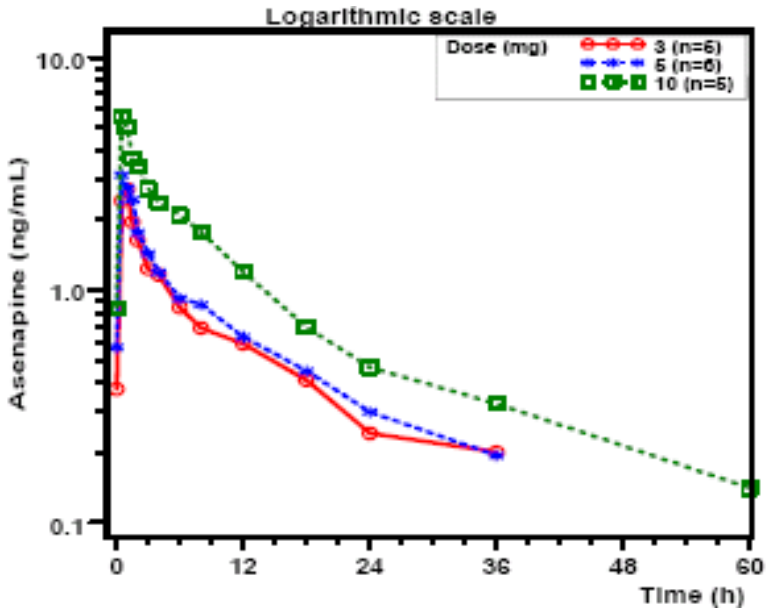


Figure 46 Mean Steady-State Desmethyl-Asenapine Concentration vs. Time Profiles after a Morning Dose – Study 25542

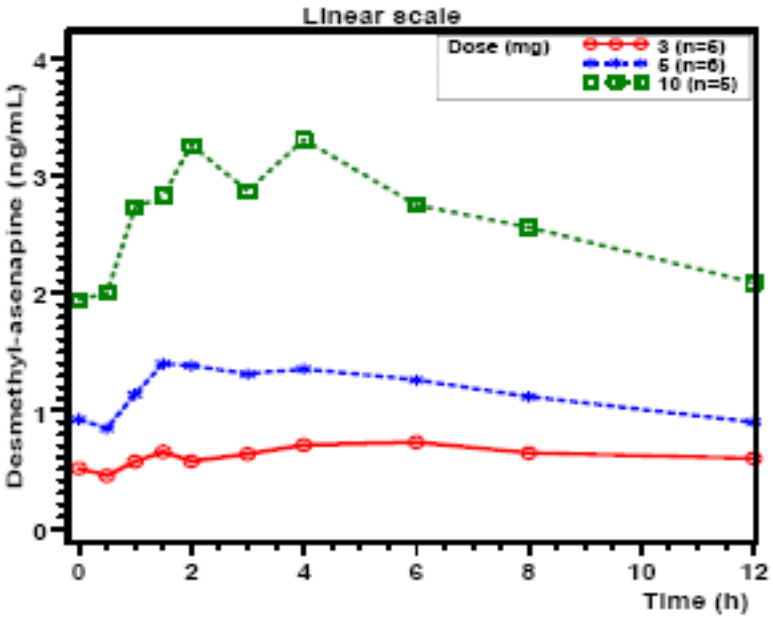


Figure 47 Mean Steady-State Dose-normalized Asenapine Concentration vs. Time Profiles after a Morning Dose – Study 25542

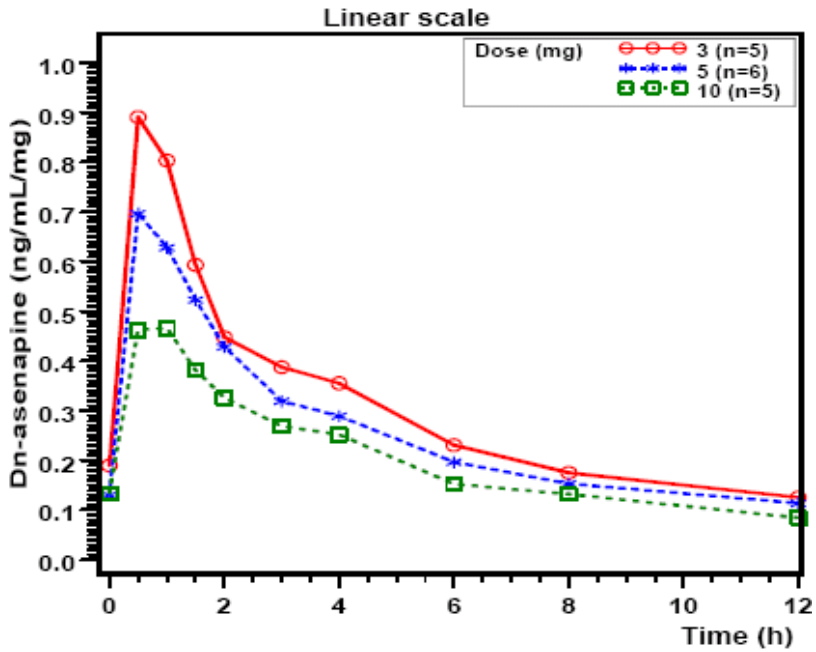


Figure 48 Mean Steady-State Desmethyl-Asenapine Semi-log Concentration vs. Time Profiles after a Morning Dose – Study 25542

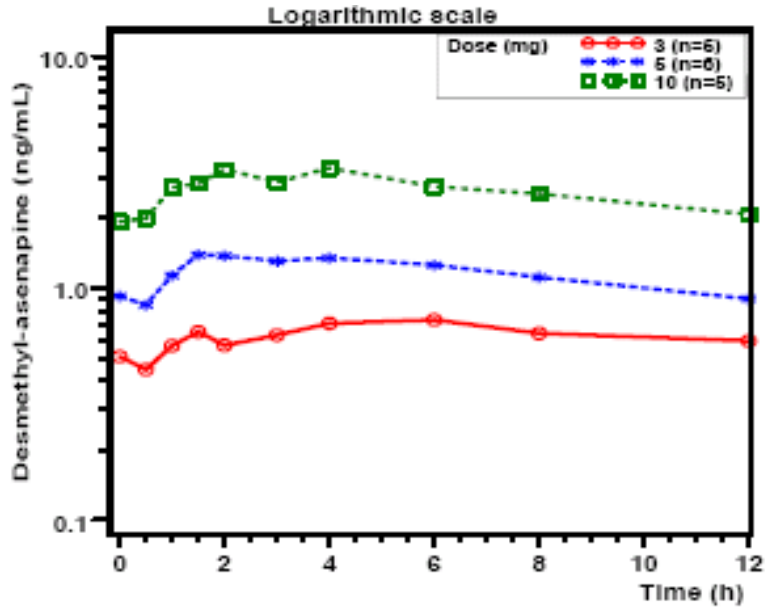


Figure 49 Mean Steady-State Dose-normalized Asenapine Concentration vs. Time Profiles after an Evening Dose – Study 25542

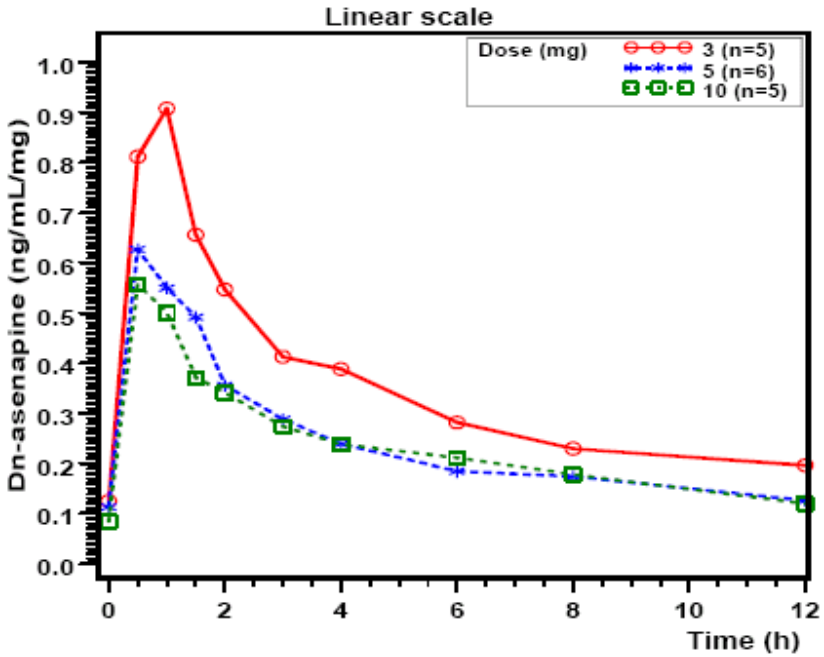
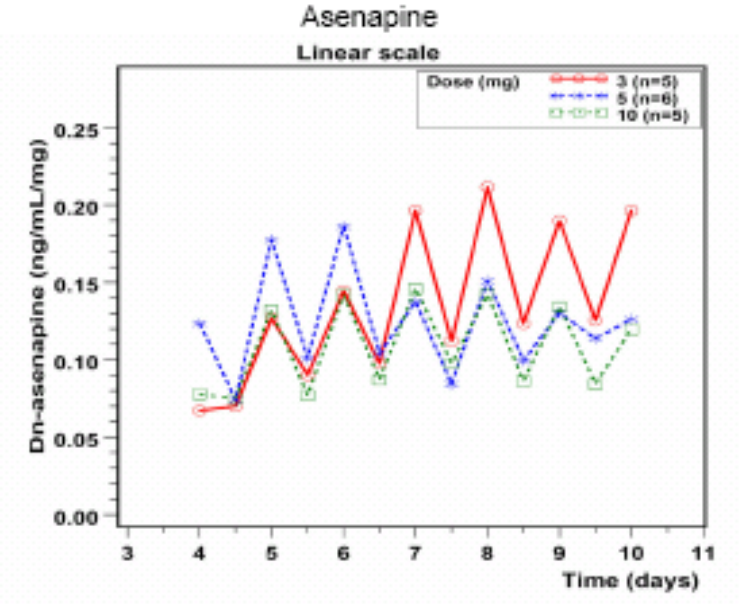


Figure 50 Mean Dose-Normalized Asenapine and Desmethyl-Asenapine pre-Dose Concentration Fluctuations from Days 4 to 10 of Dosing – Study 25542



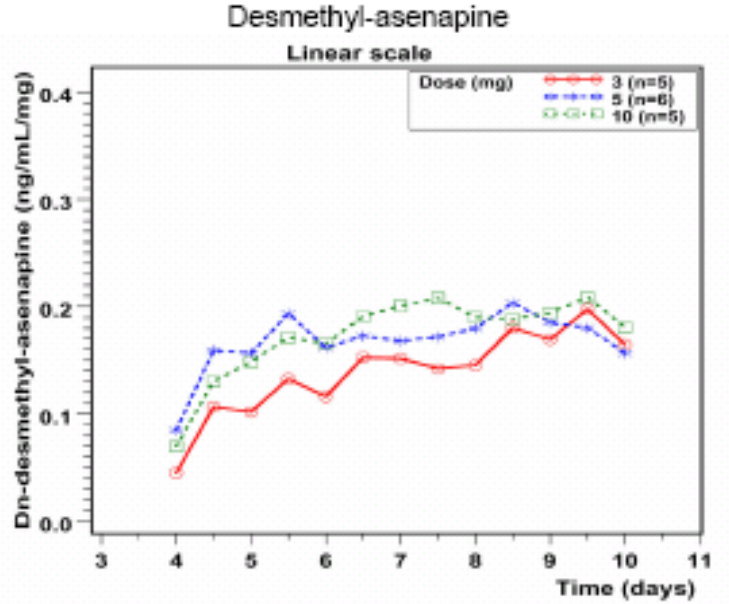


Table 55 Multiple Dose Asenapine Pharmacokinetic Metrics –Study 41012

	Asenapine			Desmethyl-Asenapine			Ratio of Means Desmethyl-Asenapine : Asenapine		
Dose	**10 mg BID**	**15 mg BID**	**20 mg BID**	**10 mg BID**	**15 mg BID**	**20 mg BID**	**10 mg BID**	**15 mg BID**	**20 mg BID**
n	2	12	3	2	12	3			
Tmax (h)	[1.25] 1.00 - 1.50	[1.05] 0.97 – 4.00	[1.03] 1.00 - 2.03	[4.00] 4.00 – 4.00	[2.05] 1.00 – 4.37	[1.50] 1.03 - 2.03			
Cmax (ng/mL)	8.84 2.17 - 15.5	7.80 ± 3.54 1.42 - 11.8	8.28 ± 3.72 4.17 - 11.4	1.33 1.23 - 1.42	3.18 ± 1.31 1.71 - 5.96	2.92 ± 0.67 2.46 - 3.69	0.15	0.41	0.35
AUC_{0-12} (ng * h/mL)	37.3 16.5 - 58.1	49.5 ± 18.9 11.4 - 76.7	55.7 ± 34.9 21.2 - 91.0	12.7 11.0 - 14.4	29.1 ± 14.8 13.1 - 62.3	23.8 ± 2.39 21.5 - 26.3	0.34	0.59	0.43
Cmin,av (ng/mL)	1.30 0.964 - 1.64	2.64 ± 1.17 1.24 - 5.01	2.74 ± 1.71 1.13 - 4.54	0.853 0.693 - 1.01	1.90 ± 1.11 0.874 - 4.49	1.33 ± 0.131 1.19 - 1.45			
dn - Cmax (ng/mL)/mg	0.884 0.217 - 1.55	0.52 ± 0.24 0.09 - 0.79	0.414 ± 0.186 0.209 - 0.570	0.133 0.123 - 0.142	0.212 ± 0.088 0.114 - 0.397	0.146 ± 0.033 0.123 - 0.185			
dn - AUC_{0-12} (ng * h/mL)/mg	3.73 1.65 - 5.81	3.30 ± 1.26 0.76 - 5.11	2.78 ± 1.75 1.06 - 4.55	1.27 1.10 - 1.44	1.94 ± 0.984 0.870 - 4.15	1.19 ± 0.120 1.08 - 1.32			
t½ (h)	38.1[a] 38.1	39.0[b] ± 26.1 18.5 - 109	31.0 ± 10.6 20.7 - 41.9	15.4 13.9 - 17.0	18.1 ± 5.18 11.4 - 28.5	15.2 ± 4.20 11.7 - 19.9			

a n = 1
b n = 11

Figure 51 Mean Asenapine Multiple Dose Cmaxs vs. Dose from Various Studies

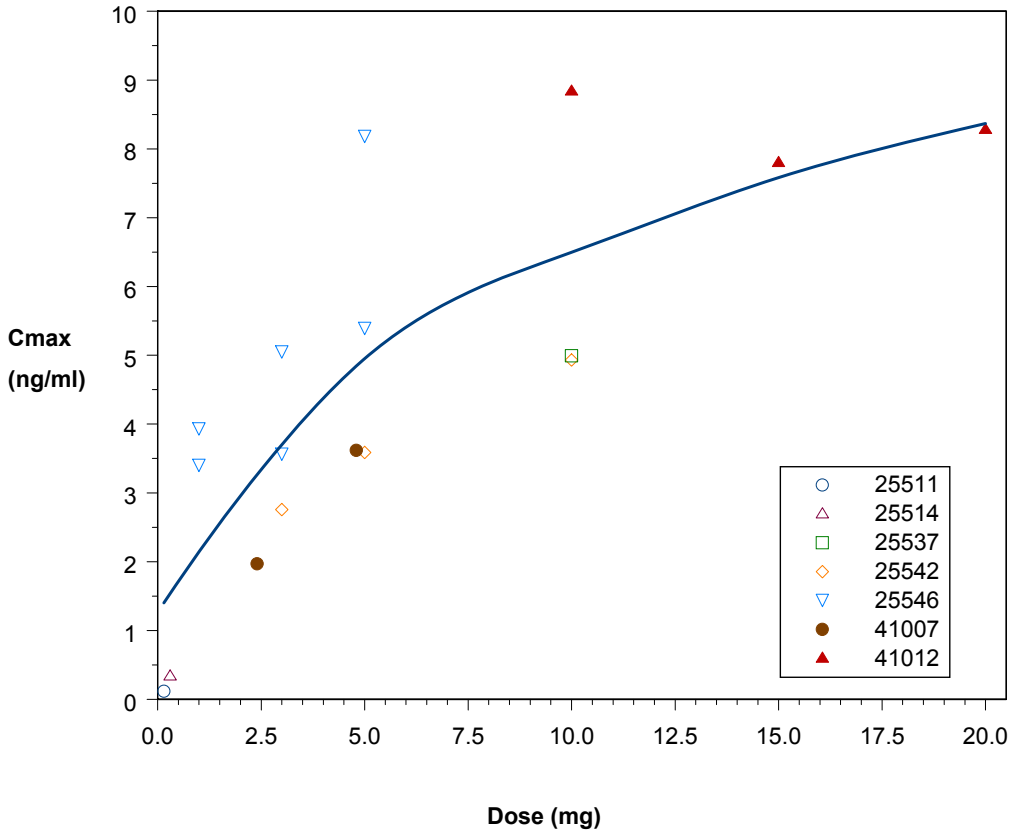


Figure 52 Mean Asenapine Multiple Dose AUCs vs. Dose from Various Studies

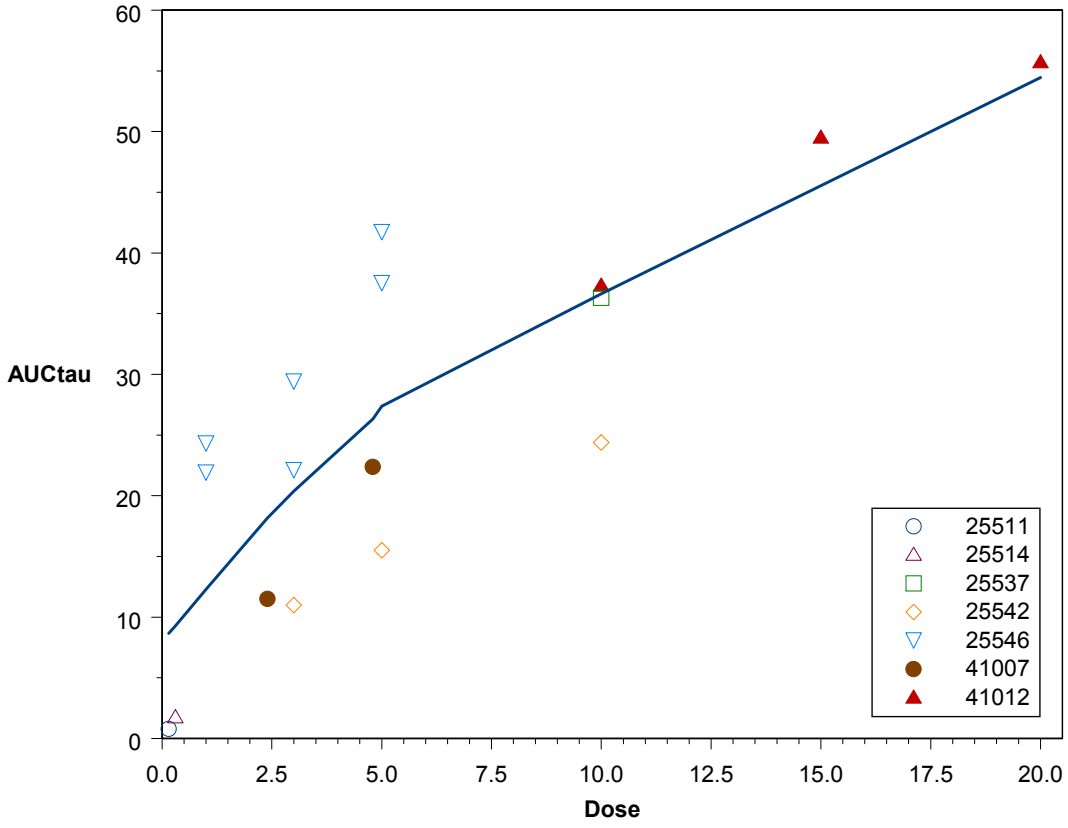


Figure 53 Mean Asenapine Dose Normalized Cmaxs and AUCs vs. Dose from Various Multiple Dose Studies

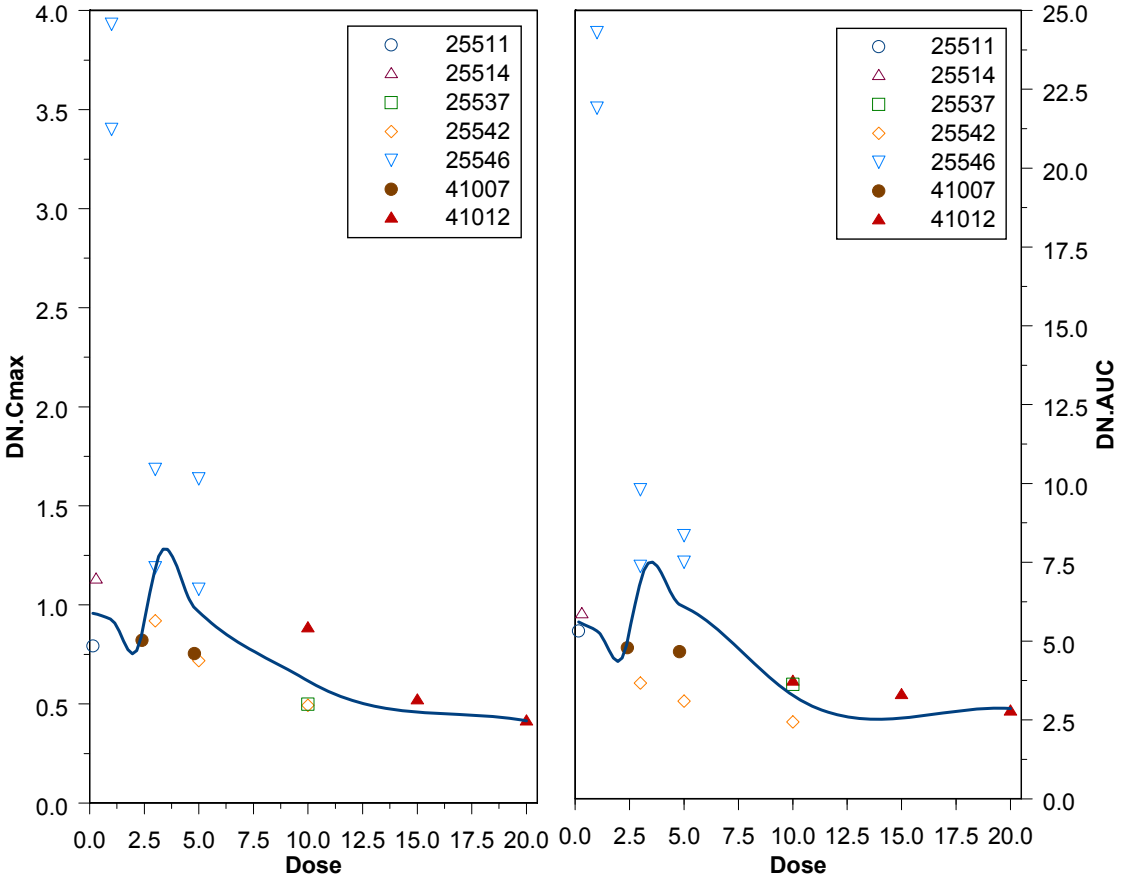


Table 56 Asenapine SL Multiple Dose Pharmacokinetic Metrics in Young Healthy Male Volunteers - Studies 25511 and 25514

Study	25511							25514
Dosage	150 mcg SL BID							300 mcg SL BID
Day No.	1	3	5	7	10	12	14	
N	18	12-17	12-17	17	6	6	6	12 (11)
Tmax (hr)	1.6 ± 0.6 1.0 - 3.1	1.3 ± 0.6 1.0 - 3.0	1.5 ± 0.6 1.0 - 3.0	1.5 ± 0.8 0.5 - 4.0	1.0 ± 0.00 1.0 - 1.0	1.2 ± 0.3 1.0 - 1 5	1.3 ± 0.5 0.75 - 2.0	1.2+0.3 0.75-1.5
Cmax (pg/ml)	127.8 ± 38.5 61.4 - 192.2	106.4 ± 42.1 61.1 - 118.0	103.4 ± 34.0 68.6 - 193.0	141.6 ± 48.1 80.1 - 23 9.5	106.0 ± 35.9 70.8 - 159.1	112.0 ± 27.8 75.2 - 150.3	143.5 ± 42.0 86.0 - 183.4	340+99.3 188.4-495.
AUC_{0-12} (pg/ml x hr^{-1})	730.4 ± 284.7 372.9 - 1476.7	—	—	832.0 ± 216.2 589.0 - 1335.1	—	—	765.4 ± 242.4 444.3 - 1064.0	1759.5+442.9 1168.5-2737.5
Clapp (L/hr x kg^{-1})	3.2 ± 1.3 1.4 - 5.9	—	—	2.6 ± 0.7 1.4 - 3.8	—	—	3.1 ± 1.3 1.7 - 4.9	2.41+0.68 1.53-4.06
t½ (h)	4.2 ± 1.4 2.0 - 7.3	—	—	7.7 ± 5.6 4.1 - 28.4	—	—	8.4 ± 7.3 2.8 - 22.7	16.2+4.75 10.8-24.3
	—	—	—	(6.4) ± (1.8) (4.1) - (11.8)	—	—	(5.5) ± (2.3) (2.8) - (8.8)	5.6+1.2 4.0-8.3
Css,min (pg/ml)	—	36.8 ± 18.3 0.00 - 61.6	47.9 ± 15.9 23.2 - 85.0	43.6 ± 10.4 28.4 - 64.5	42.3 ± 9.6 30.2 - 53.1	42.9 ± 12.04 30.8 - 63.5	33.9 ± 9.3 24.0 - 44.4	—
Css,av (pg/ml)	—	—	—	69.3 ± 18.0 49.1 - 111.3	—	—	63.8 ± 20.2 37.0 - 88.7	146.6+36.9 97.4-228.1
DF (%)	—	—	—	136.7 ± 39.5 81.5 - 202.7	—	—	176.7 - 59.5 102.8 - 248.3	179.8+39.2 108.1-268.5

5.5.3 Enantiomer Pharmacokinetics - Single Dose

Study 41028 was a single dose pharmacokinetic study in eight healthy male volunteers. Subjects received one 2.5 mg tablet of the (R,R) – asenapine enantiomer (Org 10968) and one 2.5 mg tablet of the $^{13}C_6$ labeled (S,S) – asenapine enantiomer (Org 10969) administered simultaneously.

Table 57 Comparison of Asenapine Enantiomer Pharmacokinetic Metrics after Simultaneous Single Oral Doses of 2.5 mg of each Asenapine Enantiomer in Healthy Male Volunteers – Study 41028

	Summary Statistics		Geometric Means		Geometric Mean Ratios of (S,S)-asenapine : (R,R)-asenapine (95% confidence interval)
	(S,S)-asenapine	(R,R)-asenapine	(S,S)-asenapine	(R,R)-asenapine	
Tmax (h)	[0.63] 0.5 - 1.0	[0.75] 0.5 - 1.0	—	—	—
Cmax (ng/mL)	2.40 ± 0.948	2.42 ± 0.949	2.20	2.23	0.99 (0.95 - 1.02)
$AUC_{0-\infty}$ (ng/mL x hr^{-1})	15.9 ± 5.90	17.2 ± 5.94	14.7	16.2	0.91 (0.85 - 0.98)
$AUC_{0-tlast}$ (ng/mL x hr^{-1})	15.2 ± 5.70	16.3 ± 5.52	14.1	15.3	0.92 (0.85 – 0.998)
t½ (h)	10.2 ± 4.25	12.6 ± 5.58	9.43	11.6	0.81 (0.58 - 1.13)

Table 58 Comparison of Desmethyl - Asenapine Enantiomer Pharmacokinetic Metrics after Simultaneous Single Oral Doses of 2.5 mg of each Asenapine Enantiomer in Healthy Male Volunteers – Study 41028

	Summary Statistics		Geometric Means		Geometric Mean Ratios of N-desmethyl-(S,S)–asenapine : N-desmethyl-(R,R)-asenapine (95% CI)
	N-desmethyl - (S,S)-asenapine	N-desmethyl - (R,R)-asenapine	N-desmethyl - (S,S)-asenapine	N-desmethyl - (R,R)-asenapine	
Tmax (h)	[6.0] 3.0 - 8.07	[12.0] 6.0 - 12.0	—	—	—
Cmax (ng/mL)	0.328 ± 0.139	0.109 ± 0.0326	0.308	0.105	2.9 (2.46 - 3.48)
$AUC_{0-tlast}$ (ng*h/mL)	3.55 ± 2.21	1.71 ± 1.29	3.06	1.32	2.3 (1.52 - 3.52)

The following is the sponsor's assessment of the results of this study.

*"The plasma concentrations of the (S,S) - and (R,R) - enantiomers of asenapine are similar after simultaneous single sublingual doses of 2.5 mg of the (S,S) - enantiomer and 2.5 mg of the (R,R) - enantiomer of asenapine. The mean AUC of the (S,S) - enantiomer was 8 - 9% lower than that of the (R,R) - enantiomer. This difference in mean AUC is not considered clinically relevant, although it was statistically significant due to a very low within subject variation on AUC (6.5%). When adding up the AUC0 - ∞ values of both enantiomers the result (33.1 ng*h/mL) is similar to that found in other clinical pharmacology studies with a single sublingual dose of 5 mg of the racemate, e.g. 38.5 ng*h/mL in study 041 - 029 (4).*

*Formation of the N - desmethyl metabolite seems to be enantioselective, i.e. the (S,S)-enantiomer is converted to more than two - fold higher N - desmethyl - asenapine concentrations than the (R,R)-enantiomer based on AUC0 - tlast. Although the C - t profiles of the N - desmethyl metabolites contained sometimes only a few measurable data points, the plasma concentrations of N - desmethyl - (S,S) - asenapine were consistently higher in all subjects. In two subjects (subjects 02 and 05) the N-desmethyl metabolite could be followed for at least 24 h, both for the (S,S) - and (R,R) - enantiomer: 24 h and 36 h respectively. Adding up the AUC0 - tlast values for these subjects gives 11.5 ng*h/mL and 9.6 ng*h/mL respectively. These values are similar to those found in other clinical pharmacology studies with a single sublingual dose of 5 mg of the racemate, e.g. a mean of 8.6 ng*h/mL with median tlast = 41 h in study 041 - 029 (4).*

Compared to asenapine the N - desmethyl - asenapine shows a much lower binding affinity for therapeutically relevant receptors (see Investigator Brochure). Combined with the low level of exposure to the N - desmethyl metabolite, this indicates that this metabolite does not contribute substantially to the pharmacological effects of asenapine. Thus the difference in AUC between the N - desmethyl - (R,R) - asenapine and the N - desmethyl - (S,S) - asenapine is considered to be of no clinical relevance."

This reviewer does not agree with the sponsor's assessment as the difference in exposure to the two N-desmethyl metabolites might indicate either a difference in volume of distribution due to differences in tissue penetration or binding or more likely a difference in clearance with increased exposure to other metabolites.

Lower exposure to the R,R desmethyl metabolite in spite of a higher exposure to parent may mean more exposure to the potentially toxic to N-oxide, or it may mean greater metabolism of the R,R N-desmethyl-asenapine by CYP2D6 at least initially. Although exposure to the S,S enantiomer is slightly lower, exposure to the N-desmethyl metabolite is significantly greater. Consequently, increased exposure to the S,S N-desmethyl metabolite could mean that it preferentially inhibits CYP2D6. In addition, if metabolism of N-desmethyl-asenapine by CYP2D6 is the mechanism of toxicity then this could be the more clinically important finding. Presently it's not possible to determine what the clinical consequences might be without further *in vitro* and possibly *in vivo* testing. These results might indicate a difference in risk : benefit ratio for the different enantiomers if administered separately.

5.5.4 Bioavailability

5.5.4.1 Absolute Bioavailability

Two studies were conducted to determine asenapine's absolute bioavailability. In study 25533 the IV dose was too low to result in reliable determinations of asenapine concentrations and in study 41036 even thought the IV dose was increased, concentrations were still too low to determine the terminal elimination rate, and based on estimates of half-lives from other studies the amount of error would have been more than 10% so this study was terminated prematurely. Subsequently the sponsor combined the IV pharmacokinetics from the two studies and based on estimated terminal half-lives from a number of studies as well as AUCs from these studies was able to obtain an overall estimate of average absolute bioavailability for a single 5 mg dose of approximately 35%.

Descriptions of these study reports and their conclusions follow.

5.5.4.1.1 Study 25533 - Absolute Bioavailability

In study 25533 eight healthy adult male subjects were simultaneously administered a single sublingual dose of asenapine 5 mg and 10 µg (200 nCi) of ^{14}C-asenapine by intravenous push. Analyses for the radio - labeled asenapine and N-desmethyl-asenapine were performed by accelerator mass spectrometry.

Asenapine and desmethyl-asenapine kinetics for unlabeled species were determined, however the plasma concentrations of ^{14}C-asenapine and ^{14}C-N-Desmethyl-asenapine could not be reliably determined due to insufficient reproducibility of the method used. For this reason no results were reported for the radiolabeled component and IV pharmacokinetic metrics and bioavailability were not determined. Reportable metrics from study 25533 are shown in Table 59.

According to the sponsor unchanged ^{14}C-labeled asenapine was detected in feces, lthough the exact quantity could not be determined. Based on the presence of unchanged ^{14}C-labeled asenapine in feces biliary excretion is likely.

Table 59 Pharmacokinetic Metrics after a Single Simultaneous Administration of Asenapine 5 mg Sublingually and 10 mcg (200 nCi) ^{14}C-Asenapine IV Push – Study 25533

Parameter (unit)	Asenapine		N - Desmethyl - Asenapine	
N	8		8	
Route	SL	IV	SL	IV
Tmax (h)	[1.0] (0.5 - 3.0)	—[a]	[6.0] (2.0 - 12.0)	—[a]
Cmax (ng/mL)	5.95 (40.7) 2.05 - 8.64	—	0.463 (14.0) 0.321 - 0.532	—
$AUC_{0-tlast}$ (ng·h/mL)	37.0 (24.2) 19.6 - 44.6	—	7.76 (21.70 6.08 - 11.0	—
AUC_{0-inf} (ng·h/mL)	38.3 (24.1) 19.9 - 46.6	—	8.85 (22.5 6.99 - 12.7	—
CL/f (L/h)	141 (34.6) 107 - 251	—	559 (19.9) 374 - 681	—
Vz/f (L)	3713 (42.7) 2070 - 6847	—	8311 (31.1) 5918 - 13941	—
t½ (h)	19.7 (44.2) 7.68 - 31.0	—	10.7 (38.8) 6.34 - 20.2	—

a Not reported. Based on sponsor's report it appears concentrations were too low to be reliably determined.

5.5.4.1.2 Study 41036 - Absolute Bioavailability

Study 41036 was intended as a single dose 2-way cross-over absolute bioavailability study in healthy adult males. It was preceded by a pilot study of 0.5 mg asenapine administered over 1 hour intravenously in three subjects. Due to the low dose and insufficient assay sensitivity, concentrations could only be determined out to 37 hours. With a half-life of 24 hours extrapolating to AUC_{∞} results in excessive error.

IV asenapine pharmacokinetic metrics, the raw data, and concentration vs. time plots on the untransformed and on the semi-log scale for study 41036 are shown in Table 60, Table 61, Figure 54, and Figure 55.

Table 60 Asenapine Pharmacokinetic Metrics after 0.5 mg over 1 hour IV – Study 41036

n	3
Tmax (h)	[0.98] 0.75 - 0.98
Cmax (ng/mL)	2.69 ± 0.8 (29.7) 1.79 - 3.32 [2.96]
dn - Cmax (ng/mL/mg)	5.38 ± 1.60
$AUC_{0-tlast}$ (ng/mL x hr^{-1})	8.51 ± 1.80 (21.2) 6.58 - 10.2 [8.79]
dn - $AUC_{0-tlast}$ (ng/mL x hr^{-1})	17.0 ± 3.61

Table 61 Asenapine Concentrations over Time when 0.5 mg is administered Intravenously over 1 hour – Study 41036

Sample no.	Time (hours)	Asenapine Concentration (ng/ml)		
		Subject 1	Subject 2	Subject 3
1	0	0	0	0
2	0.25	0.737	0.221	1.11
3	0.5	1.25	1.06	2.57
4	0.75	2.96	1.61	2.96
5	1.0	3.32	1.79	2.25
6	1.083	2.24	1.41	1.90
7	1.167	1.77	1.16	1.87
8	1.33	1.52	1.08	1.34
9	1.5	1.39	1.03	1.35
10	1.75	1.05	0.891	1.22
11	2	0.783	0.852	1.01
12	2.5	0.732	0.596	0.978
13	3	0.592	0.591	0.766
14	4	0.443	0.459	0.704
15	5	0.387	0.372	0.481
16	7	0.404	0.293	0.374
17	9	0.309	0.219	0.330
18	13	0.141	0.128	0.175
19	25	0.0506	0.0560	0.0623
20	37	0.0333	<0.0250	0.0286
21	49	<0.0250	<0.0250	<0.0250
22	61	<0.0250	<0.0250	<0.0250
23	73	<0.0250	<0.0250	<0.0250
AUCt		**9.0**	**6.92**	**10.33**
Estimated AUCextrap (Assuming t½ = 24 h)		**4.88**	**4.43**	**6.06**
% Extrapolated		**54.2**	**64.0**	**58.7**

Figure 54 Asenapine Concentration vs. Time Profiles after 0.5 mg IV over 1 hour – Study 41036

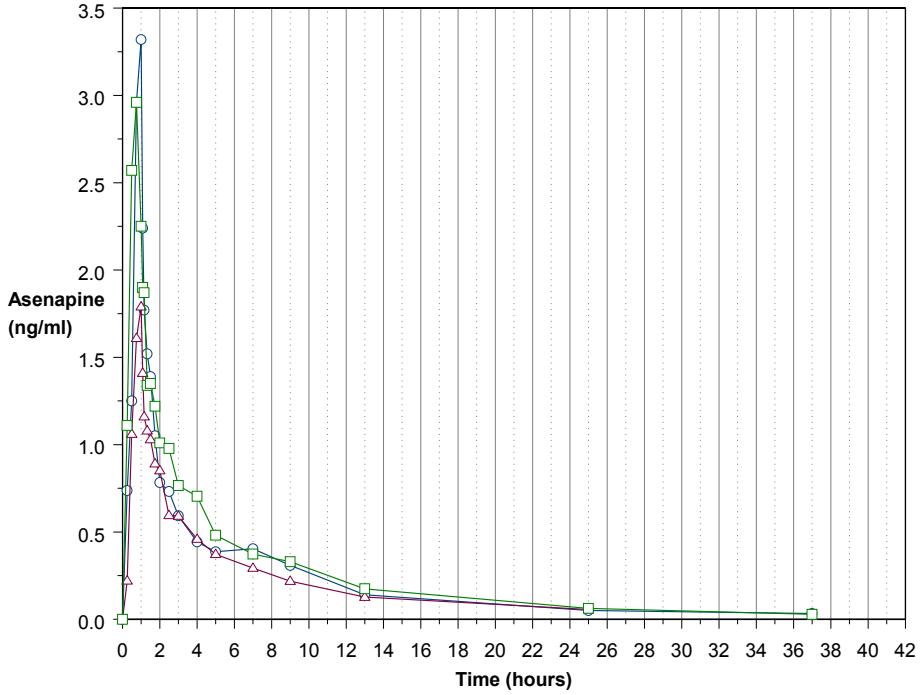
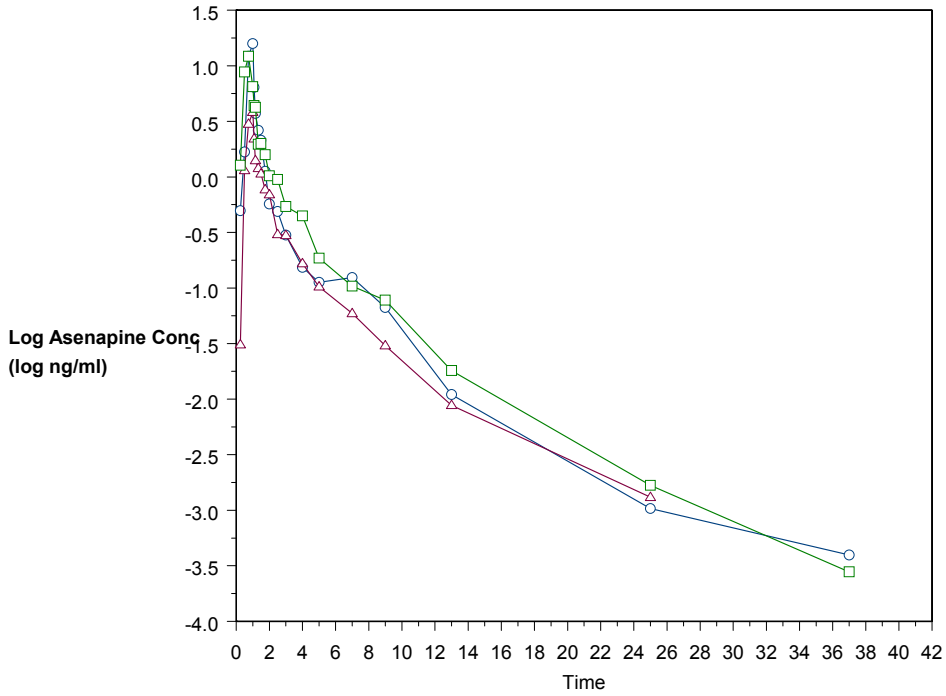


Figure 55 Asenapine Natural Log- Concentration vs. Time Profiles after 0.5 mg IV over 1 hour – Study 41036



5.5.4.1.3 Report INT00035825 – Absolute Bioavailability based on Studies 41036 and 25506

For report INT00035825, the pharmacokinetic results from intravenous administrations of asenapine from the failed absolute bioavailability study 41036 was combined with the IV data from study 25506. Both studies used doses of 0.5 mg, but study 41036 used an infusion duration of 1 hour and study 25506 a duration of 0.5 hours. Study 25506 was stopped because the intravenous dose was not well tolerated. See Table 62 for summary metrics.

An overall mean t½ from a series of PK trials, (see Table 63) was used to calculate the $AUC_{0-\infty,}^{IV}$s, for the IV data in Table 62. From these same trials, an overall estimate of $AUC_{0-\infty,}^{SL}$ was also determined in order to calculate the absolute bioavailability, (see Table 64).

The mean of 33.8 ng/mL*hr^{-1} was used as the overall $AUC_{0-\infty,}^{SL}$. Thus the overall dose normalized AUC (dn - $AUC_{0-\infty,}^{SL}$) was 6.76 ng/mL x hr^{-1} / mg.

F_{abs} was then calculated as follows:

$$F_{abs} = \frac{dn - AUC_{0-\infty,sl}}{dn - AUC_{0-\infty,iv}} \times 100\% = \frac{6.76}{19.4} \times 100\% = 34.8\%.$$

The sponsor's calculation of a 95% confidence interval for Fabs according to Fieller's theorem resulted in a 95% CI of 31.6% - 38.7%.

Table 62 Pharmacokinetic Metrics after Asenapine 0.5 mg IV Infusions by Study

Study	041036	25506	Overall
N	3	2	5
Infusion Duration	1 hour	0.5 hours	—
Tmax (h)	[0.98] 0.75 - 0.98	[0.55] 0.50 - 0.60	—
Cmax (ng/mL)	2.69 ± 0.8	2.58 ± 1.03	—
$AUC_{0 - tlast}$ (ng/mL* hr^{-1})	8.51 ± 1.80	6.55 ± 0.587	7.72 ± 1.69
$AUC_{0 - \infty,}^{IV}$ * (ng/mL* hr^{-1})	9.82 ± 1.33	9.55 ± 0.587	9.71 ± 0.997
dn - Cmax (ng/mL / mg)	5.38 ± 1.60	5.15 ± 2.05	—
dn - $AUC_{0 - tlast}$ (ng/mL* hr^{-1} / mg)	17.0 ± 3.61	13.1 ± 1.17	15.4 ± 3.39
dn - $AUC_{0 - \infty,}^{IV}$* (ng/mL* hr^{-1} / mg)	19.6 ± 2.66	19.1 ± 1.17	19.4 ± 1.99
CL (L/h)	51.6 ± 7.15	52.5 ± 3.22	51.9 ± 5.33
Vz (L)	1719 ± 238	1748 ± 107	1731 ± 178

* based on overall terminal t½ from Table 63

Table 63 Asenapine half-lives by Study after Single 5 mg SL Doses in Healthy Subjects

Metric (unit)	Study	n	Mean ± SD	Median t_{last} (h)	Group
$t_{½}$ (h)	041-029	26	22.4 ± 12.3	72	Fasting group
	041-030	32	20.2 ± 13.2	72	Sublingual group
	041-033	26	27.6 ± 17.1	72	Asenapine - only group
	25525	26	22.6 ± 9.52	72	Asenapine - only group
	25526	24	25.5 ± 15.3	72	Asenapine - only group
	25527	24	22.9 ± 8.66	72	Asenapine - only group
	25528	27	19.4 ± 9.96	72	Asenapine - only group
	25529	25	29.9 ± 18.1	72	Asenapine - only group
	25540	7	15.9 ± 5.04	60	Sublingual without charcoal group
	25545	24	17.1 ± 10.7	60	Non - smoking group
	25546	6	15.1 ± 8.01	48	Caucasian group
	A7501017	8	23.1 ± 5.68	72	Non - renally impaired group
	A7501018	8	39.2 ± 17.8	96	Non - hepatically impaired group
Overall (combined)*		263	23.1 ± 13.5		

* average of all individual values; equivalent to weighted mean

Table 64 Asenapine AUCs by Study after 5 mg SL Doses in Healthy Subjects

Metric (unit)	Study	n	Mean ± SD	Group
$AUC_{0-\infty}$ (ng/mL x hr^{-1})	041-029	26	38.5 ± 15.6	Fasting group
	041-030	32	25.6 ± 10.5	Sublingual group
	041-033	26	37.6 ± 12.9	Asenapine – only group
	25525	26	38.4 ± 11.7	Asenapine – only group
	25526	24	38.1 ± 11.2	Asenapine – only group
	25527	24	35.9 ± 10.7	Asenapine – only group
	25528	27	29.9 ± 8.67	Asenapine – only group
	25529	25	33.4 ± 10.3	Asenapine – only group
	25540	7	21.3 ± 6.11	Sublingual without charcoal group
	25545	24	24.3 ± 10.1	Non–smoking group
	25546	6	26.0 ± 10.7	Caucasian group
	A7501017	8	43.3 ± 10.9	Non-renally impaired group
	A7501018	8	55.0 ± 15.9	Non–hepatically impaired group
Overall (combined)*		263	33.8 ± 13.2	

* average of all individual values; equivalent to weighted mean

5.5.4.2 Relative Bioavailability

5.5.4.2.1 Relative Bioavailability – Oral vs. Sublingual

Study 25540 was a randomized, open label, placebo controlled, parallel design, single dose, fixed sequence study of the relative bioavailability of asenapine 5 mg administered sublingually and as an oral solution in two groups of 8 healthy adult males.

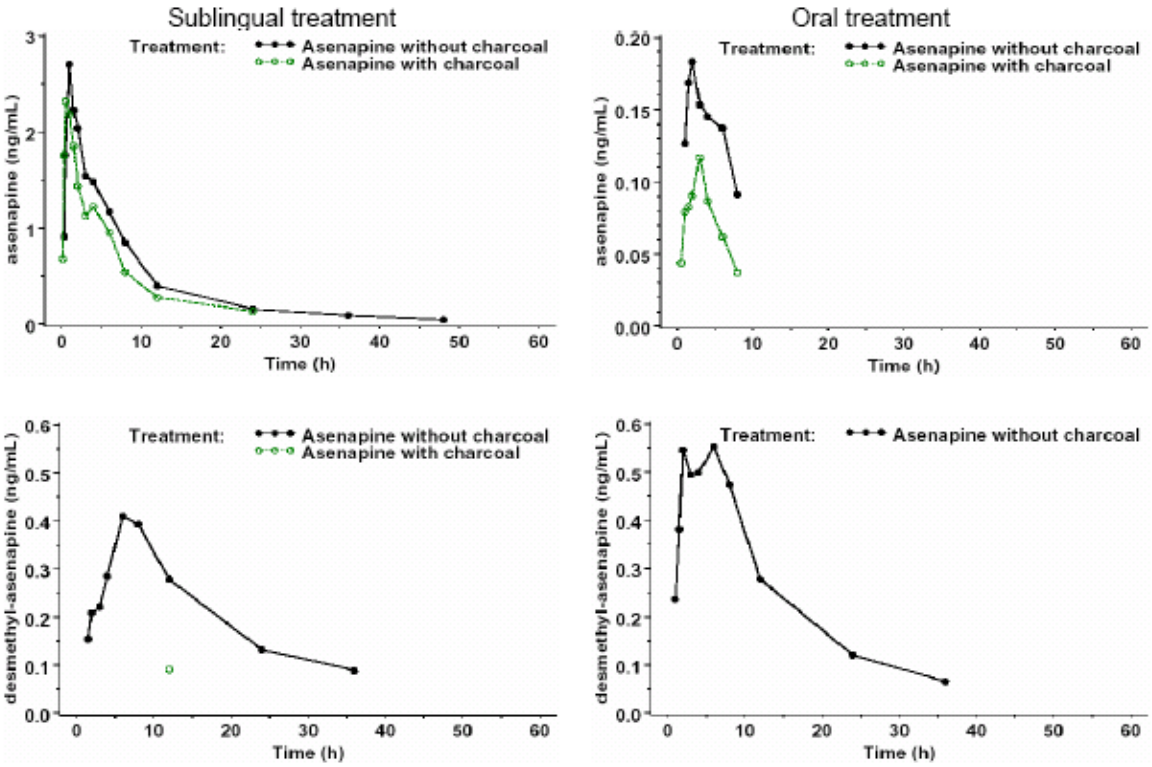
Subjects in Group 1 were administered asenapine sublingually and subjects in Group 2 were administered asenapine tablets orally dissolved in 150 ml of water. After an interperiod wash-out of 7 days subjects received the same asenapine treatment as previously, however it was administered 10 minutes after a 50 gm dose of activated charcoal in 400 ml of water.

Figure 56 shows the mean concentration-versus-time profiles for asenapine (upper panels) and desmethyl-asenapine (lower panels) after sublingual (left panels) and oral (right panels) asenapine treatment (5 mg single dose) with and without charcoal.

Based on Figure 56 the following conclusions may be drawn:

a) Asenapine peak concentrations after oral administration are approximately 1/15 (7%) those after sublingual administration
b) Desmethyl-asenapine peak concentrations are 40% higher after oral administration
c) Charcoal administration effects oral absorption more than sublingual absorption, with a decrease in asenapine exposure after oral administration of approximately 50% compared to a decrease in asenapine exposure of approximately 25% after sublingual administration.
d) The effect of charcoal administration on desmethyl-asenapine exposure is even greater than the effect on asenapine.
e) There is significant enterohepatic circulation of asenapine, but it is much greater for desmethyl-asenapine.

Figure 56 Mean Asenapine and Desmethyl-Asenapine Concentration vs. Time Profiles after Administration Sublingually and as an Oral Solution in the Absence and Presence of Activated Charcoal – Study 25540



Pharmacokinetic summary metrics are shown in Table 65. The values confirm the conclusions made from Figure 56.

Quantitatively the relative bioavailability of asenapine after oral administration compared to sublingual administration is approximately 7% with an estimated absolute oral bioavailability of around 3%.

In addition, the exposure to desmethyl-asenapine is only 4.6% lower after oral administration, however the rapid delivery results in a 60% higher peak desmethyl concentration after oral administration.

These results indicate that the first pass effect is not due to metabolism to desmethyl-asenapine but rather to a different elimination pathway. Based on Figure 56 it cannot be due to biliary excretion of asenapine and is unlikely due to glucuronidation because this tends to be a low affinity pathway. The most likely pathways responsible for the first pass effect are either N-oxidation or 11-hydroxylation. Depending upon which pathway it is, the clinical ramifications regarding labeling may vary greatly, as an N-oxide is likely much more toxic.

Table 65 Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics and Relative Bioavailability after Single 5 mg Oral vs. SL Doses in the Presence and Absence of 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	0.096 ± 0.048	0.428 ± 0.210
	GeoMean Cmax	1.87	2.70	0.0838	0.371
	$AUC_{0\text{-}tlast}$ (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 [b]
	GeoMean AUC_∞	12.4	20.4	—	9.86
	$t_{½}$ (h)	11.1 ± 5.46	15.9 ± 5.04	—	15.1 ± 4.32 [b]
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 ± 0.079	—	0.598 ± 0.117
	GeoMean Cmax	0.126	0.189	—	0.588
	$AUC_{0\text{-}tlast}$ (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 [a]	1.87 ± 0.768	—	9.56 ± 1.63
	GeoMean AUC_∞	0.824	1.75	—	9.41
	$t_{½}$ (h)	4.19 ± 0.671 [a]	6.75 ± 3.72	—	10.5 ± 2.72
Geometric Mean Ratios Oral : SL	Cmax	0.067	0.070	—	1.584
	AUC_∞	0.066	0.086	—	0.954
Estimated Absolute Oral Bioavailability			~ 3.0%	—	—

a n = 7
b n = 6

5.5.4.2.2 Relative Bioavailability – Supra-lingual and Buccal vs. Sublingual

Study 25512 was a 3-way 3-period crossover study of the relative bioavailability of asenapine 200 mcg, (2 x 100 mcg rapidly dissolving gelatin and mannitol tablets) administered via the supra-lingual and buccal routes as compared to sublingually in 23 healthy young males.

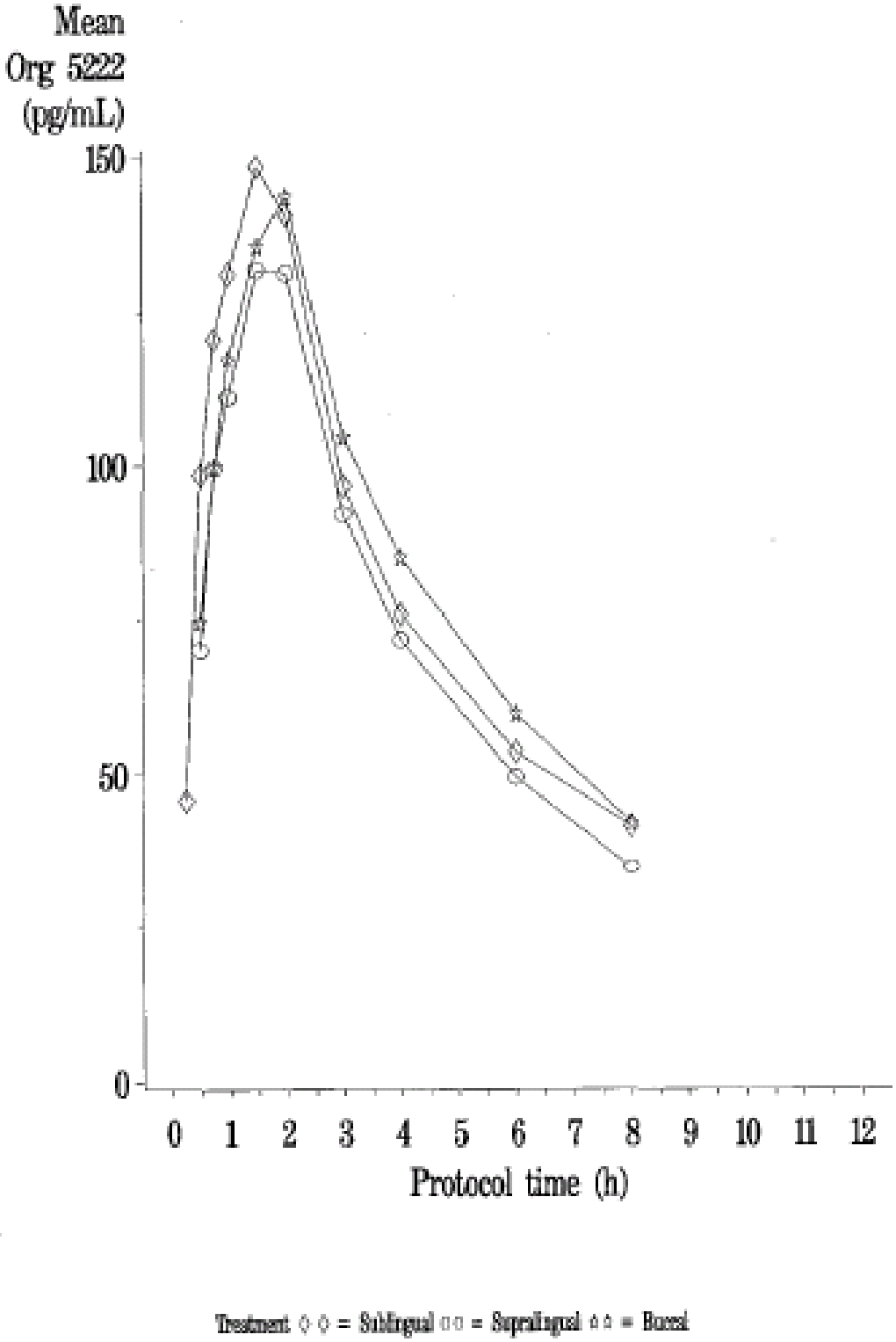
Both the lingual and buccal routes had lower Cmaxs, AUCs and delayed Tmaxs as compared to the sublingual route, with absorption via the supralingual route being less than the buccal route. The supralingual route was bioinequivalent to sublingual administration and although the buccal route met the criteria for bioequivalence, it barely did so, (see Table 66 and Figure 57). Since this formulation is different than the to-be-marketed formulation and since the dose used is in a range where bioavailability is greater than with clinical dosages no conclusions can be drawn regarding bioequivalence under clinical dosing conditions.

Table 66 Comparative Bioavailability of Asenapine 200 mcg after Supralingual, Buccal, and Sublingual Administration of a Development Formulation – Study 25512

	Summary Statistics			Geometric Means			Geometric Mean Ratios (90% CI)	
	Supralingual	Buccal	Sublingual	Supralingual	Buccal	Sublingual	Supralingual : Sublingual	Buccal : Sublingual
N	23a	23a	23a	—	—	—	—	—
Tmax	1.66 ± 0.32	2.1 ± 0.8	1.38 ± 0.35	—	—	—	—	—
Cmax	150.8 ± 63.5	152.2 ± 48.5	157.3 ± 43.2	135.85	143.2	151.42	0.90 (0.77 - 1.05)	0.95 (0.81 - 1.11)
AUC	864.2 ± 290.5	955.8 ± 212.6	966.8 ± 233.7	799.9	929.7	944.4	0.85 (0.75 - 0.96)	0.98 (0.87 - 1.12)
t½	4.31 ± 1.18	4.36 ± 0.89	4.88 ± 1.02	—	—	—	—	—

a n = 21 for t½

Figure 57 Comparison of Mean Asenapine Concentration vs. Time Profiles after Supralingual, Buccal, and Sublingual Administration of a Development Formulation – Study 25512



5.5.5 Bioequivalence

5.5.5.1 Pivotal BE Study (b) (4) - Study A7501015

Study A7501015 examined the effect of different (b) (4) on the on the bioequivalence of asenapine 5 mg tablets.

This was a single-center, open-label, randomized, single dose, 3-treatment, 3-way crossover, bioequivalence study in healthy volunteers comparing the pharmacokinetic parameters following 3 treatments. Thirty-eight subjects Healthy male and/or female subjects between the ages of 18 and 55 years, inclusive were randomized to the study, and 32 completed the study.

On Study Days 1, 8, and 15, subjects received 1 of the 3 treatments indicated below in random order:

A: Reference: Asenapine 5 mg (b) (4)
(clinical formulation).

B: Test 1: Asenapine 5 mg (b) (4)
(proposed commercial formulation).

C: Test 2: Asenapine 5 mg (b) (4)
(proposed commercial formulation)

In addition to bioequivalence the study assessed the organoleptic properties of the formulations through a taste test questionnaire.

Results are shown in Table 67, Figure 58, and Figure 59.

Table 67 Asenapine Pharmacokinetic Parameters Following Sublingual Administration of 5-mg Asenapine Tablets Manufactured (b) (4) With (b) (4) Supplied by (b) (4) Formulation (Test 1) and a (b) (4) Formulation (Test 2) - Study A7501015

(b) (4)	Least-Squares Mean Parameter Values[a]		Ratio	90% Confidence Interval
	(b) (4) Tablet (Test1)	(b) (4) Tablet (Reference)		
N	33	36		
Cmax, ng/mL	3.07	2.96	104	91.51 to 117.45
AUC(0-tlqc), ng*hr/mL	21.9	21.6	101	91.19 to 112.51
AUC(0-∞), ng*hr/mL	23.4	23.2	101	91.15 to 111.73
tmax, hr	1.00	1.06		Not Applicable
t½, hr	12.3	13.4		Not Applicable
	(b) (4) Tablet (b) (4) (Test2)	(b) (4) Tablet (Reference)		
N	34	36		
Cmax, ng/mL	3.23	2.96	109	96.66 to 123.64
AUC(0-tlqc), ng*hr/mL	23.5	21.6	109	97.96 to 120.53
AUC(0-∞), ng*hr/mL	24.8a	23.2	107	96.79 to 118.55
tmax, hr	1.11	1.06		Not Applicable
t½, hr	13.0b	13.4		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference). 90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

a It's stated in the text of the clinical study report that these are geometric means

b N = 33 (t½ could not be determined for all subjects).

Figure 58 Individual Asenapine Cmax and AUCs by Treatment for (b) (4) Pivotal BE Study A7501015

(b) (4)

Figure 59 Individual Desmethyl-Asenapine Cmax and AUCs by Treatment for (b) (4) in Pivotal BE Study A7501015

Figure 4. Individual Desmethyl Asenapine Cmax (Upper Panel, ng/mL) and AUC(0-∞) (Lower Panel, ng·hr/mL) Values Following Sublingual Administration of 5-mg Asenapine Tablets Manufactured (b) (4) and (b) (4) (Test 1) and a (b) (4) (Test 2) (Study 7501015)

(b) (4)

5.5.5.2 Pivotal BE Study (b) (4) - Study A7501016

Study A7501016 examined the effect of different (b) (4) of asenapine maleate on the bioequivalence of asenapine 5 mg tablets. According to the sponsor the rationale is as follows:

'Asenapine is currently developed as a sublingual formulation, which quickly disintegrates in the saliva. Clinical supplies (b) (4) used in Phase 3 clinical trials have been manufactured with (b) (4) active pharmaceutical ingredient (API). Future drug supplies for the provisional market image of asenapine may be manufactured with (b) (4) API. The bioequivalence between the (b) (4) differences of these 2 formulations needs to be determined. Thus, this study was conducted to determine whether future commercial formulations could be manufactured with the (b) (4) API.'

However, based on information from study 41026, which is reported in the next section, the rationale for decreasing (b) (4) appears to be in order to mask the bitter taste of asenapine.

Study A7501016 was a randomized, open-label, single-dose, 2-way crossover study of single 5 mg sublingual doses administered a week apart in 36 healthy male and female volunteers between the ages of 18 and 55 years.

Treatments were as follows:

A = Asenapine 5 mg (b) (4) tablet (TBM formulation)
B = Asenapine 5 mg (b) (4) tablet (Phase 3 formulation; CTF).

Table 68 Summary of Asenapine Pharmacokinetic Parameter Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) - Study A7501016

Parameter	Least-Squares Mean Parameter Values[c]		Ratio	90% Confidence Interval
	(b) (4) Tablet (Test)	(b) (4) Tablet (Reference)		
N	35	34		
Cmax ng/mL	2.95	3.25	90.6	80.80 to 101.65
AUC(0-tlqc) ng*hr/mL	21.2	23.0	92.1	83.62 to 101.45
AUC(0-∞) ng*hr/mL	23.1a	25.1b	92.0	83.69 to 101.18
Tmax hr	1.13	1.12		Not Applicable
t½ hr	18.7a	19.1b		Not Applicable

a N=33;
b N = 32 (t½ could not be determined for all subjects)
Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference). 90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.
c In the text of the study report it indicates that these are geometric means

This study was discovered while writing the pertinent CPB questions. Although the sponsor's conclusions are that the formulations are bioequivalent, the comparison is on the least square means and there is no mention of geometric means. In addition, the datafiles could not be opened and the basis of these calculations could not be verified. Thus bioequivalence cannot be assured presently and further verification is needed. Whether this is an internal or external issue is unknown.

Table 69 Summary of Desmethyl Asenapine Pharmacokinetic Parameter Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) - Study A7501016

Parameter	Least-Squares Mean Parameter Values[a]		Ratio	90% Confidence Interval
	(b) (4) Tablet (Test)	(b) (4) Tablet (Reference)		
N	35	34		
Cmax ng/mL	0.604	0.623	97.0	92.48 to 101.66
AUC(0-tlqc) ng*hr/mL	11.3	11.3	99.9	95.81 to 104.15
AUC(0-∞) ng*hr/mL	13.6	13.3a	102	96.94 to 107.10
Tmax hr	5.44	5.17		Not Applicable
t½ hr	15.6	14.7a		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.
a In the text of the study report it indicates that these are geometric means

A cursory review of the bioanalytic method indicates that the precision of the assay may be unacceptably high at the lower end and thus estimates of AUC and half-life may be off.

Table 70 Accuracy and Precision of Asenapine Quality Control Samples – Study A7501016

QC	A	B	C	D	E
Nominal Concentration	0.075	0.75	1.5	6.0	15.0
Measured Mean Concentraion	0.0753	0.82	1.55	6.53	16.20
SD	0.0137	0.079	0.201	0.246	0.581
%CV (Precision)	18.2	9.7	13.0	3.8	3.6
Accuracy	100.4	109.3	103.3	108.8	108.0
Bias	0.4	9.3	3.3	8.8	8.0

Figure 60 Mean Plasma Asenapine Concentration-Time Profiles Following Administration of Asenapine 5 mg (b) (4) Tablets (Filled Circles; Reference) and 5 mg (b) (4) Tablets (Open Circles, Test) (Study A7501016)

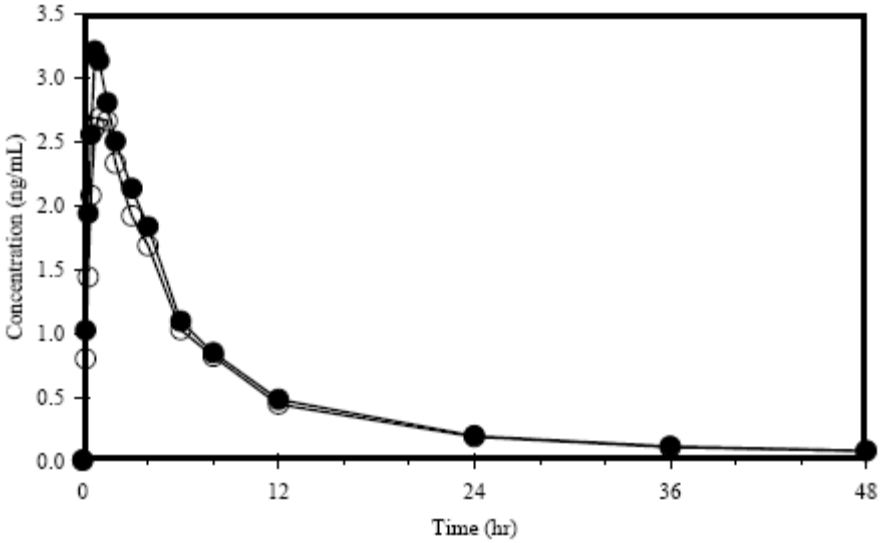


Figure 61 Mean Plasma Asenapine Concentration-Time Profiles Following Administration of Asenapine 5 mg (b) (4) Tablets (Filled Circles; Reference) and 5 mg (b) (4) Tablets (Open Circles, Test) (Study A7501016)

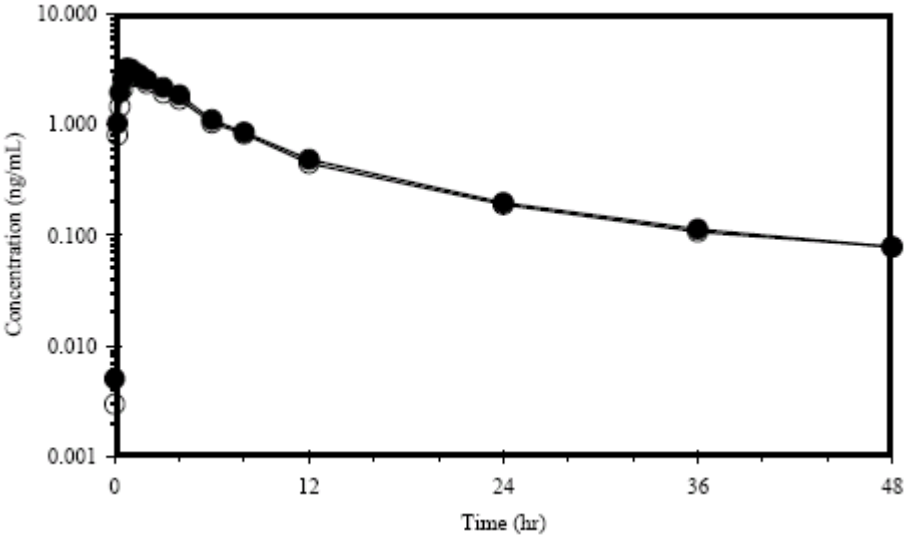


Figure 62 Asenapine Cmax Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) (Study A7501016)

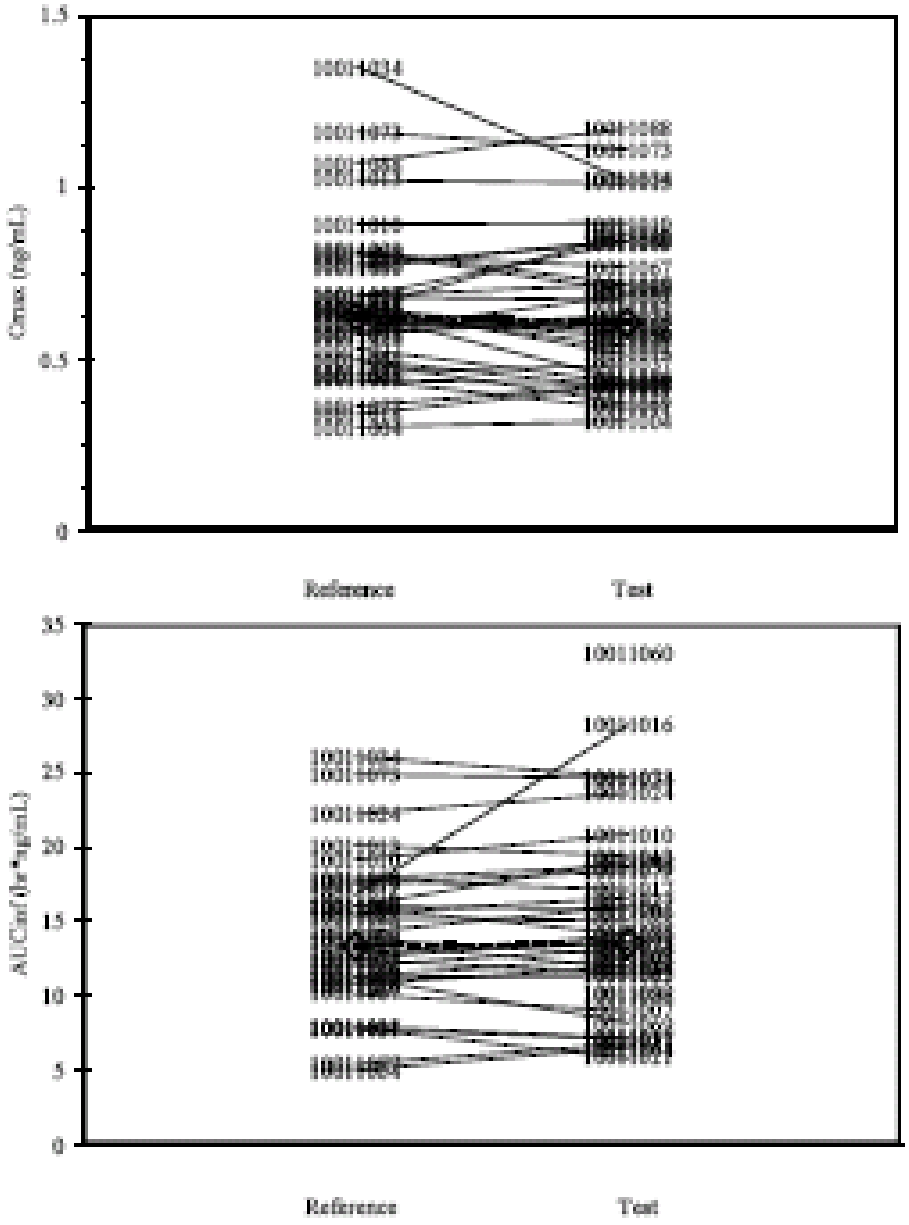
(b) (4)

Figure 63 Asenapine AUC(0-∞)Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) (Study A7501016)

(b) (4)

Figure 64 Desmethyl- Asenapine Cmax (Upper Panel, ng/mL) and AUC(0-∞) (Lower Panel, ng·hr/mL) Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) (Study A7501016)

Figure 4. Desmethyl Asenapine Cmax (Upper Panel, ng/mL) and AUC(0-∞) (Lower Panel, ng·hr/mL) Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) (Study A7501016)



Individual subjects are identified by numbers; mean values are represented by diamonds.

According to the sponsor three subjects withdrew from the study during the treatment phase. Two subjects were withdrawn due to lack of compliance, and 1 withdrew consent. No subjects withdrew due to adverse events. All subjects were analyzed for safety.

During telemetry monitoring, 10 subjects experienced bradycardia; eight subjects experienced tachycardia; seven subjects experienced sinus pause, 3 subjects experienced junctional rhythm; and 1 subject experienced bradycardia with junctional rhythm (Appendix B9.3).

The central nervous system, gastrointestinal system, and cardiovascular systems were the body systems most frequently affected by adverse events in the (b) (4) tablet treatment group (Table 13.6.4). The most frequently reported adverse events were somnolence (35 subjects), oral hypoaesthesia (22 subjects), dizziness (11 subjects), bradycardia and tachycardia (7 subjects each), dysgeusia, oral paraesthesia and sinus arrest (5 subjects each), nausea (4 subjects), hypotension and nodal rhythm (3 subjects each), and oral paraesthesia and sinus arrest (5 subjects each), nausea (4 subjects each), headache (3 subjects each), and acne, headache, hypoaesthesia, and restless legs syndrome (2 subjects each) (Table 13.6.5).

All other adverse events were single occurrences.

Subject 1001026 was an alcoholic

Several subjects experienced potentially clinically significant increases in triglycerides and lipid values.

Subject 10011008 had a value of 245 mg/dL on Day 8. Values at Baseline and at the Follow-up visit on Day 15 were 128 mg/dL and 80 mg/dL, respectively.

Subject 10011017 had a value of 323 mg/dL on Day 8. Values at Baseline and at the Follow-up visit on Day 15 were 80 mg/dL and 61 mg/dL, respectively.

- Subject 10011024 had a value of 344 mg/dL on Day 8. Values at Baseline and at the Follow-up visit on Day 15 were 141 mg/dL and 149 mg/dL, respectively.

- Subject 10011026 had values of 243 mg/dL on Day 1 and 168 mg/dL on Day 12. The value at Baseline was 83 mg/dL.

Subject 10011046 had a value of 1573 mg/dL on Day 8. Values at Baseline and at the Follow-up visit on Day 15 were 55 mg/dL and 42 mg/dL, respectively.

AEs are shown on the following pages from this study. There are a disturbing number of cases of sinus arrest and other cardiac findings, with these single 5 mg doses in healthy volunteers.

Regimen	Asenapine 5mg sublingual tablet (b) (4)		Asenapine 5mg sublingual tablet (b) (4)	
Number of Subjects	(N=34)		(N=35)	
Adverse Event	Number	(%) of Subjects	Number	(%) of Subjects
--Somnolence	34	(100.0)	35	(100.0)
-- oral Hypoaesthesia	25	(73.5)	22	(62.9)
--Dizziness	13	(38.2)	11	(31.4)
--Bradycardia	4	(11.8)	7	(20.0)
--Tachycardia	10	(29.4)	7	(20.0)
--Dysgeusia	8	(23.5)	5	(14.3)
--Paraesthesia oral	5	(14.7)	5	(14.3)
--Sinus arrest	5	(14.7)	5	(14.3)
--Nausea	4	(11.8)	4	(11.4)
--Hypotension	6	(17.6)	3	(8.6)
--Nodal rhythm	1	(2.9)	3	(8.6)
--Acne	0	(0.0)	2	(5.7)
--Headache	3	(8.8)	2	(5.7)
--Hypoaesthesia	2	(5.9)	2	(5.7)
--Restless legs syndrome	0	(0.0)	2	(5.7)
--Anxiety	0	(0.0)	1	(2.9)
--Bradyphrenia	0	(0.0)	1	(2.9)
--Depilation	0	(0.0)	1	(2.9)

Regimen	Asenapine 5mg sublingual tablet (b) (4)	Asenapine 5mg sublingual tablet (b) (4)
Number of Subjects	(N=34)	(N=35)
Number (%) of subjects reporting TESS AEs	34 (100.0)	35 (100.0)
All TESS AEs	34 (100.0)	35 (100.0)
Associated TESS AEs		
Number (%) of subjects reporting TESS AEs by Maximum Intensity		
All TESS AEs	0 (0.0)	1 (2.9)
Mild	33 (97.1)	33 (94.3)
Moderate	1 (2.9)	1 (2.9)
Severe		
Mild	0 (0.0)	1 (2.9)
Moderate	33 (97.1)	33 (94.3)
Severe	1 (2.9)	1 (2.9)
Number of total TESS AE reports by intensity		
All TESS AEs	166	154
Mild	50	54
Moderate	114	99
Severe	2	1
Associated TESS AEs	154	142
Mild	42	47
Moderate	110	94
Severe	2	1
Number of: Withdrawals due to TESS Adverse Events		
Serious TESS AEs	0	0
Deaths	0	0

	Asenapine 5mg sublingual tablet	Asenapine 5mg sublingual tablet
Regimen	(b) (4)	(b) (4)
Number of Subjects	(N=34)	(N=35)
Body System/Adverse Event	Number (%) of Subjects	Number (%) of Subjects
Nervous system disorders	34 (100.0)	35 (100.0)
--Somnolence	34 (100.0)	35 (100.0)
--Dizziness	13 (38.2)	11 (31.4)
--Dysgeusia	8 (23.5)	5 (14.3)
--Paraesthesia oral	5 (14.7)	5 (14.3)
--Headache	3 (8.8)	2 (5.7)
--Hypoaesthesia	2 (5.9)	2 (5.7)
--Restless legs syndrome	0 (0.0)	2 (5.7)
--Dizziness postural	1 (2.9)	1 (2.9)
--Coordination abnormal	1 (2.9)	0 (0.0)
--Syncope	1 (2.9)	0 (0.0)
Gastrointestinal disorders	25 (73.5)	22 (62.9)
--Hypoaesthesia oral	25 (73.5)	22 (62.9)
--Nausea	4 (11.8)	4 (11.4)
--Oral discomfort	4 (11.8)	1 (2.9)

Table 13.6.4. Summary of TESS Adverse Events by Body System (Sorted by Body System and Decreasing Frequency) A PHASE 1, OPEN-LABEL, SINGLE-DOSE, BIOEQUIVALENCE STUDY OF THE (b) (4) FORMULATIONS OF (b) (4) ASENAPINE TABLETS (5 MG) IN HEALTHY VOLUNTEERS (Protocol A7501016)

Regimen	Asenapine 5mg sublingual tablet (b) (4)	Asenapine 5mg sublingual tablet (b) (4)
Number of Subjects	(N=34)	(N=35)
Body System/Adverse Event	Number (%) of Subjects	Number (%) of Subjects
Skin and subcutaneous tissue disorders (cont.)		
--Dermatitis allergic	0 (0.0)	1 (2.9)
--Dermatitis	1 (2.9)	0 (0.0)
--Dermatitis contact	1 (2.9)	0 (0.0)
--Erythema	1 (2.9)	0 (0.0)
--Rash	1 (2.9)	0 (0.0)
--Skin exfoliation	1 (2.9)	0 (0.0)
Psychiatric disorders	7 (20.6)	2 (5.7)
--Anxiety	0 (0.0)	1 (2.9)
--Bradyphrenia	0 (0.0)	1 (2.9)
--Restlessness	7 (20.6)	1 (2.9)
Respiratory, thoracic and mediastinal diso	2 (5.9)	2 (5.7)
--Nasal congestion	0 (0.0)	1 (2.9)
--Pharyngeal hypoaesthesia	0 (0.0)	1 (2.9)
--Dry throat	1 (2.9)	0 (0.0)
--Sneezing	1 (2.9)	0 (0.0)
Eye disorders	1 (2.9)	1 (2.9)

Table 13.6.4. Summary of TESS Adverse Events by Body System (Sorted by Body System and Decreasing Frequency) A PHASE 1, OPEN-LABEL, SINGLE-DOSE, BIOEQUIVALENCE STUDY OF THE (b) (4) FORMULATIONS OF (b) (4)ONIZED ASENAPINE TABLETS (5 MG) IN HEALTHY VOLUNTEERS (Protocol A7501016)

Regimen	Asenapine 5mg sublingual tablet (b) (4)	Asenapine 5mg sublingual tablet (b) (4)
Number of Subjects	(N=34)	(N=35)
Body System/Adverse Event	Number (%) of Subjects	Number (%) of Subjects
--Eyelid oedema	0 (0.0)	1 (2.9)
--Vision blurred	1 (2.9)	0 (0.0)
General disorders and administration site	0 (0.0)	1 (2.9)
--Feeling of relaxation	0 (0.0)	1 (2.9)
Investigations	1 (2.9)	1 (2.9)
--Heart rate decreased	0 (0.0)	1 (2.9)
--Blood pressure decreased	1 (2.9)	0 (0.0)
Surgical and medical procedures	0 (0.0)	1 (2.9)
--Depilation	0 (0.0)	1 (2.9)
Infections and infestations	1 (2.9)	0 (0.0)
--Upper respiratory tract infection	1 (2.9)	0 (0.0)
Injury, poisoning and procedural complica	2 (5.9)	0 (0.0)
--Incision site complication	1 (2.9)	0 (0.0)
--Sunburn	1 (2.9)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (2.9)	0 (0.0)
--Back pain	1 (2.9)	0 (0.0)

Information provided on the drug supplies are shown in Table 71.

Table 71 Reference and Test Batch Information Included in Study Report - Study A7501016

Test/Ref	Drug	Lot Number	FID Number	Strength	Formulation
Reference	Asenapine	05-024601	D0501645	5 mg	(b) (4)
Test	Asenapine	05-024604	D0501720	5 mg	(b) (4)

No information was provided on the actual (b) (4) of comparison in the study report. Upon checking with the chemistry reviewer on April 14, 2008 he was unaware that the (b) (4) had changed. While looking for the (b) (4) with the chemistry reviewer we found that in amendment 007 an additional additional manufacturing site was proposed that used a (b) (4)

In this review the stated (b) (4)
asenapine maleate drug substance varies (b) (4) and apparently this was found by this reviewer under the drug product section of the submission. On April 14, 2008 upon further review it was found that the (b) (4) specification was (b) (4) and no (b) (4) information was included in the batch analyses submitted.

The following was then also found in the original submission under the drug substance section:

(b) (4)

Tested from batch P onwards, results found ranging from (b) (4). Batch AT had a (b) (4) A deviating (b) (4) was intentionally obtained to support manufacturability and bioavailability studies.

(b) (4)

The (b) (4) distribution is determined (b) (4)

(b) (4)

The proposed acceptance criterion on (b) (4) can therefore be fully justified both from a manufacturability and from a biopharmaceutical point of view.'

In summary only this single batch used in the bioequivalence study has a (b) (4), and all efficacy and safety data was generated with (b) (4)

Table 72 Subject Demographics Study - A7501016

Subject Number	Age at Day 1	Sex (Hormonal Status)	Race	Height (cm)	Weight (kg)	BMI (kg/m2)	Smoking Status	Alcohol Drinks per Week
10011002	25	Male	Caucasian	189.2	79.2	22.1	Never Smoked	5
10011004	22	Male	Caucasian	196.2	91.1	23.7	Never Smoked	0
10011005	20	Male	Caucasian	186.1	98.5	28.4	Never Smoked	0
10011007	20	Male	Caucasian	176.5	59.4	19.1	Never Smoked	0
10011008	19	Female (Premenopausal)	Caucasian	164.5	65.0	24.0	Never Smoked	0
10011009	23	Male	Other-HISPANIC	170.2	54.4	18.8	Never Smoked	0
10011010	38	Male	Caucasian	165.7	72.4	26.4	Past Smoker	2
10011011	22	Male	Caucasian	174.0	82.6	27.3	Current Smoker	4
10011013	19	Female (Premenopausal)	Caucasian	159.4	57.7	22.7	Never Smoked	0
10011016	19	Female (Premenopausal)	Caucasian	174.0	72.8	24.0	Never Smoked	0
10011017	19	Male	Caucasian	168.9	83.3	29.2	Past Smoker	0
10011018	25	Female (Premenopausal)	Caucasian	172.1	69.4	23.4	Current Smoker	2
10011021	33	Male	Caucasian	183.5	89.9	26.7	Current Smoker	1
10011022	24	Male	Caucasian	184.2	82.4	24.3	Never Smoked	0
10011024	43	Male	Caucasian	170.8	76.6	26.3	Never Smoked	0
10011026	24	Male	Caucasian	177.2	83.1	26.5	Current Smoker	10
10011027	18	Female (Premenopausal)	Black	170.8	70.8	24.3	Never Smoked	0
10011034	19	Female (Premenopausal)	Caucasian	166.4	59.2	21.4	Never Smoked	0
10011035	30	Male	Caucasian	171.5	68.2	23.2	Never Smoked	1
10011037	22	Female (Premenopausal)	Caucasian	170.2	60.6	20.9	Never Smoked	4
10011039	19	Male	Caucasian	191.1	80.7	22.1	Current Smoker	1
10011046	19	Male	Caucasian	196.2	90.7	23.6	Past Smoker	0
10011058	45	Female (Premenopausal)	Caucasian	161.3	67.8	26.1	Past Smoker	0
10011059	38	Female (Premenopausal)	Black	175.3	95.7	31.1	Never Smoked	2
10011060	50	Female (Premenopausal)	Caucasian	161.9	73.3	28.0	Never Smoked	0
10011066	45	Male	Caucasian	173.4	73.0	24.3	Never Smoked	1
10011067	27	Female (Premenopausal)	Caucasian	162.6	61.7	23.3	Current Smoker	3
10011069	20	Female (Premenopausal)	Black	162.6	75.3	28.5	Never Smoked	0
10011073	24	Female (Premenopausal)	Caucasian	163.8	65.1	24.3	Never Smoked	2
10011074	30	Female (Premenopausal)	Caucasian	170.2	71.9	24.8	Never Smoked	0
10011075	42	Male	Black	180.3	75.6	23.3	Current Smoker	2
10011077	32	Male	Caucasian	186.1	81.0	23.4	Never Smoked	3
10011079	24	Male	Caucasian	175.3	77.6	25.3	Past Smoker	1
10011080	20	Male	Caucasian	181.0	63.3	19.3	Never Smoked	0
10011086	26	Male	Caucasian	183.5	85.9	25.5	Past Smoker	0
10011088	20	Male	Caucasian	176.5	63.6	20.4	Never Smoked	0

5.5.5.3 BE Study- (b) (4) Tablet - Study 41026

This was an open label, randomized, two-way cross-over trial to assess the relative bioavailability of asenapine tablets made via (b) (4) versus (b) (4) techniques in 24 healthy male volunteers of at 18 - 45 years of age inclusive.

One asenapine tablet (5 mg; sublingual) was to be given on Days 1 and 8. A 48-hr pharmacokinetic profile was to be made after each asenapine dosing. A questionnaire was to be used to assess themouth feel and taste of the two asenapine formulations.

Results

Disintegration time after administration of the (b) (4) tablet was statistically significantly shorter (mean 01:36 mm:ss) compared to the disintegration time after administration of the (b) (4) tablet (mean 03:48 mm:ss).

Both tablets were reported to be generally acceptable. The time to dissolve was reported to be more acceptable after the (b) (4) tablet compared to the (b) (4) tablet. The taste of the (b) (4) tablets was reported to be more acceptable compared to the taste of the (b) (4) tablet.

The taste was generally described to be bitter.

Table 73 Bioequivalence Testing Comparing Asenapine Sublingual Tablets Manufactured by (b) (4) – Study 41026

	Test	Ref	Geometric Mean Parameter		Conclusion
	(b) (4)	(b) (4)	Point estimate of μ(dc) / μ(fd)	90% confidence interval	
N	24	24			
Cmax (ng/mL)	4.32	5.02	0.86	0.78 -0.95	Not bioequivalent
AUC0-tlast (ng*h/mL)	27.5	32.4	0.85	0.78 - 0.91	Not bioequivalent
AUC0-∞ (ng*h/mL)	29.2	34.3	0.85	0.79 - 0.91	Not bioequivalent

5.5.6 Intrinsic Factors and Special Populations

5.5.6.1 Race and Ethnicity

As asenapine is a CYP2D6 substrate, and CYP2D6 activity is trimodally distributed with different frequencies by race and ethnicity, race and ethnicity would be expected to result in differences in metabolism. Specifically 7%- 10% of Caucasians are expected to be poor metabolizers and 17% of Ethiopians are expected to be extensive metabolizers.

5.5.6.1.1 Comparative Asenapine Pharmacokinetics in Caucasians and Japanese – Study 25546

Study 25546 was a double blind, randomized, placebo controlled, parallel group, two-period single and multiple dose study with asenapine in nonsmoking and light smoking healthy Japanese and Caucasian males 20 – 45 years old. In one treatment period asenapine was dosed as a single 1, 3, or 5 mg sublingual dose and in the other after a 1, 2, or 3 day titration 3, 5, or 10 mg was dosed BID for 6 days. There was an interperiod washout of at least 6 days.

Asenapine, desmethyl-asenapine, asenapine-glucuronide and N-oxide-asenapine concentrations were measured in plasma and urine at several time points. For the first three analytes, plasma and urine pharmacokinetic parameters were calculated.

For the metabolite asenapine 11-O-sulfate, concentrations in plasma were measured for the 5-mg single- and multiple-dose regimen and a limited set of PK parameters were calculated.

Neither genotyping nor phenotyping was performed although samples were obtained. Genotyping was only to be performed if the sponsor decided to do the analysis. This is troublesome as sponsors are required to perform provide all pertinent information for evaluation of safety.

Since the prevalence of CYP2D6 poor metabolizers in the Caucasian population is 7%-10% chances are good that not even a single CYP2D6 poor metabolizer was enrolled out of the 24 Caucasians studied. Even if there is one PM in just one group he is unlikely to disturb the mean by much and since the sponsor did not include information on genotype the implications would likely be overlooked. In the unlikely event that there is more than one poor metabolizer, the difference could easily be explained away by genotyping without mentioning the clinical implications.

Table 74 shows a summary of subject demographics by race and dose group.

Table 75 and Table 76 respectively show single and multiple dose pharmacokinetics for asenapine in Japanese and Causcasians. There are no obvious differences between the groups although there is a hint that bioavailability may be lower at the 5 mg dose.

Table 77 and Table 78 respectively show single and multiple dose pharmacokinetics for desmethyl-asenapine in Japanese and Causcasians. There is a significantly delayed Tmax in Caucasians as compared with Japanese on multiple dosing.

Table 79 and Table 80 respectively show single and multiple dose pharmacokinetics for asenapine glucuronide in Japanese and Causcasians.

Table 81 shows a comparison of geometric mean pharmacokinetic ratios of asenapine, desmethyl-asenapine, and asenapine glucuronide by race, with no clear differences by group. Table 82 shows the results of dose proportionality testing for asenapine. Table 83 and Table 84 a comparison of urinary excretion rates by dosage and race for asenapine, desmethyl-asenapine, and asenapine glucuronide.

Lastly Table 85 shows a comparison of the pharmacokinetics of asenapine-11-O-sulfate at a dose of 5 mg in Japanese and Caucasians.

For most of these metrics there is no clear difference between Japanese and Caucasians. However, exposure to asenapine 11-O-sulfate is lower in Japanese. However as variability is large any differences could be due to the small number of subjects employed.

Alhtough the the pharmacokinetics of the N-oxide metabolite was supposed to be determined in this study this reviewer could find no raw data. The only information was a statement to the effect that concentrations were so low as to preclude calculation of pharmacokinetic parameters. The available raw data will need to be obtained and reviewed.[6]

Due to the small sample size no firm conclusions can be drawn from this study.

Table 74 Summary of Subject Demographics by Race and Dose Group – Study 25546

	Caucasian			Japanese		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Dosages	1 mg SD	3 mg SD	5 mg SD	1 mg SD	3 mg SD	5 mg SD
	3 mg BID	5 mg BID	10 mg BID	3 mg BID	5 mg BID	10 mg BID
n (%)	8 (100%)	8 (100%)	9 (100%)	8 (100%)	8 (100%)	8 (100%)
Age (years)	22.9 ± 2.2	23.9 ± 2.6	24.0 ± 3.2	22.9 ± 1.5	24.5 ± 2.7	28.5 ± 4.5
Weight (kg)	72.5 ± 8.1	71.7 ± 5.9	72.1 ± 5.4	63.2 ± 6.1	62.2 ± 8.7	64.3 ± 3.9
Height (cm)	176.5 ± 6.7	178.3 ± 4.4	179.3 ± 5.4	173.5 ± 5.8	170.6 ± 4.2	171.1 ± 3.8
BMI (kg/m^2)	23.2 ± 1.6	22.5 ± 1.5	22.4 ± 0.9	21.0 ± 1.7	21.3 ± 2.6	21.9 ± 1.2

[6] Potential comment for sponsor in followup meeting.

Table 75 Pharmacokinetic Metrics of Asenapine after Single Doses in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	1 mg	3 mg	5 mg	1 mg	3 mg	5 mg
N	6	6	6	6	6	6
Tmax (h)	0.7 0.33 - 2.00	1.0 0.50 - 1.00	1.25 0.50 - 4.03	1.50 1.00 - 2.00	1.00 0.50 - 1.50	0.50 0.50 - 1.50
Cmax (ng/mL)	1.10 (36.1) 0.803 - 1.64	3.58 (44.4) 1.80 - 5.51	3.31 (51.7) 1.40 - 5.59	1.02 (15.4) 0.765 - 1.17	2.90 (36.8) 0.846 - 3.70	3.99 (44.9) 1.19 - 5.61
dn-Cmax (ng/mL/mg)	1.10 (36.1) 0.803 - 1.64	1.19 (44.4) 0.600 - 1.84	0.662 (51.7) 0.280 - 1.12	1.02 (15.4) 0.765 - 1.17	0.968 (36.8) 0.282 - 1.23	0.797 (44.9) 0.238 - 1.12
$AUC_{0-tlast}$ (ng/mL x hr^{-1})	7.78 (34.1) 4.87 - 11.3	22.0 (38.2) 11.3 - 28.6	25.0 (30.7) 15.4 - 33.6	6.81 (14.5) 5.14 - 8.24	19.3 (34.0) 6.77 - 25.3	24.9 (41.4) 7.91 - 34.4
dn-$AUC_{0-tlast}$ (ng/mL x hr^{-1} / mg)	7.78 (34.1) 4.87 - 11.3	7.34 (38.2) 3.77 - 9.53	5.00 (30.7) 3.08 - 6.71	6.81 (14.5) 5.14 - 8.24	6.45 (34.0) 2.26 - 8.45	4.98 (41.4) 1.58 - 6.87
AUC_∞ (ng/mL x hr^{-1})	8.47 (34.8) 5.09 - 12.5	23.2 (37.6) 11.7 - 29.9	26.4 (30.1) 15.9 - 34.9	7.50 (17.9) 5.17 - 9.31	20.0 (33.1) 7.18 - 25.8	26.0 (41.0) 8.24 - 35.4
dn-AUC_∞ (ng/mL x hr^{-1} / mg)	8.47 (34.8) 5.09 - 12.5	7.73 (37.6) 3.90 - 9.97	5.28 (30.1) 3.17 - 6.98	7.50 (17.9) 5.17 - 9.31	6.65 (33.1) 2.39 - 8.59	5.20 (41.0) 1.65 - 7.07

Table 76 Steady-State Pharmacokinetic Metrics of Asenapine in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	3 mg BID	5 mg BID	10 mg BID	3 mg BID	5 mg BID	10 mg BID
N	6	6	5	6	6	4
Tmax (h)	0.50 0.50 - 1.50	0.50 0.50 - 1.50	1.00 0.33 - 1.50	0.50 0.50 - 2.00	1.50 0.50 - 2.00	0.75 0.33 - 3.00
Cmax,ss (ng/mL)	3.93 (23.6) 2.46 - 4.85	5.05 (51.0) 1.84 - 7.96	5.39 (46.2) 2.50 - 8.82	3.40 (22.3) 2.52 - 4.36	3.56 (51.0) 1.50 - 6.69	8.18 (66.2) 3.19 - 13.3
dn-Cmax,ss (ng/mL/mg)	1.31 (23.6) 0.820 - 1.62	1.01 (51.0) 0.368 - 1.59	0.539 (46.2) 0.250 - 0.882	1.13 (22.3) 0.840 - 1.45	0.712 (51.0) 0.300 - 1.34	0.818 (66.2) 0.319 - 1.33
AUCss,0-12 (ng/mL x hr^{-1})	24.3 (26.3) 13.9 - 32.5	29.4 (35.1) 14.2 - 40.5	37.5 (44.3) 19.6 - 61.2	21.9 (11.1) 18.0 - 24.4	22.1 (37.3) 10.7 - 34.0	41.7 (46.2) 23.6 - 64.5
dn-AUCss,0-12 (ng/mL x hr^{-1} / mg)	8.09 (26.3) 4.64 - 10.8	5.87 (35.1) 2.84 - 8.10	3.75 (44.3) 1.96 - 6.12	7.29 (11.1) 6.01 - 8.15	4.43 (37.3) 2.15 - 6.81	4.17 (46.2) 2.36 - 6.45
CLss/F (L/h)	133 (32.9) 92.2 - 215	195 (45.3) 124 - 352	312 (43.1) 163 - 509	139 (11.9) 123 - 166	259 (44.1) 147 - 465	283 (45.0) 155 - 423
wn-CLss/F (L/h/kg)	2.09 (38.1) 1.29 - 3.58	3.20 (57.0) 1.72 - 6.80	4.85 (42.5) 2.63 - 7.61	1.95 (25.8) 1.48 - 2.89	3.78 (52.4) 1.95 - 7.35	4.02 (42.0) 2.24 - 5.55
t½ (h)	38.3 (57.6) 22.8 - 79.5	35.5 (56.7) 17.3 - 74.2	27.8 (28.6) 17.4 - 37.0	28.9 (23.6) 18.3 - 37.1	25.7 (51.5) 16.7 - 51.6	34.1 (73.6) 13.2 - 68.0

Table 77 Pharmacokinetic Metrics of Desmethyl-Asenapine after Single Doses in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	1 mg	3 mg	5 mg	1 mg	3 mg	5 mg
N	6	6	6	6	6	6
Tmax (h)	8.00 6.00-12.0	6.00 6.00-8.00	7.01 6.00-12.0	6.00 6.00-12.0	7.00 2.00-8.00	6.00 6.00-8.00
Cmax (ng/mL)	0.129 (25.7) 0.0805-0.172	0.306 (30.0) 0.186-0.450	0.524 (42.4) 0.133-0.802	0.0942 (46.1) 0.0583-0.175	0.269 (21.6) 0.165-0.315	0.599 (36.8) 0.403-1.03
dn-Cmax (ng/mL/mg)	0.129 (25.7) 0.0805-0.172	0.102 (30.0) 0.0620-0.150	0.105 (42.4) 0.0266-0.160	0.0942 (46.1) 0.0583-0.175	0.0898 (21.6) 0.0550-0.105	0.120 (36.8) 0.0806-0.206
$AUC_{0-tlast}$ (ng/mL x hr^{-1})	1.47 (23.6) 0.936-1.91	4.46 (41.2) 2.51-7.43	10.7 (51.9) 1.54-16.7	0.684 (65.0) 0.239-1.24	4.11 (29.8) 2.00-5.36	10.7 (47.1) 6.48-20.0
dn-$AUC_{0-tlast}$ (ng/mL x hr^{-1} / mg)	1.47 (23.6) 0.936-1.91	1.49 (41.2) 0.837-2.48	2.14 (51.9) 0.309-3.33	0.684 (65.0) 0.239-1.24	1.37 (29.8) 0.666-1.79	2.14 (47.1) 1.30-4.01
AUC_{∞} (ng/mL x hr^{-1})	6.59 (85.6) 2.49-17.8	5.77 (35.1) 3.32-8.56	12.7 (47.2) 2.56-19.2	6.79# (23.1) 5.68-7.89	5.27 (25.2) 3.22-6.68	13.5 (50.6) 7.75-25.9
dn-AUC_{∞} (ng/mL x hr^{-1} / mg)	6.59 (85.6) 2.49-17.8	1.92 (35.1) 1.11-2.85	2.55 (47.2) 0.511-3.83	6.79# (23.1) 5.68-7.89	1.76 (25.2) 1.07-2.23	2.70 (50.6) 1.55-5.19
t½ (h)	36.6 (68.8) 9.70-76.6	14.5 (44.7) 9.13-25.6	15.5 (21.9) 9.97-18.6	54.1# (78.3) 24.1-84.0	12.7 (21.0) 8.59-16.0	17.1 (42.4) 8.68-26.9

Table 78 Steady-State Pharmacokinetic Metrics of Desmethyl-Asenapine in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	3 mg BID	5 mg BID	10 mg BID	3 mg BID	5 mg BID	10 mg BID
N	6	6	5	6	6	4
Tmax (h)	6.00 3.00-8.00	5.00 3.00-6.00	1.50 1.50 - 6.05	6.00 2.00-6.02	4.03 2.00-6.05	5.01 0.33-8.00
Cmax (ng/mL)	0.974 (22.8) 0.694-1.26	1.21 (37.3) 0.681-1.78	2.43 (66.9) 0.648-4.50	0.789 (34.0) 0.535-1.23	1.23 (27.5) 0.710-1.72	3.29 (65.2) 1.67-6.43
dn-Cmax (ng/mL/mg)	0.325 (22.8) 0.231-0.420	0.242 (37.3) 0.136-0.356	0.243 (66.9) 0.0648-0.450	0.263 (34.0) 0.178-0.410	0.245 (27.5) 0.142-0.344	0.329 (65.2) 0.167-0.643
AUC_{0-12} (ng/mL x hr^{-1})	9.74 (21.4) 7.25-12.8	11.5 (37.5) 5.91-16.4	23.1 (69.8) 5.95-45.4	7.61 (36.0) 4.38-11.4	11.8 (24.6) 6.93-14.8	27.7 (51.7) 14.0-47.6
dn-AUC_{0-12} (ng/mL x hr^{-1} / mg)	3.25 (21.4) 2.42-4.27	2.30 (37.5) 1.18-3.28	2.31 (69.8) 0.595-4.54	2.54 (36.0) 1.46-3.79	2.36 (24.6) 1.39-2.96	2.77 (51.7) 1.40-4.76
t½ (h)	15.8 (30.0) 8.48-22.5	21.8 (59.4) 9.00-46.6	18.7 (26.5) 14.2-27.0	16.5 (44.1) 8.82-27.7	19.0 (26.2) 10.4-23.7	17.2 (12.6) 14.7-20.0

Table 79 Pharmacokinetic Metrics of Asenapine Glucuronide after Single Doses in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	1 mg	3 mg	5 mg	1 mg	3 mg	5 mg
N	6	6	6	6	6	6
Tmax (h)	6.00 4.00-6.00	5.00 4.00-8.00	6.00 4.00-6.02	6.00 4.00-6.00	6.00 4.00-6.00	4.00 4.00-8.00
Cmax (ng/mL)	1.70 (36.8) 1.05-2.69	4.16 (51.1) 1.27-7.65	8.90 (56.3) 2.16-15.3	1.49 (43.7) 0.978-2.69	4.41 (25.4) 2.68-5.90	6.53 (24.3) 4.88-9.31
dn-Cmax (ng/mL/mg)	1.70 (36.8) 1.05-2.69	1.39 (51.1) 0.423-2.55	1.78 (56.3) 0.432-3.06	1.49 (43.7) 0.978-2.69	1.47 (25.4) 0.893-1.97	1.31 (24.3) 0.976-1.86
$AUC_{0-tlast}$ (ng/mL x hr^{-1})	15.6 (40.1) 8.54-24.8	43.9 (43.8) 13.1-68.8	99.4 (51.8) 20.7-150	11.4 (46.7) 5.13-18.0	46.6 (26.9) 24.3-59.4	71.1 (36.6) 44.6-116
dn-$AUC_{0-tlast}$ (ng/mL x hr^{-1} / mg)	15.6 (40.1) 8.54-24.8	14.6 (43.8) 4.35-22.9	19.9 (51.8) 4.15-30.1	11.4 (46.7) 5.13-18.0	15.5 (26.9) 8.09-19.8	14.2 (36.6) 8.92-23.3
AUC_{∞} (ng/mL x hr^{-1})	19.2 (29.3) 11.7-27.5	49.5 (46.2) 15.7-79.9	107 (51.0) 26.0-155	15.1 (34.4) 10.7-21.9	52.1 (28.5) 27.1-66.8	77.2 (35.0) 49.3-121
dn-AUC_{∞} (ng/mL x hr^{-1} / mg)	19.2 (29.3) 11.7-27.5	16.5 (46.2) 5.22-26.6	21.4 (51.0) 5.21-30.9	15.1 (34.4) 10.7-21.9	17.4 (28.5) 9.03-22.3	15.4 (35.0) 9.85-24.2
t½ (h)	5.52 (19.3) 4.11-6.80	12.3 (82.9) 5.17-27.3	11.6 (74.9) 4.01-28.4	5.24 (27.1) 3.52-7.35	10.5 (79.2) 4.93-26.0	13.4 (74.3) 4.36-31.5

Table 80 Steady-State Pharmacokinetic Metrics of Asenapine-Glucuronide in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	3 mg BID	5 mg BID	10 mg BID	3 mg BID	5 mg BID	10 mg BID
N	6	6	5	6	6	4
Tmax (h)	4.00 3.00-6.00	4.00 3.00-6.00	4.00 3.00- 6.05	4.00 3.00-4.00	4.00 3.00-4.00	3.50 3.00 - 4.00
Cmax (ng/mL)	9.77 (40.2) 6.04-15.3	15.7 (34.6) 10.3-25.6	35.5 (73.2) 2.48-58.9	9.40 (38.5) 6.33-15.2	16.5 (25.9) 10.7-23.0	33.7 (30.4) 23.7-47.8
dn-Cmax (ng/mL/mg)	3.26 (40.2) 2.01-5.10	3.14 (34.6) 2.06-5.12	3.55 (73.2) 0.248-5.89	3.13 (38.5) 2.11-5.07	3.29 (25.9) 2.14-4.60	3.37 (30.4) 2.37-4.78
AUC_{0-12} (ng/mL x hr^{-1})	81.9 (42.0) 49.2-131	124 (34.8) 90.7-207	282 (73.4) 26.1-496	76.8 (37.6) 53.8-117	129 (20.4) 87.1-166	261 (20.4) 193-323
dn-AUC_{0-12} (ng/mL x hr^{-1} / mg)	27.3 (42.0) 16.4-43.7	24.8 (34.8) 18.1-41.4	28.2 (73.4) 2.61-49.6	25.6 (37.6) 17.9-39.0	25.7 (20.4) 17.4-33.2	26.1 (20.4) 19.3-32.3
t½ (h)	15.7 (35.6) 8.50-22.5	18.8 (44.4) 10.6-33.7	12.7 (34.2) 8.56-19.1	13.6 (27.5) 9.57-18.9	15.8 (12.4) 13.8-19.2	18.6 (19.4) 14.9-23.1

Table 81 Comparison of Single Dose and Steady-State Dose Normalized Geometric Mean Pharmacokinetic Ratios of Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide by Race – Study 25546[a]

Dosing	Metric	Asenapine		Desmethyl - Asenapine		Asenapine - Glucuronide	
		μ(Jap.) : μ(Cauc.) Point Estimate	95% CI	μ(Jap.) : μ(Cauc.) Point Estimate	95% CI	μ(Jap.) : μ(Cauc.) Point Estimate	95% CI
Single Dose [a] (n=36)	dn-Cmax	1.02	0.74 - 1.42	1.09	0.84 - 1.42	1.04	0.76 - 1.43
	dn-AUC0-tlast	1.10	0.83 - 1.46	1.33	0.91 - 1.94	1.14	0.80 - 1.62
	dn-AUC0-inf	1.11	0.84 - 1.47	0.91#	0.60 - 1.37	1.11	0.81 - 1.53
	CL/F	0.90	0.68 - 1.19	—	—	—	—
	wn-CL/F	1.02	0.77 - 1.35	—	—	—	—
	Vz/F	1.15	0.77 - 1.71	—	—	—	—
	wn-Vz/F	1.30	0.87 - 1.96	—	—	—	—
	t½	1.27	0.84 - 1.94	0.88#	0.60 - 1.29	1.02	0.68 - 1.53
Steady State [a] (n=33)	dn-Cmax	1.05	0.74 - 1.50	0.93	0.66 - 1.30	0.87	0.56 - 1.34
	dn-AUC0-12	1.09	0.84 - 1.42	0.96	0.69 - 1.34	0.89	0.60 - 1.34
	CL/F	0.92	0.70 - 1.20	—	—	—	—
	wn-CL/F	1.02	0.76 - 1.37	—	—	—	—
	Vss,z/F	1.07	0.69 - 1.66	—	—	—	—
	wn-Vss,z/F	1.19	0.76 - 1.86	—	—	—	—
	t½	1.17	0.84 - 1.63	1.04	0.79 - 1.36	0.94	0.75 - 1.18

a metrics are grand means of dose normalzed values

Table 82 Results of Single Dose and Steady-State Dose Proportionality Testing for Asenapine in Caucasians and Japanese – Study 25546

Parameter	Point Estimate of μ(doseH)/ μ(doseL)	95% Confidence Interval	Point Estimate of μ(doseH)/ μ(doseL)	95% Confidence Interval
	Single dose (n=36)			
	Japanese, 5 mg/1 mg SD		Caucasian, 5 mg/1 mg SD	
dn-Cmax	0.56	0.32 - 0.98	0.70	0.40 - 1.23
dn-AUC0-tlast	0.65	0.40 - 1.05	0.66	0.41 - 1.08
dn-AUC0-inf	0.63	0.39 - 1.02	0.63	0.39 - 1.03
CL/F	1.59	0.98 - 2.58	1.58	0.97 - 2.57
wn-CL/F	1.60	0.99 - 2.61	1.56	0.96 - 2.53
t½	1.54	0.74 - 3.19	1.20	0.58 - 2.48
	Japanese, 5 mg/3 mg SD		Caucasian, 5 mg/3 mg SD	
dn-Cmax	0.54	0.30 - 0.95	0.80	0.45 - 1.41
dn-AUC0-tlast	0.71	0.43 - 1.15	0.75	0.46 - 1.22
dn-AUC0-inf	0.71	0.44 - 1.15	0.76	0.47 - 1.23
CL/F	1.41	0.87 - 2.30	1.32	0.81 - 2.15
wn-CL/F	1.39	0.85 - 2.26	1.26	0.78 - 2.05
t½	0.92	0.44 - 1.90	1.40	0.68 - 2.90
	Steady state (n=33)			
	Japanese, 10 mg/3 mg b.i.d. SS		Caucasian, 10 mg/3 mg b.i.d. SS	
dn-Cssmax	0.39	0.21 - 0.71	0.60	0.32 - 1.16
dn-AUCss0-12	0.44	0.28 - 0.70	0.53	0.33 - 0.86
CLss/F	2.26	1.43 - 3.56	1.89	1.16 - 3.07
wn-CLss/F	2.26	1.36 - 3.77	1.97	1.14 - 3.39
t½ss	0.78	0.44 - 1.38	0.98	0.53 - 1.80
	Japanese, 10 mg/5 mg b.i.d. SS		Caucasian, 10 mg/5 mg b.i.d. SS	
dn-Cssmax	0.56	0.30 - 1.03	1.05	0.55 - 2.01
dn-AUCss0-12	0.63	0.40 - 0.99	0.92	0.57 - 1.50
CLss/F	1.59	1.01 - 2.51	1.08	0.67 - 1.76
wn-CLss/F	1.55	0.93 - 2.58	1.09	0.64 - 1.88
t½ss	0.84	0.48 - 1.49	1.17	0.64 - 2.15

Table 83 Comparison of Urinary Excretion of Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide in Caucasians and Japanese – Study 25546

		Japanese			Caucasian		
fe,u (%) SD	Dosage	1 mg	3 mg	5 mg	1 mg	3 mg	5 mg
	N	6	6	6	6	6	6
	Asenapine	0.0167 (60.9)	0.0364 (104)	0.0292 (92.9)	0.00167 (245)	0.0169 (91.2)	0.0173 (128)
	Desmethyl-Asenapine	0.582 (47.9)	0.266 (30.0)	0.128 (39.0)	0.0935 (86.8)	0.0797 (75.5)	0.0991 (49.9)
	Asenapine Glucuronide	7.11 (35.2)	5.59 (28.1)	12.9 (41.1)	11.7 (31.9)	11.3 (30.3)	9.1 (34.7)
fe,u (%) SS	Dosage	3 mg BID	5 mg BID	10 mg BID	3 mg BID	5 mg BID	10 mg BID
	N	6	6	5	6	6	4
	Asenapine	0.0925 (38.2)	0.0648 (65.7)	0.0414 (91.1)	0.0655 (47.8)	0.0392 (60.1)	0.0434 (52.3)
	Desmethyl-Asenapine	0.179 (22.8)	0.106 (21.1)	0.0474 (34.5)	0.0939 (54.6)	0.0884 (19.6)	0.0724 (27.0)
	Asenapine Glucuronide	8.08 (42.0)	8.57 (13.6)	16.6 (71.0)	17.3 (33.2)	17.3 (15.5)	16.2 (22.5)

Table 84 Comparison of Pharmacokinetic Metrics for Urinary Excretion of Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide in Caucasians and Japanese – Study 25546

Parameter	p-value for Race		
	Asenapine	Desmethyl - Asenapine	Asenapine - Glucuronide
	Single dose (n=36)		
CL,R (L/h)	0.052	0.029	<0.0001
wn - CL,R (L/h/kg)	0.047	0.019	<0.0001
fe	0.018	<0.0001	0.038
	Steady state (n=33)		
CLss,R (L/h)	0.392	0.210	<0.0001
wn - CLss,R (L/h/kg)	0.197	0.044	<0.0001
fess	0.218	0.057	0.0002

Table 85 Single 5 mg and Multiple Dose 5 mg BID Steady-State Pharmacokinetic Metrics of Asenapine-11-O-Sulfate in Japanese & Caucasians– Study 25546

Parameter (unit)	Summary Statistics		Geometric Means		Geometric Mean Ratio Japanese : Caucasian (95% CI)
Race	Japanese	Caucasian	Japanese	Caucasian	
n	4	5	4	5	
	5 mg Single Dose				
Tmax (h)	4.00 2.00-6.00	3.02 1.50-4.03			
Cmax (ng/mL)	0.983 (78.8) 0.176-2.04	2.78 (66.0) 0.581-5.27	0.717	2.19	0.33 0.10 – 1.02
AUC_{tlast} (ng·h/mL)	9.17 (79.4) 1.42-18.8	17.7 (73.9) 4.49-39.1			
AUC_{0-inf} (ng·h/mL)	11.2 (72.4) 1.84-21.0	20.1 (62.9) 8.91-41.2	8.14	17.2	0.47 0.16 - 1.38
t½ (h)	21.0 (81.7) 4.38-44.8	24.0 (86.3) 4.99-57.0			
	Steady-State 5 mg BID				
Tmax (h)	3.00 3.00-4.00	3.00 2.00-4.00			
Cmax (ng/mL)	3.23 (67.3) 0.747-5.96	2.96 (34.9) 1.75-4.25	1.93	1.92	1.01 0.32 - 3.15
$Cmax^{ss}_{corr}$ (ng/mL)	2.27 (50.6) 0.646-3.09	2.14 (51.7) 1.11-3.78			
$AUCss,_{0-12}$ (ng·h/mL)	19.8 (85.9) 4.08-42.9	17.0 (19.2) 12.0-20.6	14.2	16.7	0.85 0.29 - 2.50
t½ (h)	21.1 (30.3) 14.6-27.2	26.7 (28.1) 15.7-35.1			

5.5.6.2 Gender

No specific gender study was performed. Since asenapine is a CYP1A2 substrate and drugs that are substrates of CYP1A2 tend to have higher exposures in women and the elderly, the effect of gender and age will need to be examined. In at least two PK studies, the elderly study and a pivotal BE study there may be sufficient numbers of women to allow for a comparison. However, for the BE study the availability of gender data was not realized until too late in the review cycle and the study in the elderly was hidden. By the time the reviewer realized that this data might be extractable there was insufficient time to extract the data and analyze it for the review.

5.5.6.3 Elderly

It was originally thought that no specific study in the elderly was performed. This was surprising since asenapine is a CYP1A2 substrate and drugs that are substrates of CYP1A2 tend to have higher exposures in women and the elderly and in particular elderly women. In addition cardiac toxicity and death is a known concern with using antipsychotics in the elderly. On May 5th, 2008 it was realized that summary statistics including ranges of pharmacokinetic metrics had been reported.

According to the interim report the first 33 elderly subjects greater than 65 years of age with psychosis enrolled in the study would have the pharmacokinetics and safety of asenapine assessed.

Subjects were dosed BID as per Figure 65.

Figure 65 BID Dosage Regimens for Asenapine in Elderly PK and S/T Study A7501021

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Days 7-42/EOT*
Group A (BID)	2 mg	2 mg	5 mg	5 mg	10 mg	10 mg	5-10 mg
Group B (BID)	5 mg	5 mg	5 mg	5 mg	10 mg	10 mg	5-10 mg

Subject demographics are shown in Table 86.

Table 86 Subject Demographics for Elderly PK and Safety / Tolerability Study A7501021

N	Age (yrs)	Gender M/F (%)	Race / Ethnicity Caucasian / Black / Palestinian
33	72.6 ± 5.43 65 - 85 [72]	12 / 21 (36.4 / 63.6)	22 / 10 / 66.7 / 30.3 / 3.03

For the interim analysis it was assumed that the asenapine dose administered at Day 4 was 5 mg and at Day 8 was 10 mg

Figure 66 shows the sponsor's comparison of PK parameters of elderly and adult schizophrenic patients indicating a 40% increase in exposure to asenapine and a doubling of exposure to desmethyl-asenapine.

Figure 66 Sponsor's Comparison of PK Parameters of Elderly and Adult Schizophrenic Patients – Study A7501021

Table 3 Comparison of PK parameters between elderly and adult schizophrenia patients

Parameter	Dose	Elderly patients	Adult patients	% difference Elderly vs Adult
Asenapine				
C_{max} (ng/mL)	5 mg BID	5.58 (70.2)	4.23 (45.3)	+32 %
	10 mg BID	8.51 (72.1)	6.56 (50.9)	+30 %
AUC_{0-12} (ng·h/mL)	5 mg BID	34.6 (58.9)	26.6 (38.4)	+30 %
	10 mg BID	61.2 (68.2)	43.4 (53.1)	+41%
N-desmethylasenapine				
C_{max} (ng/mL)	5 mg BID	1.89 (80.0)	1.02 (38.8)	+85%
	10 mg BID	4.30 (98.1)	2.21 (48.3)	+95%
AUC_{0-12} (ng·h/mL)	5 mg BID	16.2 (67.9)	9.65 (38.9)	+68%
	10 mg BID	38.0 (89.7)	19.6 (35.7)	+94%

Source: Appendix A, Table 4-1 and Table 4-2 and Clinical Trial Report A7501001, Table 48 and Table 49.

Table 87 shows the complete descriptive statistics of steady−state pharmacokinetic metrics for both asenapine and N−desmethylasenapine for the pharmacokineticallyevaluable group and it compares them to the range of exposures from the multiple-dose dose titration study 41012 the maximal asenapine exposure is nearly triple and the maximal N-desmethyl-asenapine exposure is 11 times higher and 3 times higher than seen in the healthy volunteer from the IV study who experienced asystole.

Although the data from study 41012 is only based on 2 subjects when the other doses are examined it still appears that maximal exposures in the elderly are 3 fold higher.What's especially troubling the combination of the large number of drop outs, the high maximum exposures seen in the elderly, the higher risk in the elderly, and the lack of and apparent hiding of the data. In addition without the raw data we are unable to determine if there is any relationship of age and / or gender and the high asenapine and desmethyl asenapine concentrations.

Table 87 Asenapine and N−Desmethyl-asenapine Steady−State Pharmacokinetic Metrics in the Elderly for the Pharmacokinetically Evaluable Group – Study A7501021 and Comparison to MD PK from Dose Titration Study 41012

Population	Asenapine Dose	Day	Metric	N	Summary Statistics	
					Asenapine	Desmethyl-asenapine
Elderly	5 mg BID	4	Tmax,ss (h)	32	2.33 ± 2.87 (123) 0.5 - 1.0 [12.0]	4.52 ± 3.8 (84.1) 0.5 - 12.0 [4.0]
			Cmax,ss (ng/mL)	32	5.58 ± 3.92 (70.2 0.296 - 4.06 [18.9]	1.89 ± 1.51 (80.0) 0.28 - 6.75 [1.28]
			AUCτ (ng*h/mL)	32	34.6 ± 20.4 (58.9) 2.21 - 30.0 [85.4]	16.2 ± 11.0 (67.9) 2.43 - 37.8 [10.5]
			Cmin,ss (ng/mL)	32	2.27 ± 1.87 (82.4) 0.106 - 1.72 [8.43]	1.12 ± 0.79 (70.7) 0.0525 - 2.9 [0.771]
	10 mg BID	8	Tmax,ss (h)	29	2.44 ± 2.48 (102) 0.5 - 8.0 [2.0]	4.37 ± 2.75 (62.9) 0.917 - 12.0 [4.0]
			Cmax,ss (ng/mL)	29	8.51 ± 6.14 (72.1) 1.89 - 27.0 [7.86]	4.3 ± 4.22 (98.1) 0.89 - 18.4 [3.02]
			AUCτ (ng*h/mL)	29	61.2 ± 41.8 (68.2) 13.5 - **144** [42.2]	38.0 ± 34.1 (89.7) 9.82 - **155** [23.2]
			Cmin,ss (ng/mL)	28	4.18 ± 3.41 (81.8) 1.01 - 12.9 [2.53]	2.36 ± 1.78 (75.7) 0.662 - 7.86 [1.78]
Young	Study 41012 Dose Titration Study 10 mg BID	10	Tmax,ss (h)	2	[1.25] 1.00 - 1.50	[4.00] 4.00 – 4.00
			Cmax,ss (ng/mL)		8.84 2.17 - 15.5	1.33 1.23 - 1.42
			AUCτ (ng*h/mL)		37.3 16.5 - **58.1**	12.7 11.0 - **14.4**
			Cmin,ss (ng/mL)		1.30 0.964 - 1.64	0.853 0.693 - 1.01

Figure 67 Mean Asenapine Steady-State Concentration vs. Time Profiles in the Elderly – Study A7501021

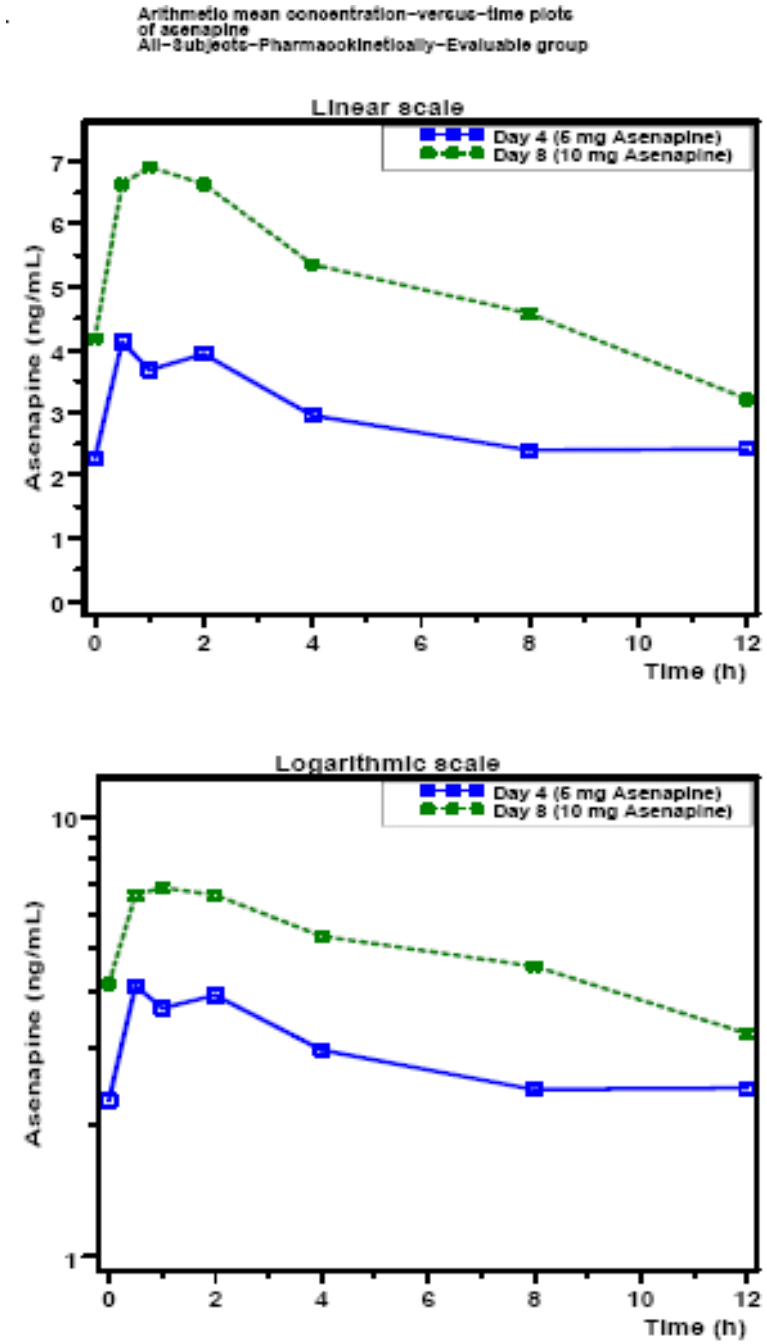
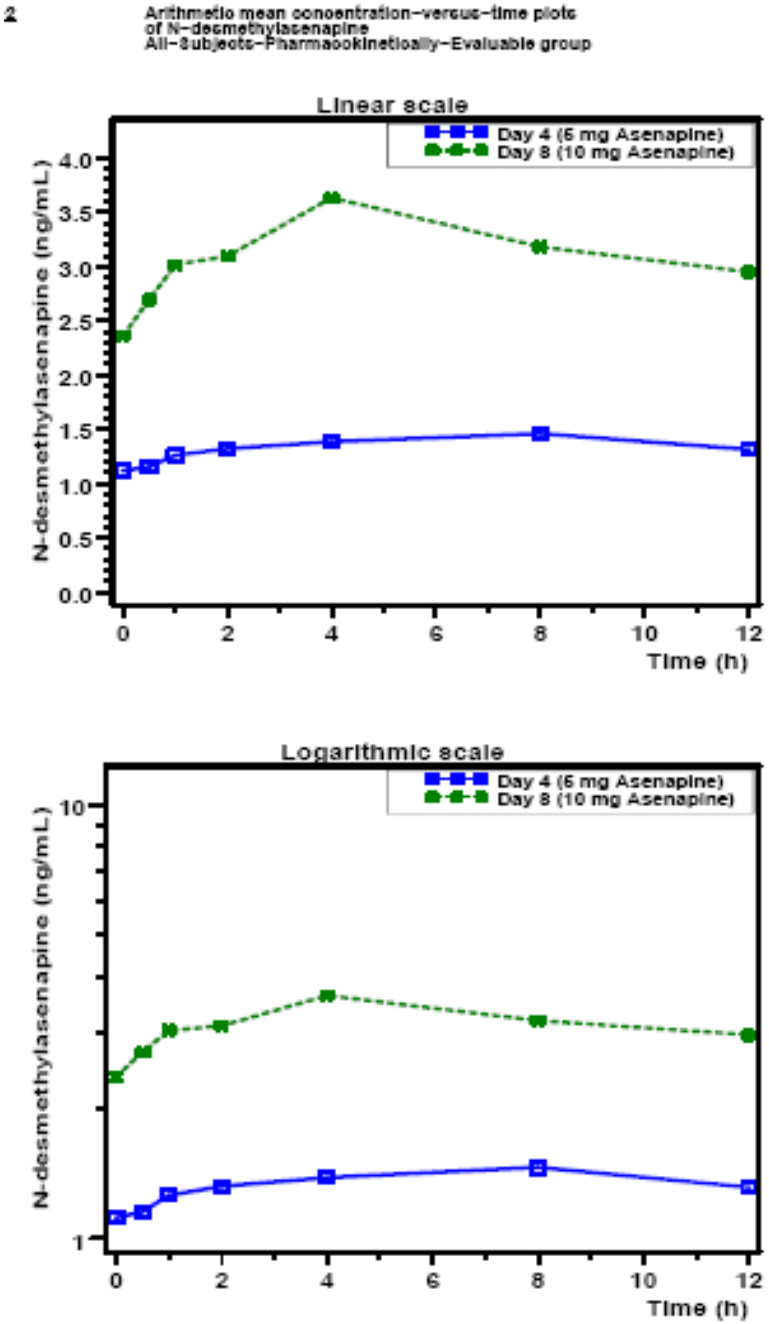


Figure 68 Mean Desmethyl-Asenapine Steady-State Concentration vs. Time Profiles in the Elderly – Study A7501021



5.5.6.4 Pediatrics - Adolescents - Study A7501022

Study A7501022 was a randomized, double-blind, placebo-controlled, 4-way parallel-group, multiple-dose study in 40 male and female adolescent patients 12 – 17 years of age. Asenapine at dosages ranging from 1 to 10 mg was administered BID sublingually for 10 days. Each group contained 10 subjects (8 active, 2 placebo).

Subjects had to have a documented history of schizophrenia, bipolar disorder, autism, conduct disorder, oppositional defiant disorder, or any condition for which the chronic use of antipsychotic medication (i.e., risperidone, olanzapine, haloperidol) was potentially warranted and/or administered.[7]

Maintenance medication was tapered and discontinued over a period of up to 3 days, placebo was administered on Day 0 and asenapine or placebo was administered over 10 - 11 days.

Treatment regimens were as follows.

Group	Regimen
1	Asenapine 1 mg SL BID x 10 days
2	Asenapine 3 mg SL BID x 10 days
3	Asenapine 5 mg SL BID x 10 days
4	Asenapine 5 mg SL BID on day 1 then 10 mg SL BID x 10 days

No raw pharmacokinetic data or metrics were supplied. It appears that many of the subjects were on Adderal® for ADHD and were also diagnosed with bipolar disorder or psychosis. There were a high percentage of blacks enrolled in this study. This raises the question whether this is simply due the recruiting area or to more black children being placed on antipsychotics for ADHD due to their socioeconomic circumstances, or whether it an intentional attempt to minimize Caucasians due the higher likelihood that they would be CYP2D6 poor metabolizers. In addition, since African American children are more likely to be at the upper end of the height and weight spectrum they would thus be more likely to have exposures that are more similar to adults and less likely to experience adverse effects.

A summary of the reported asenapine pharmacokinetic metrics by dose is shown in Table 88 and desmethyl-asenapine pharmacokinetic metrics in Table 89.

Examination of patient demographics revealed that 0 / 17 females and only 5 / 23 males had body weights of $\leq$ 45 kg, (see Table 90). This is significant as 45 kg is the median population weight in adolescents between 12 – 17 years of age.

This is shown graphically in Figure 69 where body mass in kg is plotted vs. age in years by gender and by race. Curves for population medians and 95% confidence intervals are also superimposed along with a cubic spline fit to the subjects data which demonstrates that the mean weights in this population tends to be closer to the 80th percentile. The data from this population thus likely underestimates the true exposure measured by AUC that would be expected in the actual treated population.

Thus unless further information is obtained, studies in adolescents are likely to result in excessively high concentrations in adolescents. Since, there appears to be a very narrow safety margin between therapeutic and potentially hepatotoxic doses this indicates that adolescents may be at higher risk for

[7] This raises ethical issues with this study as these are off-label uses and in spite of the off-label use of antipsychotics in practice there are questions as to whether off-label use for these conditions is even appropriate, i.e. has it been adequately studied and if so has the need and use been appropriately documented in these subjects. Since these subjects were largely on Adderall and had ADHD, the addition of an antipsychotic with a dopaminergic agent in and of itself is questionable. In addition analysis of the bipolar studies in this submission argues that this particular use is likely an inappropriate off-label use. All of these factors raise ethical issues whether some or all of this data is even usable to support an NDA for an appropriate use, i.e. should we refuse to use some or all of the data similar to the practice of refusing to use data obtained unethically such as from medical experiments conducted on holocaust victims.

hepatotoxicity if dosage is not adjusted. This is especially worrisome with off label use in even younger children as a sublingual formulaton would be a natural choice for prescribers to use off label, and the lack of appropriate dosage strengths might mean an even greater proportion of the dose would be swallowed as compared with adults and thereby increase the risk of hepatotoxicity.

Another concern with adolescents is the greater propensity for ingestion of high fat meals and the alterations in hepatic blood flow and increase in potentially hepatotoxic metabolites this might entail.

Table 88 Summary of Asenapine Pharmacokinetic Parameter Values following q12h Administration of Sublingual Tablet Doses to Adolescent Subjects receiving Antipsychotics - Study A7501022

Asenapine Dose	1 mg	3 mg	5 mg	10 mg
N (n)	8 (7)	8 (5)	8 (8)	8 (8)
Tmax (hr)	0.705 (0.25 - 1.5)	0.890 (0.0 - 1.5)	1.04 (0.0 - 2.8)	1.28 (0.0 - 3.0)
Cmax (ng/mL)	1.03 (49.6)	2.64 (55.6)	3.54 (47.9)	2.77 (81.8)
Cmin (ng/mL)	0.253 (53.8)	0.793 (49.8)	1.02 (41.9)	0.901 (55.8)
AUC(0-τ) (ng/mL x hr^{-1})	6.56 (60.8)	15.8 (49.5)	22.9 (47.5)	19.7 (54.0)
CL/F (L/min)	3.21 (43.5)	4.53 (83.5)	6.81 (138)	10.3 (42.8)
Vd/F (L)	7750 (64.4)	12100 (90.0)	14700 (79.5)	19700 (47.3)
t½ (hr)	29.3 (40.9)	25.6 (24.6)	32.3 (37.5)	22.6 (21.7)

N = Number of subjects.
n = Number of subjects where t½ and Vd/F were determined.

Table 89 Summary of Desmethyl-Asenapine Pharmacokinetic Parameter Values following q12h Administration of Sublingual Asenapine Tablet Doses to Adolescent Subjects receiving Antipsychotics - Study A7501022

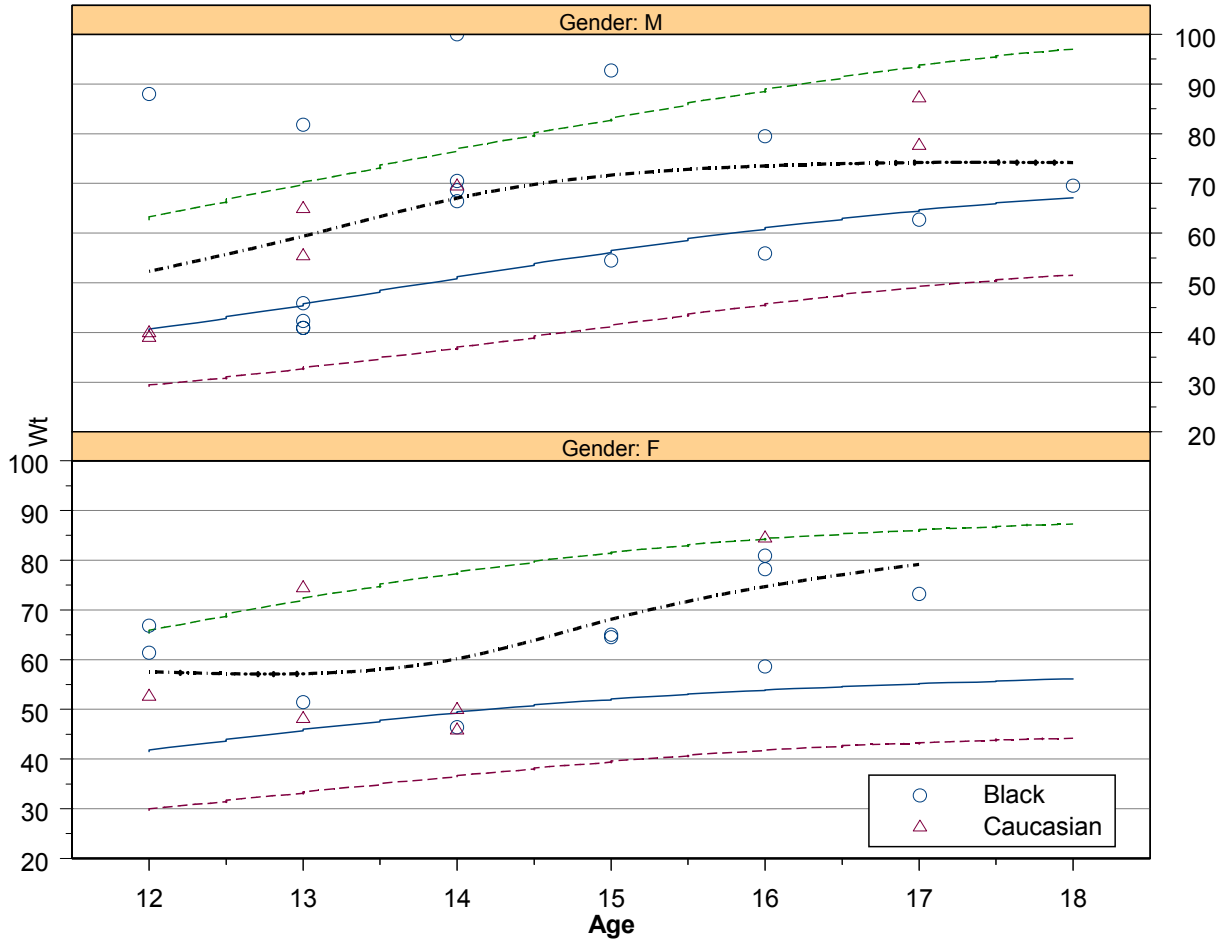
Asenapine Dose	1 mg	3 mg	5 mg	10 mg
N (n)	8 (5)	8 (5)	8 (8)	8 (6)
Tmax (hr)	3.04 (0.50 - 12)	1.82 (0.28 - 6.0)	4.00 (0.0 - 11)	3.59 (0.78 - 4.0)
Cmax (ng/mL)	0.430 (67.7)	1.04 (63.2)	1.40 (37.4)	2.96 (74.5)
Cmin (ng/mL)	0.219 (57.5)	0.621 (67.8)	0.800 (37.6)	1.07 (83.5)
AUC(0-τ) (ng/mL x hr^{-1})	4.03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

N = Number of subjects.
n = Number of subjects where t½ was determined.

Table 90 Demographic Characteristics of Adolescent Subjects in Study - A7501022

Row	Site	Subject	Age (yrs)	Gender	Sexual Maturation	Race/Ethnicity	Height (cm)	Weight (kg)	BMI	Smoking Status	Weekly Alcohol Consumption (Units / week)
1	1002	10021010	12	Female		Caucasian	152.4	52.7	22.7	Never Smoked	
2	1001	10011010	12	Female		Black	154.9	61.4	25.6	Never Smoked	
3	1001	10012016	12	Female	Premenarchal	Black	160	66.8	26.1	Never Smoked	
4	1002	10021001	13	Female		Caucasian	145	48.2	22.9	Never Smoked	
5	1001	10011012	13	Female		Black	154.9	51.4	21.4	Never Smoked	
6	1002	10021012	13	Female		Caucasian	155	74.5	31	Current Smoker	6
7	1001	10012020	14	Female	Premenarchal	Caucasian	149	45.9	20.7	Never Smoked	
8	1001	10011009	14	Female		Black	157.5	46.4	18.7	Never Smoked	
9	1002	10021016	14	Female		Caucasian	157	50	20.3	Current Smoker	
10	1001	10011004	15	Female		Black	165.1	64.5	23.7	Never Smoked	
11	1001	10011002	15	Female		Black	162.6	65	24.6	Never Smoked	
12	1002	10021006	15	Female		Black	182.8	104.5	31.3	Never Smoked	
13	1002	10021007	16	Female	Premenarchal	Black	157.5	58.6	23.6	Never Smoked	
14	1001	10011001	16	Female		Black	165.1	78.2	28.7	Never Smoked	
15	1002	10021003	16	Female		Black	165.1	80.9	29.7	Never Smoked	
16	1002	10021005	16	Female		Caucasian	167.6	84.5	30.1	Never Smoked	
17	1001	10011006	17	Female		Black	157.5	73.2	29.5	Never Smoked	
18	1001	10011014	12	Male		Caucasian	143	39.1	19.1	Never Smoked	
19	1001	10011015	12	Male		Caucasian	146	40	18.8	Never Smoked	
20	1001	10012019	12	Male		Black	149.9	88	39.2	Never Smoked	
21	1001	10011013	13	Male		Black	152	40.9	17.7	Never Smoked	
22	1002	10022020	13	Male		Black	145	40.9	19.5	Never Smoked	
23	1002	10021015	13	Male		Black	152	42.3	18.3	Never Smoked	
24	1002	10021014	13	Male		Black	155	45.9	19.1	Never Smoked	
25	1002	10021009	13	Male		Caucasian	167.6	55.5	19.8	Never Smoked	
26	1002	10021011	13	Male		Caucasian	152	65	28.1	Never Smoked	
27	1002	10022017	13	Male		Black	178	81.8	25.8	Never Smoked	
28	1001	10012018	14	Male		Black	171	66.4	22.7	Never Smoked	
29	1001	10011011	14	Male		Black	157.5	68.6	27.7	Never Smoked	
30	1002	10021013	14	Male		Caucasian	170	69.5	24	Never Smoked	
31	1002	10022021	14	Male		Black	152	70.5	30.5	Never Smoked	
32	1001	10011003	14	Male		Black	182.9	100	29.9	Never Smoked	
33	1002	10022019	15	Male		Black	168	54.5	19.3	Never Smoked	
34	1001	10011007	15	Male		Black	177.8	92.7	29.3	Never Smoked	
35	1002	10022018	16	Male		Black	142	55.9	27.7	Never Smoked	
36	1001	10011008	16	Male		Black	167.6	79.5	28.3	Never Smoked	
37	1001	10012017	17	Male		Black	162.6	62.7	23.7	Never Smoked	
38	1002	10021002	17	Male		Caucasian	185.4	77.7	22.6	Past Smoker	1
39	1002	10021008	17	Male		Caucasian	162.6	87.3	33	Past Smoker	
40	1001	10011005	18	Male		Black	185.4	69.5	20.2	Never Smoked	

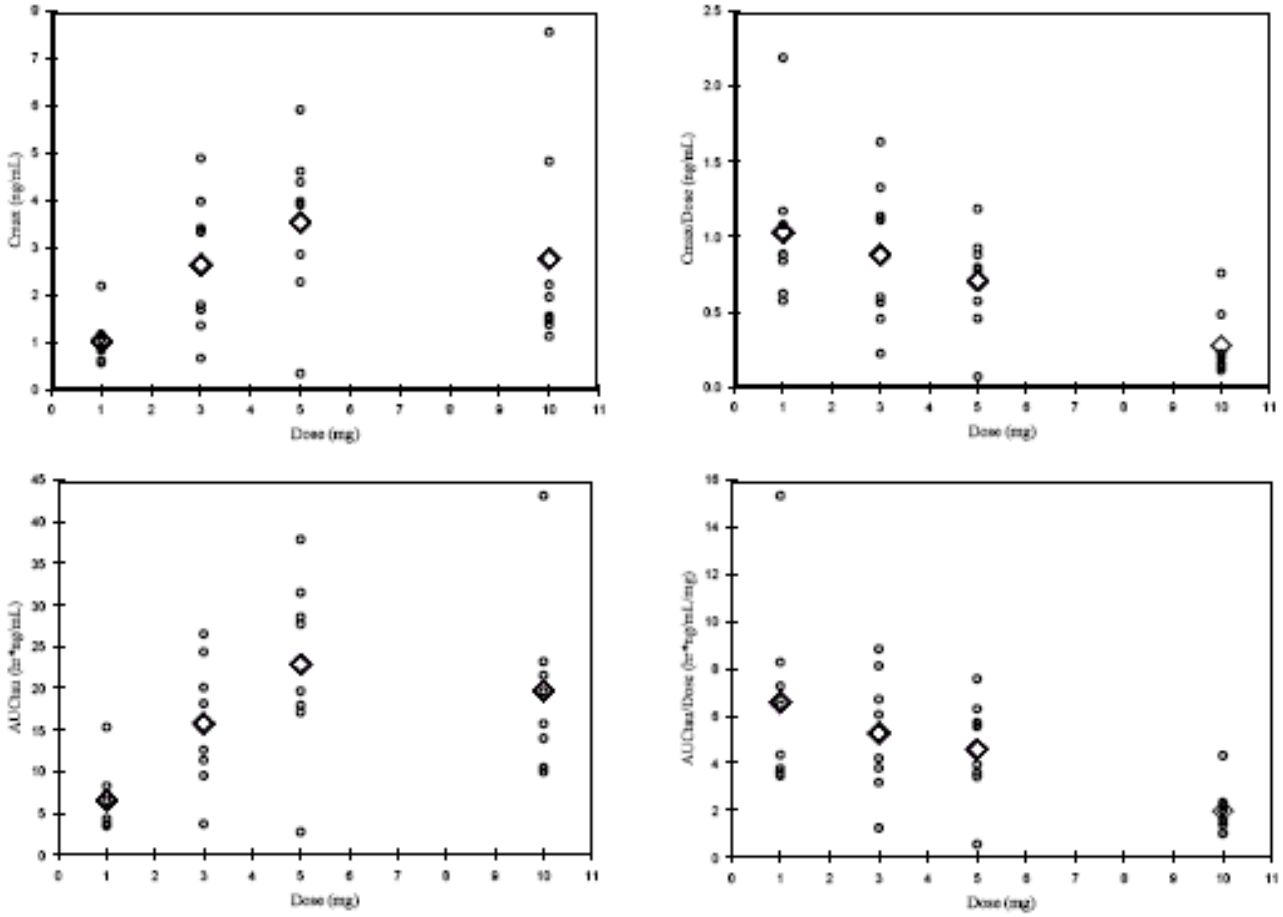
Figure 69 Adolescent Subjects Body Mass (kg) vs. Age (years) by Gender and Race, with Superimposed Curves for Population Medians and 95% Confidence Intervals along with a Cubic Spline Fit to the Subject's Data – Study A7501022



Plots of un-normalized and dose-normalized asenapine Cmax and AUCs by dose indicate that at least two subjects, (1 at 1 mg and 1 at 10 mg), were likely poor metabolizers. When dose and dose dependent bioavailability are considered, if an expected dose of 5 mg is used the mean and range of concentrations of Cmax and AUC seen with the 5 mg dose as shown in Figure 70 are similar to or slightly higher than exposures seen in adults at the same dosage in other studies, (see Table 53, and Table 76).

Figure 70 Unnormalized and Dose-normalized Asenapine Cmax and AUCs by Dose in Adolescent Subjects – Study A7501022

Figure 4. Asenapine Cmax (Upper Panel) and AUC(0-∞) (Lower Panel)Values Following q12h Administration of Sublingual Asenapine Tablet Doses to Adolescent Subjects With A Psychotic Disorder, Study A7501022



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

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 $AUC_{0-tlast}$ and the Child-Pugh score. An even stronger (negative) correlation was found between $AUC_{0-tlast}$ 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

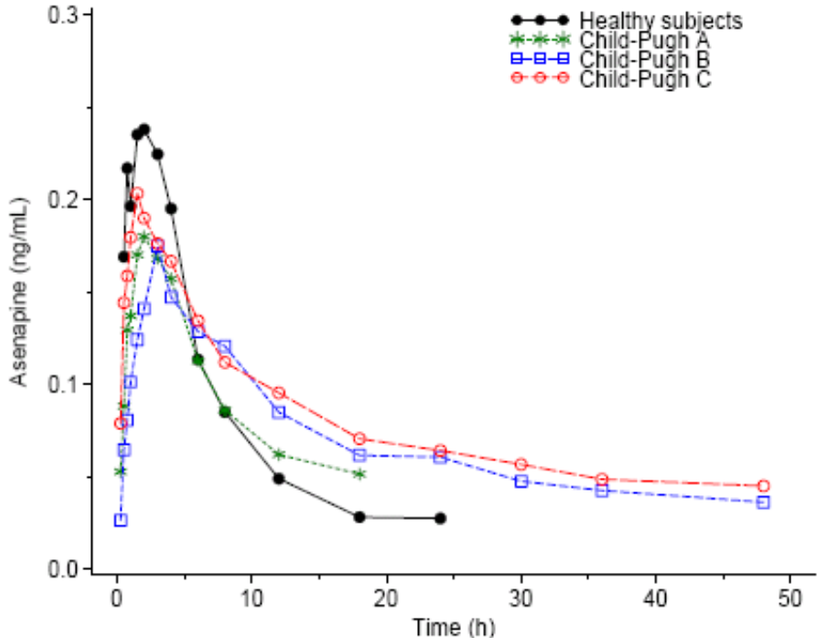


Table 94 Selected Laboratory Values in Subject 37- Study 25522

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

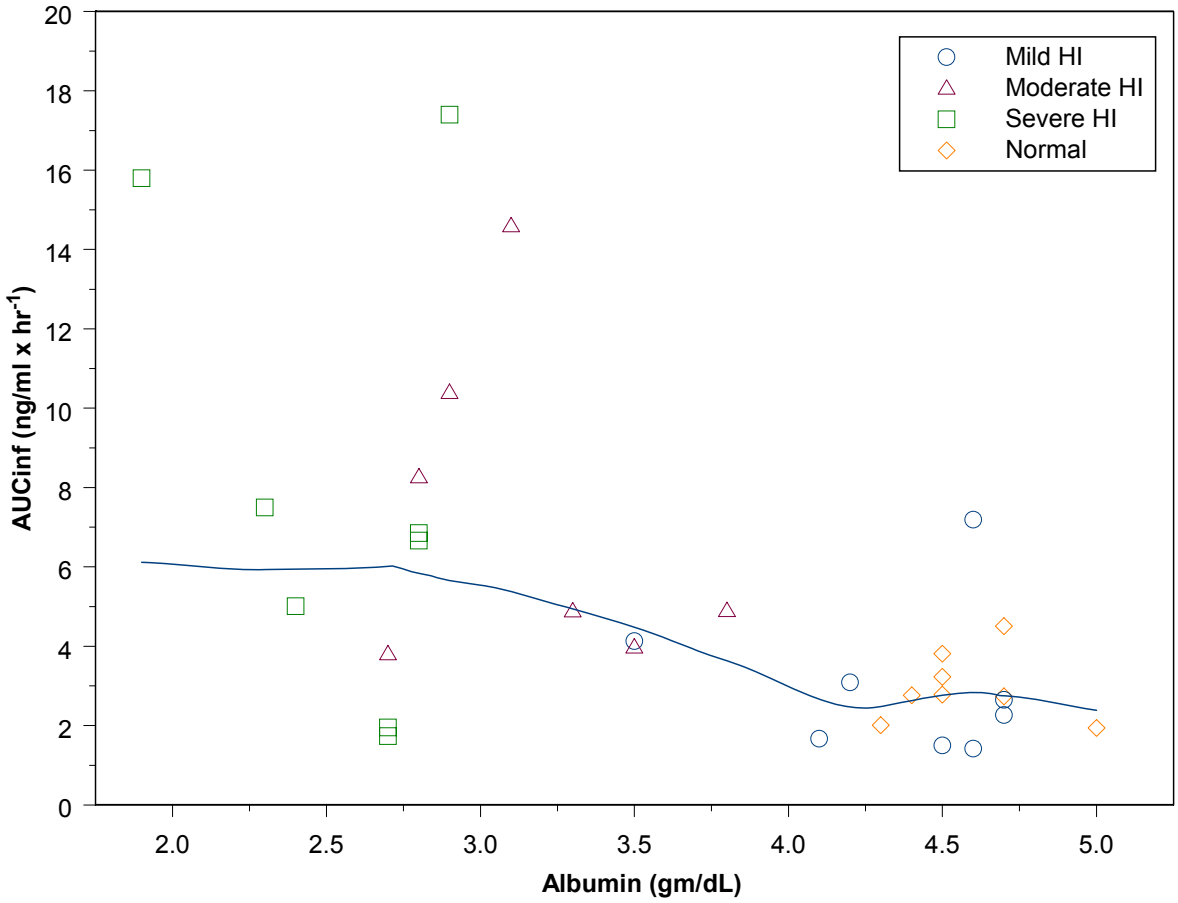


Figure 73 Asenapine AUCinf vs. Fraction Unbound (%) – Study 25522

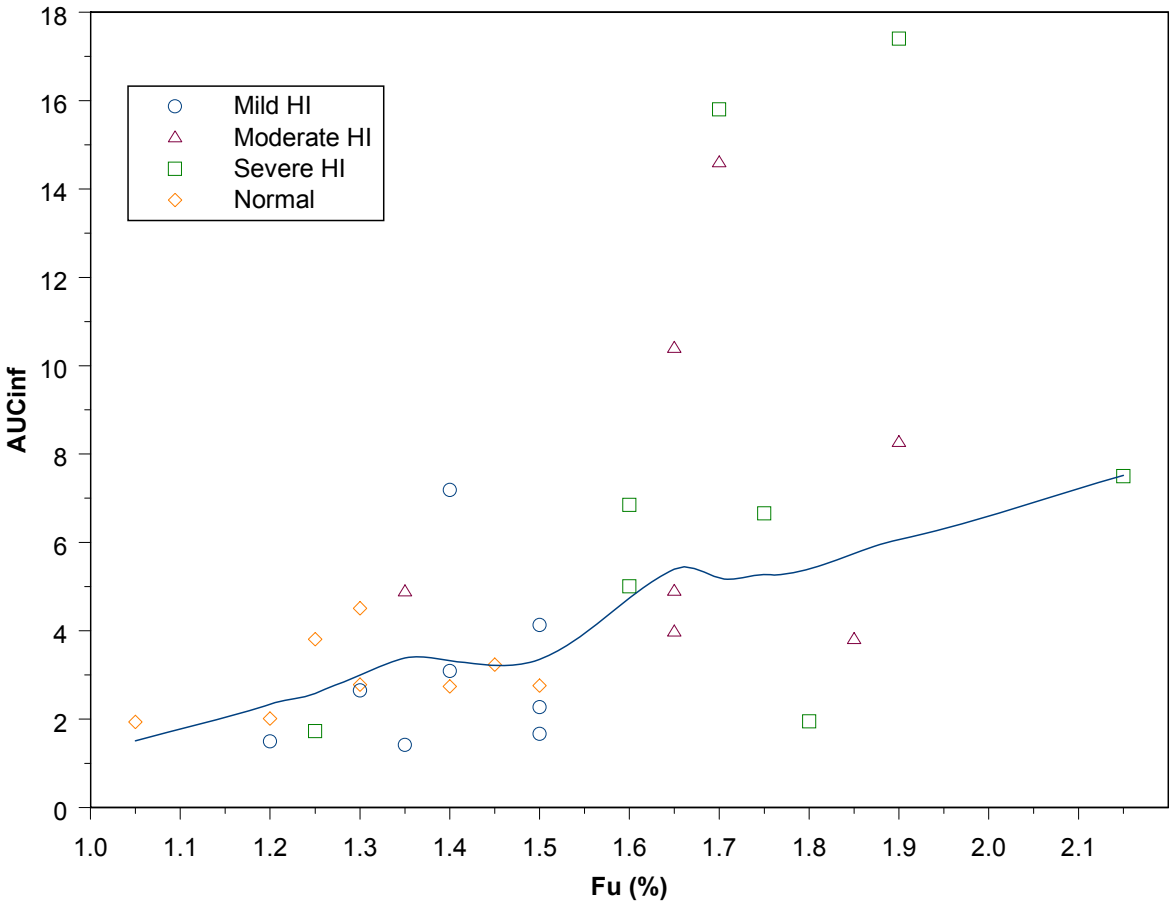


Figure 74 Asenapine AUCinf vs. Degree of Hepatic Impairment – Study 25522

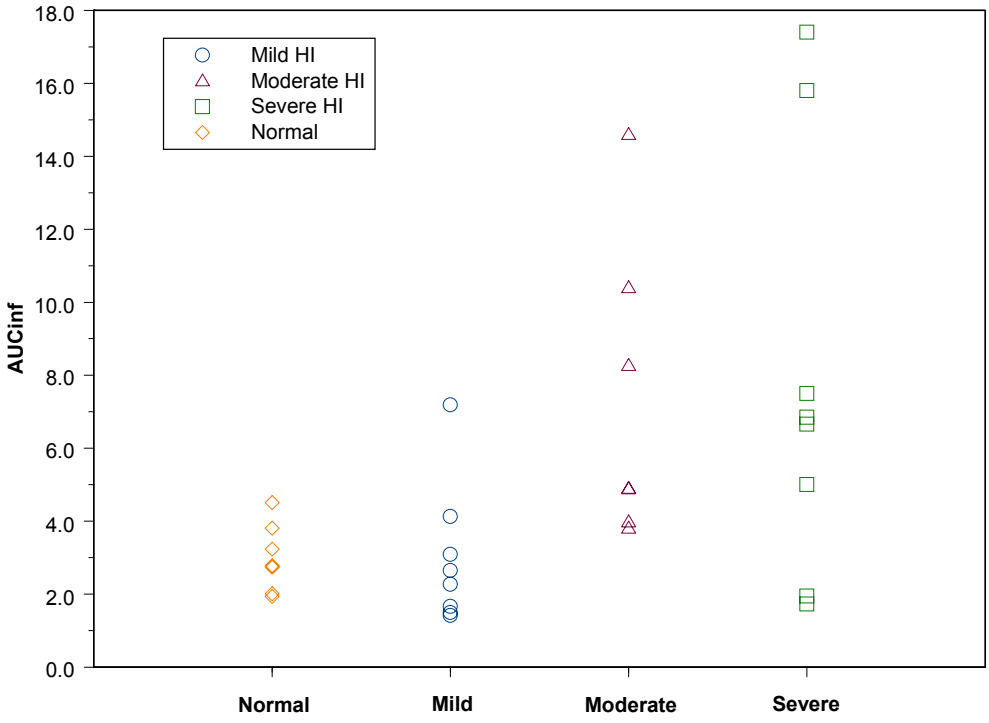
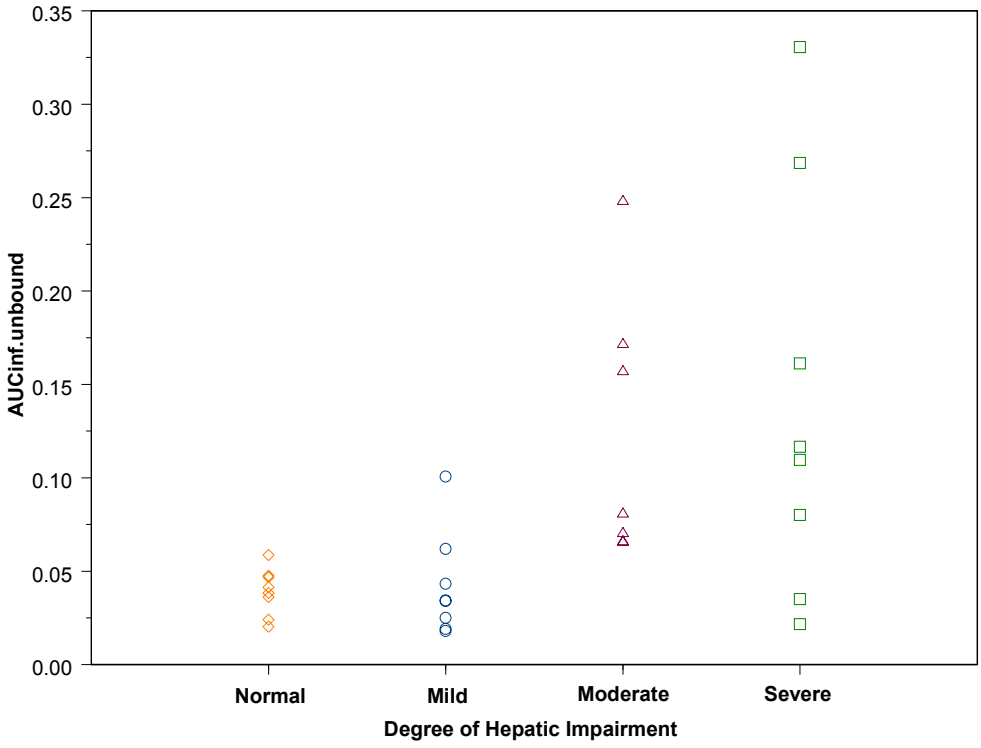


Figure 75 Asenapine Unbound AUCinf vs. Degree of Hepatic Impairment – Study 25522



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

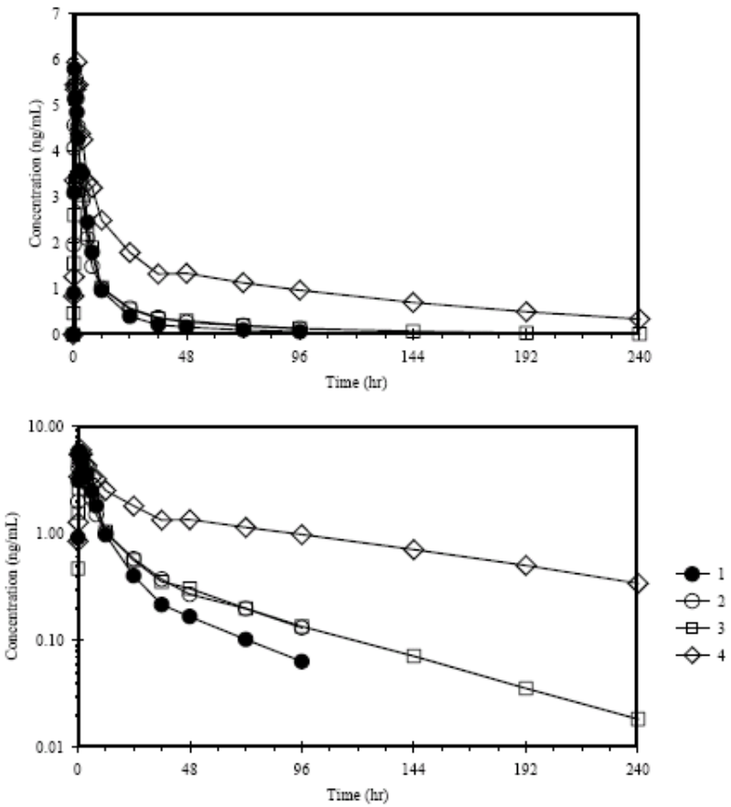


Figure 77 Linear and Semi-log Plots of Asenapine Glucuronide Concentration vs. Time Profiles for a Single 5 mg Sublingual Dose by Degree of Hepatic Impairment – Study A7501018

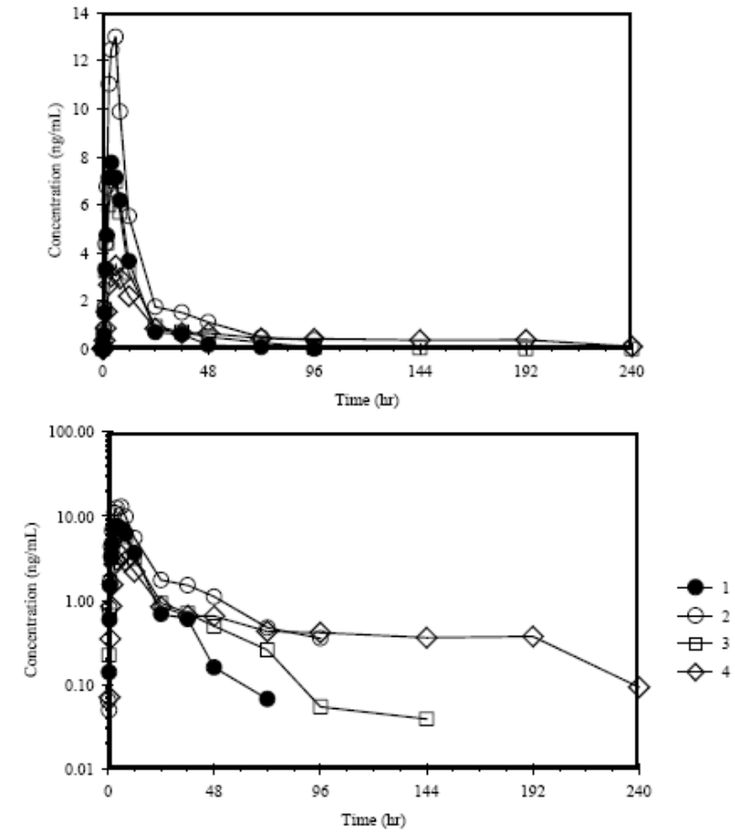


Figure 78 Linear and Semi-log Plots of Desmethyl-Asenapine Concentration vs. Time Profiles for a Single 5 mg Sublingual Dose by Degree of Hepatic Impairment – Study A7501018

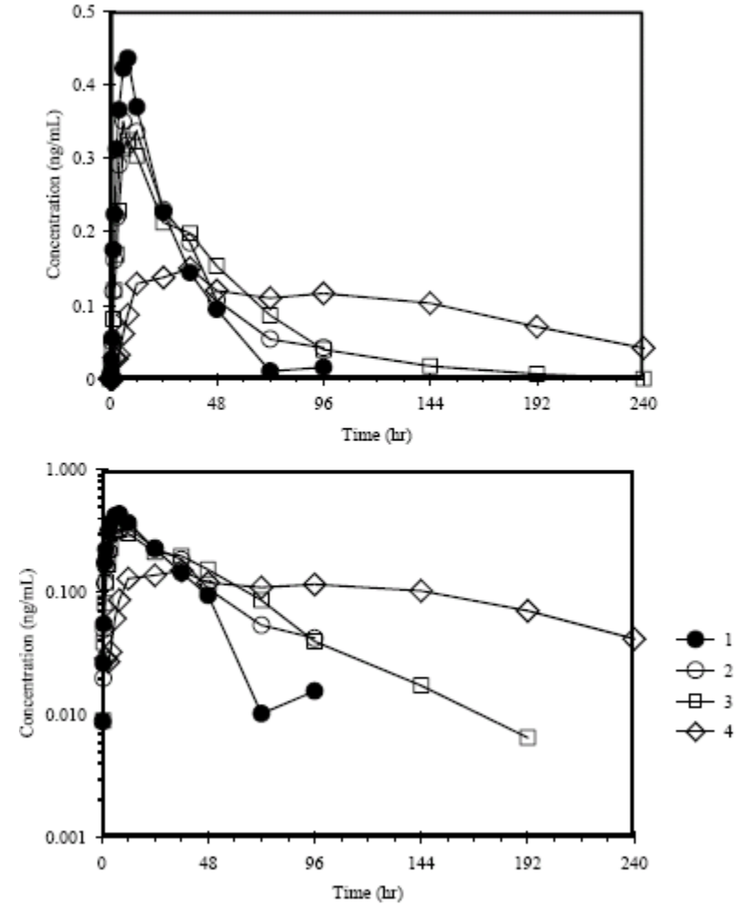


Figure 79 Individual Asenapine Cmax and AUC∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018

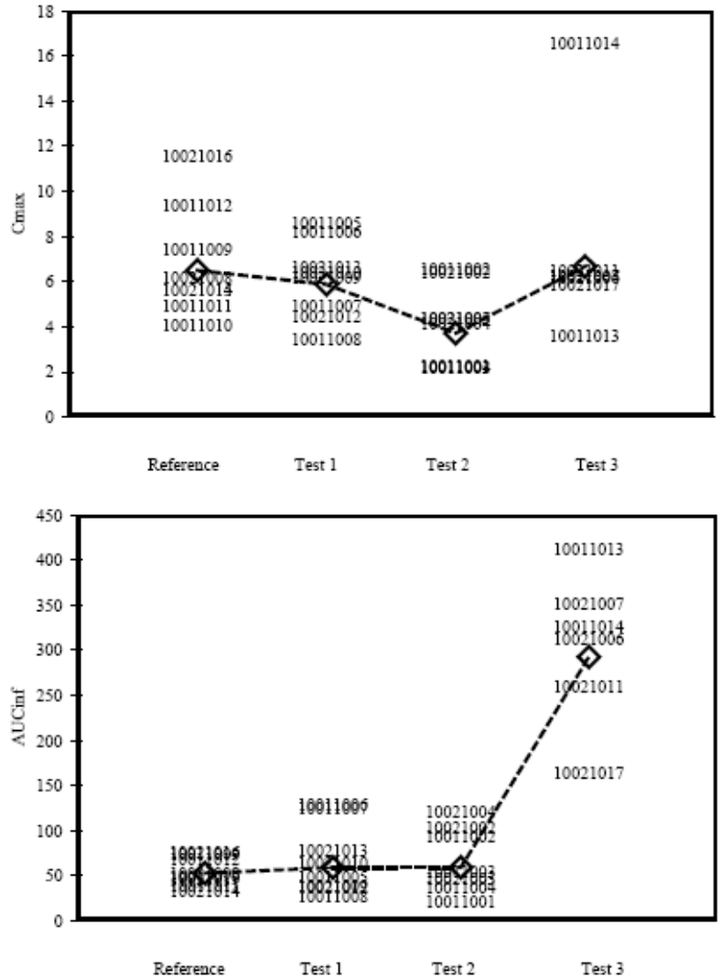


Figure 80 Individual Asenapine Glucuronide Cmax and AUC∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018

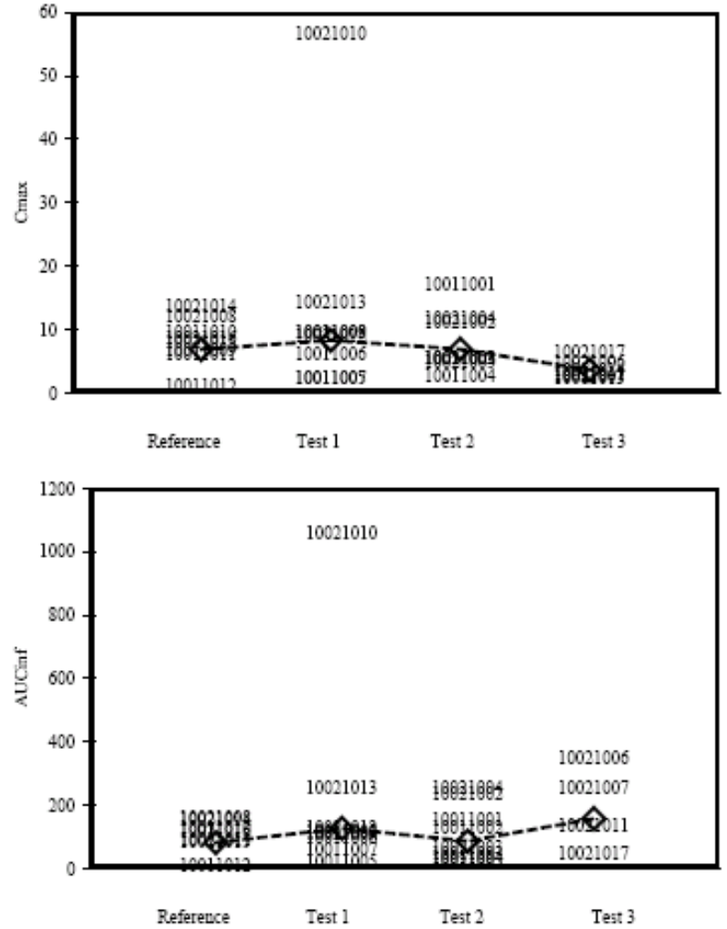


Figure 81 Individual Desmethyl-Asenapine Cmax and AUC∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018

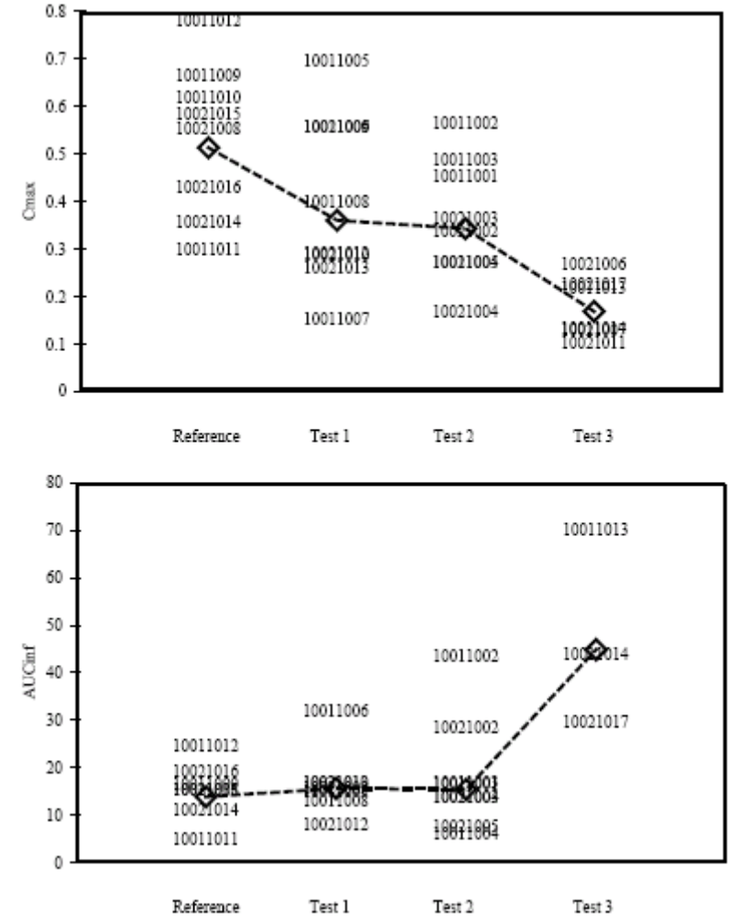
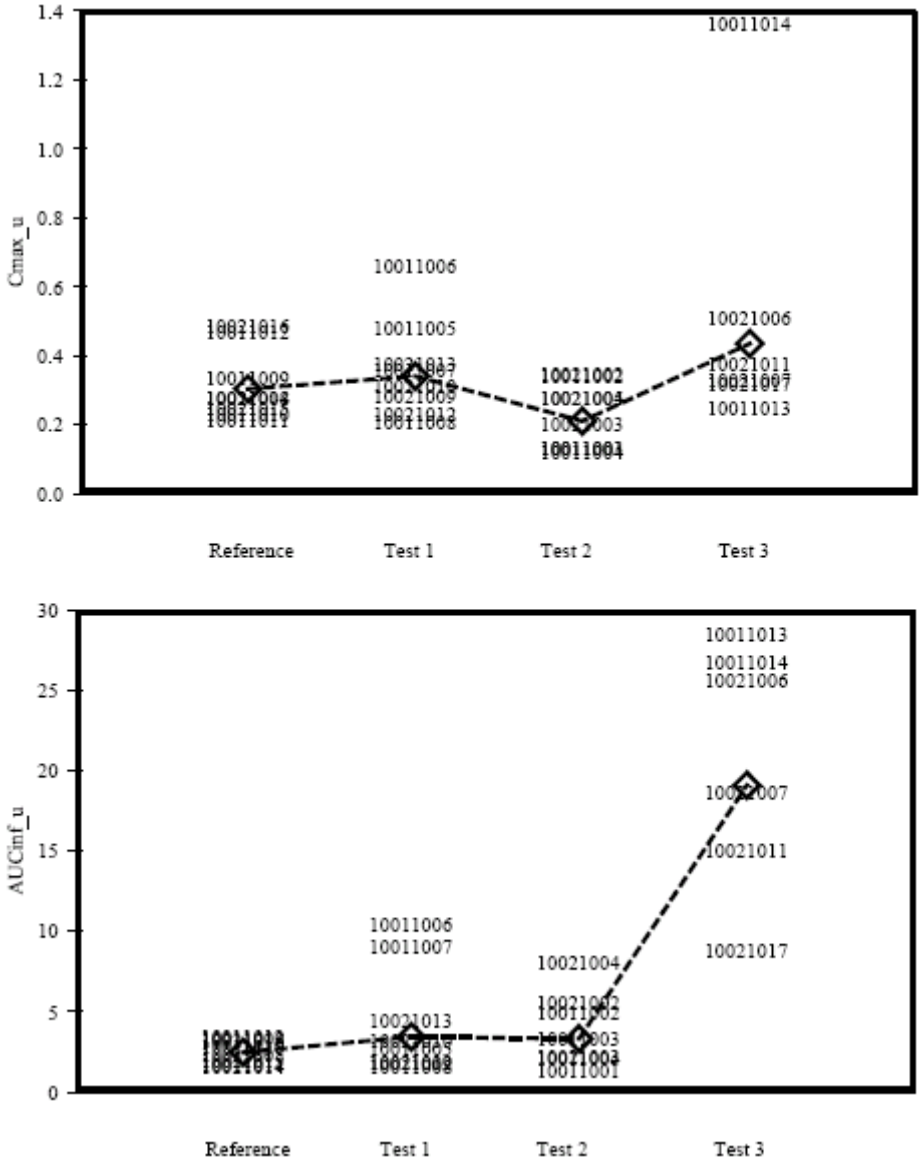


Figure 82 Individual Unbound Asenapine Cmax,u and AUCu∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018



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

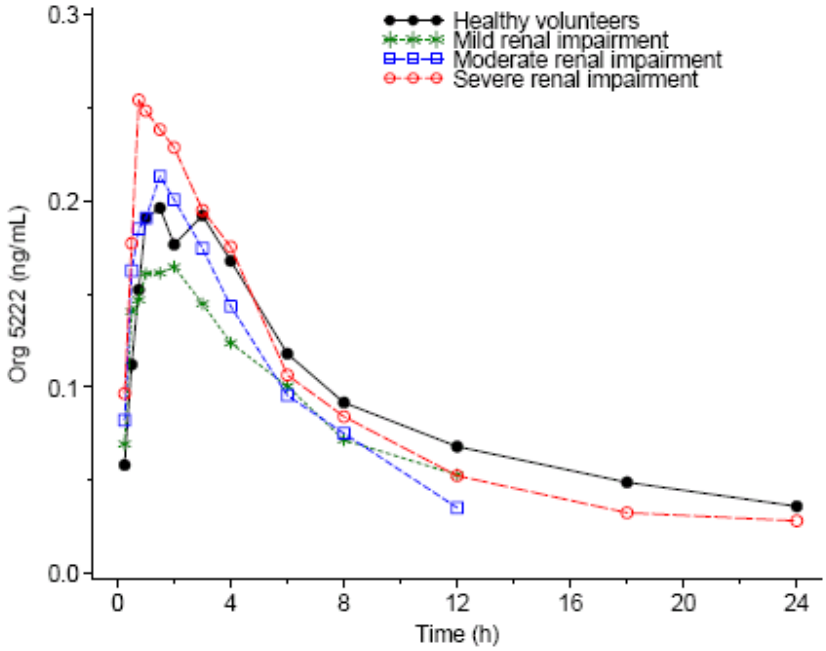


Figure 84 Asenapine AUCt vs. Creatinine Clearance - Study 25521

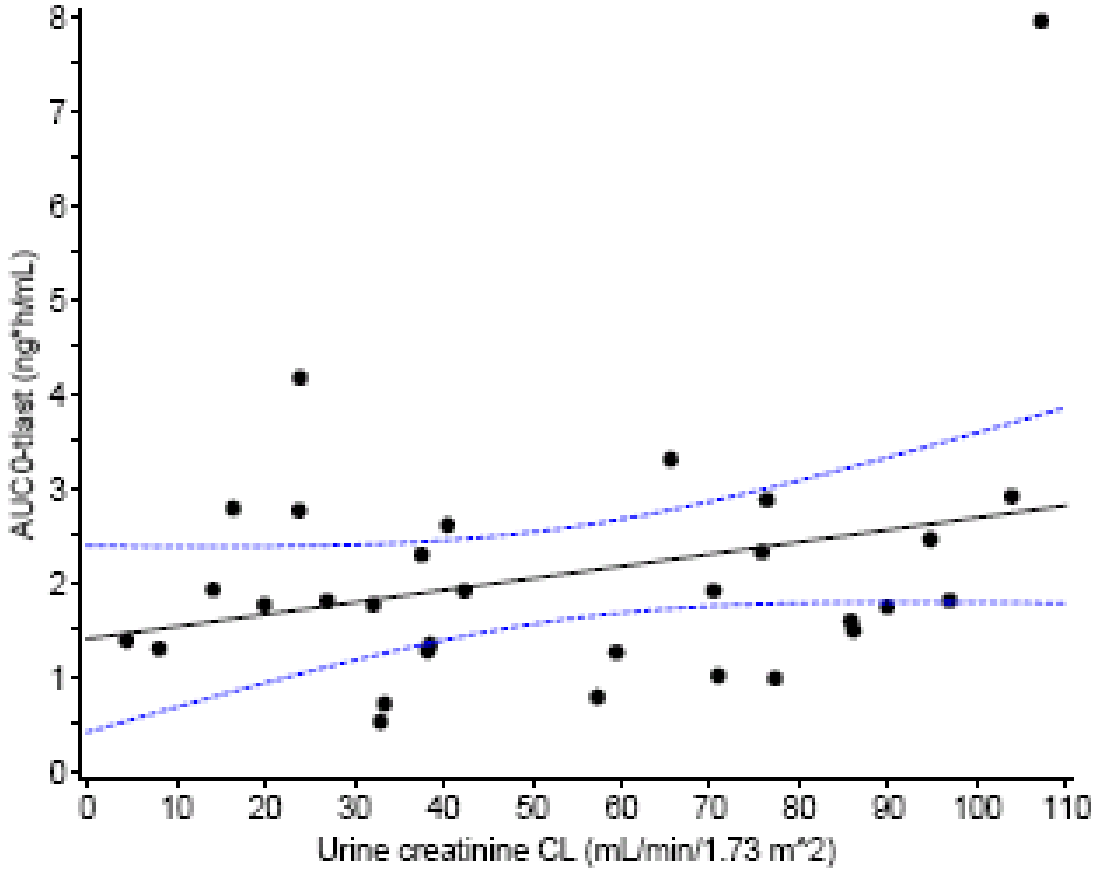


Figure 85 Asenapine Weight Normalized Apparent Clearance vs. Creatinine Clearance – Renal Impairment Study 25521

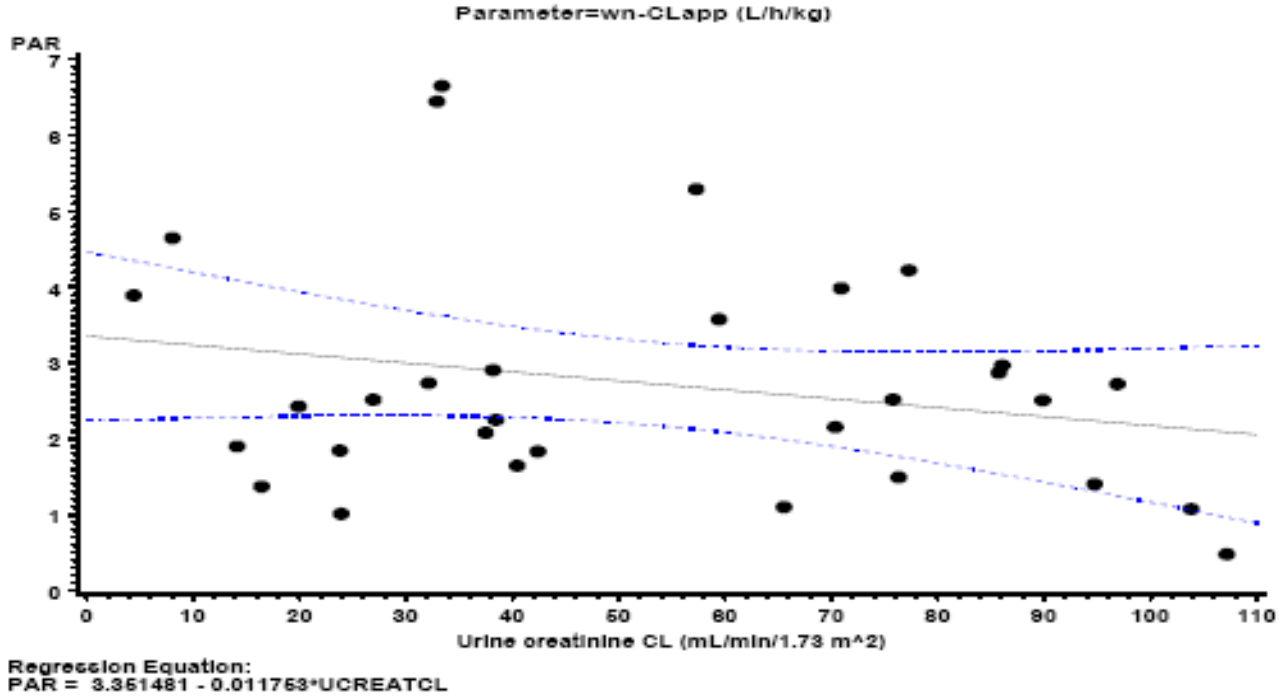


Table 103 Renal Impairment Study Individual Subject Demographic Characteristics- Study 25521

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^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

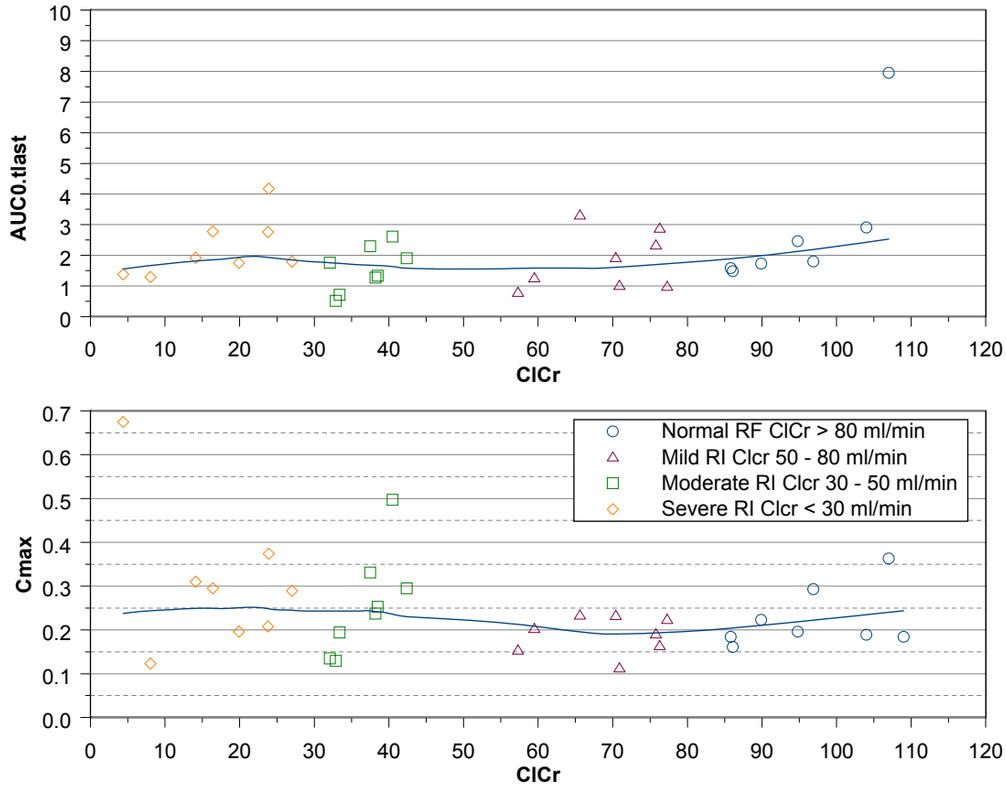


Table 106 Individual Asenapine Pharmacokinetic Metrics – Study 25521

Group	Subject	Cmax (ng/mL)	Tmax (h)	AUC_{0-12h} (ng*h/mL)	$AUC_{0-tlast}$ (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

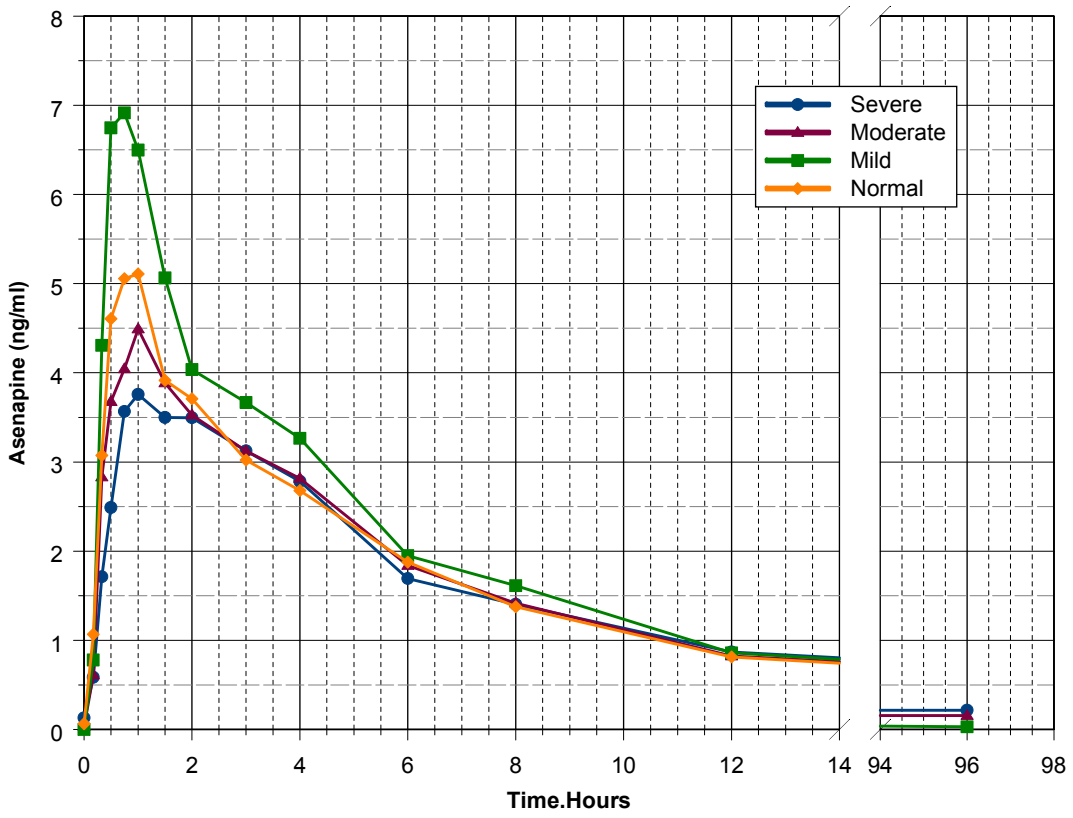


Figure 88 Mean Desmethyl-Asenapine Concentration vs. Time Profiles by Degree of Renal Function – Study A7501017

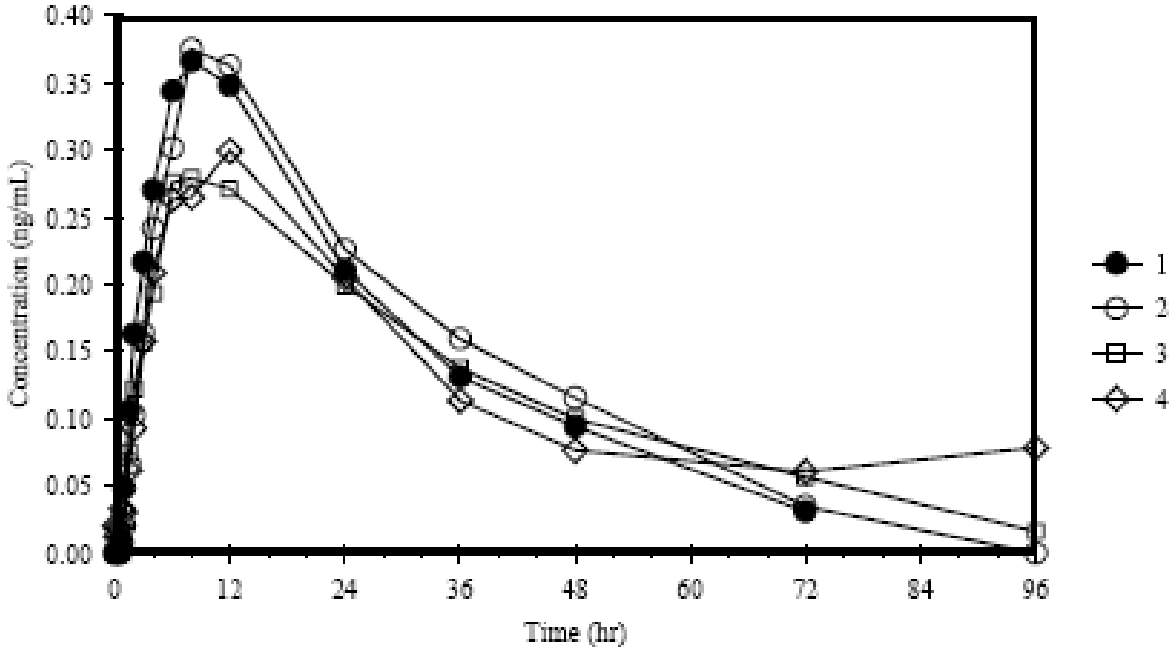


Figure 89 Plots of Asenapine AUCt, AUCinf, and Cl/F vs. Clcr – Study A7501017A

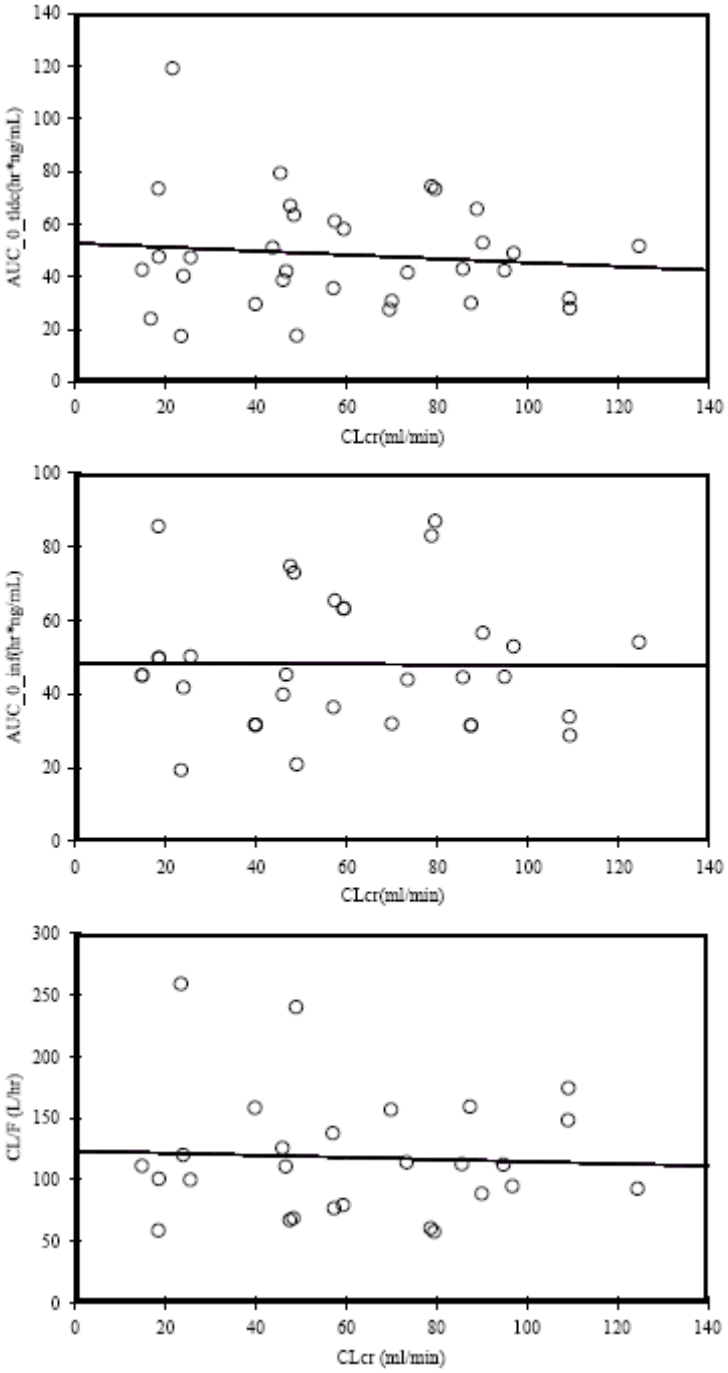


Figure 90 Plots of Desmethyl-Asenapine AUCt and AUCinf vs. Clcr – Study A7501017A

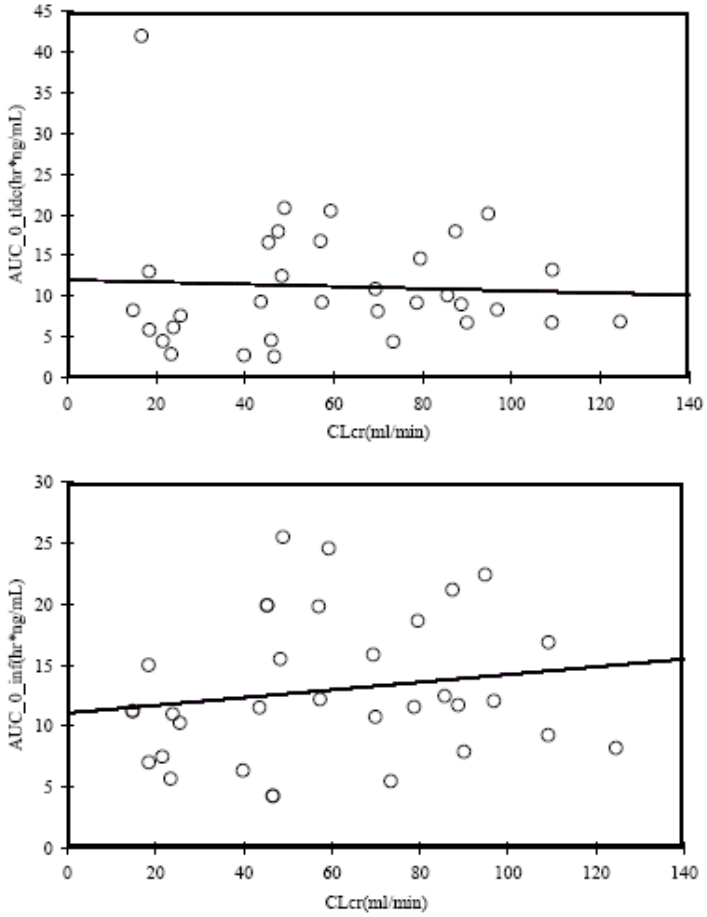


Table 108 Individual Subject Demographics for Renal Impairment Study A7501017

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			
t½ (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	Group 2	Group 3	Group 4
	Normal	Mild	Moderate	Severe
	>80 mL/min	51 - 80 mL/min	30 - 50 mL/min	<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

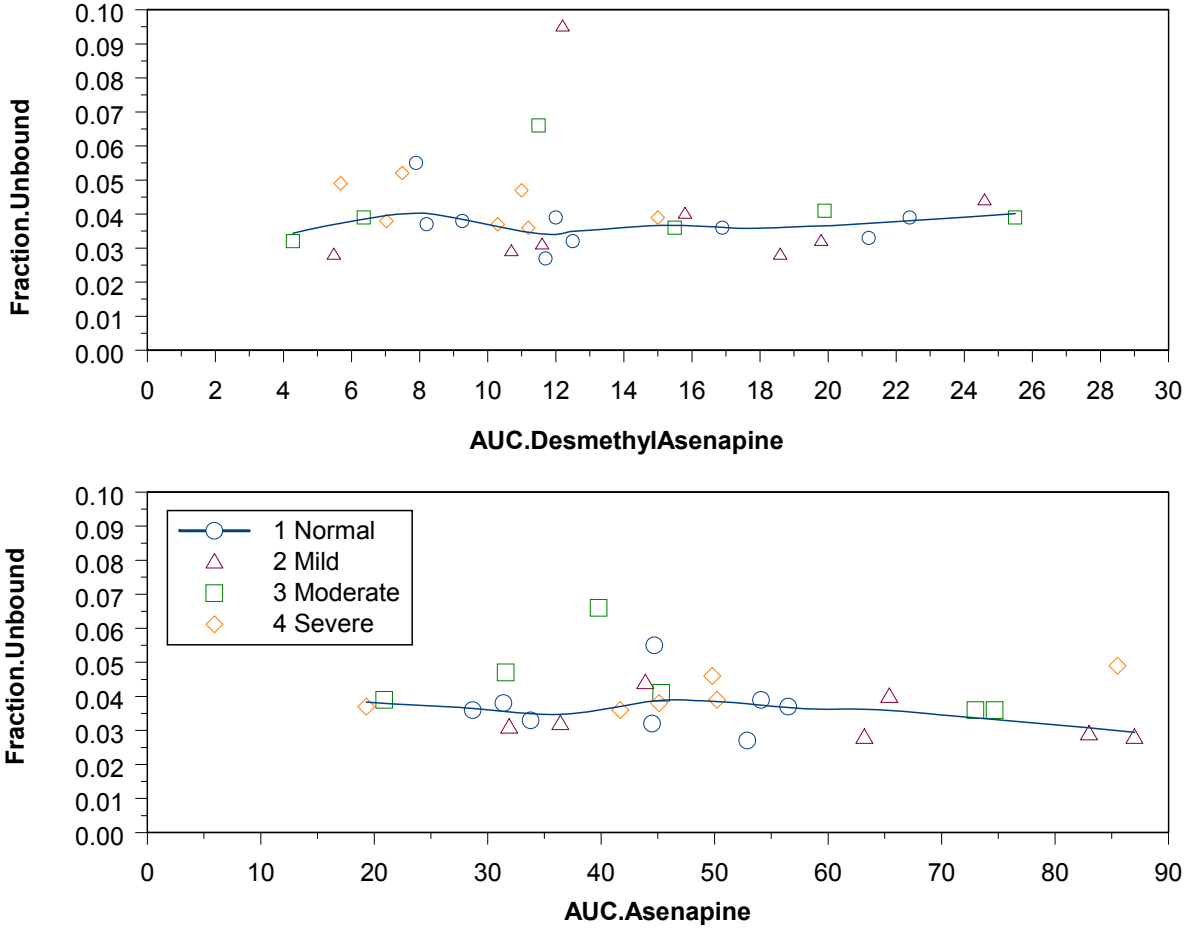


Figure 92 Desmethyl-Asenapine Unbound AUC vs. Creatinine Clearance – Study A7501017

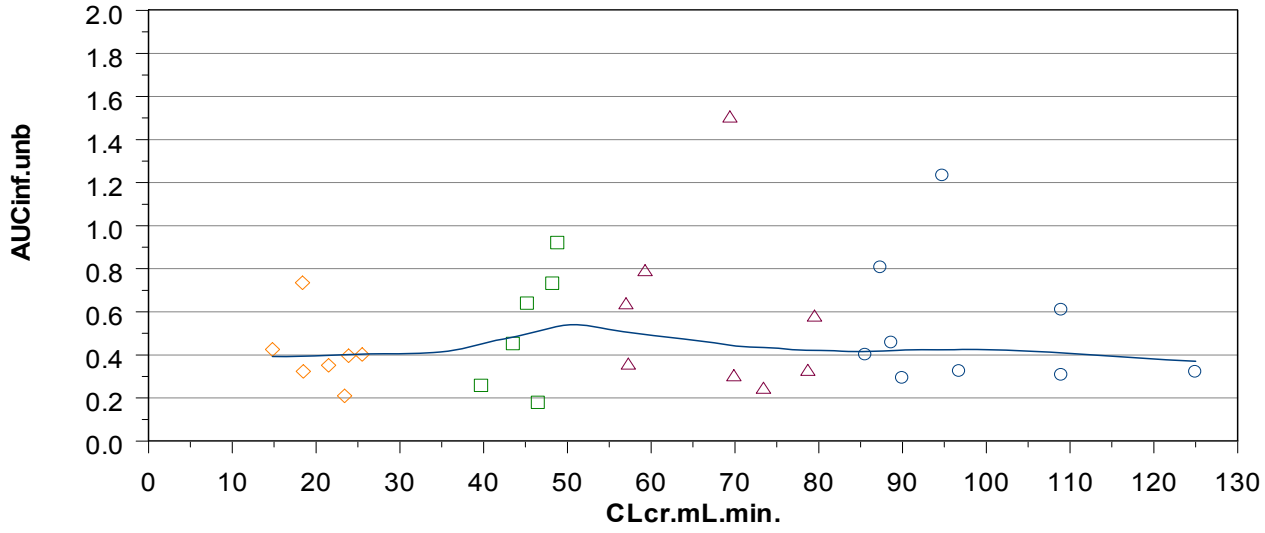


Figure 93 Desmethyl-Asenapine Total AUC vs. Creatinine Clearance – Study A7501017

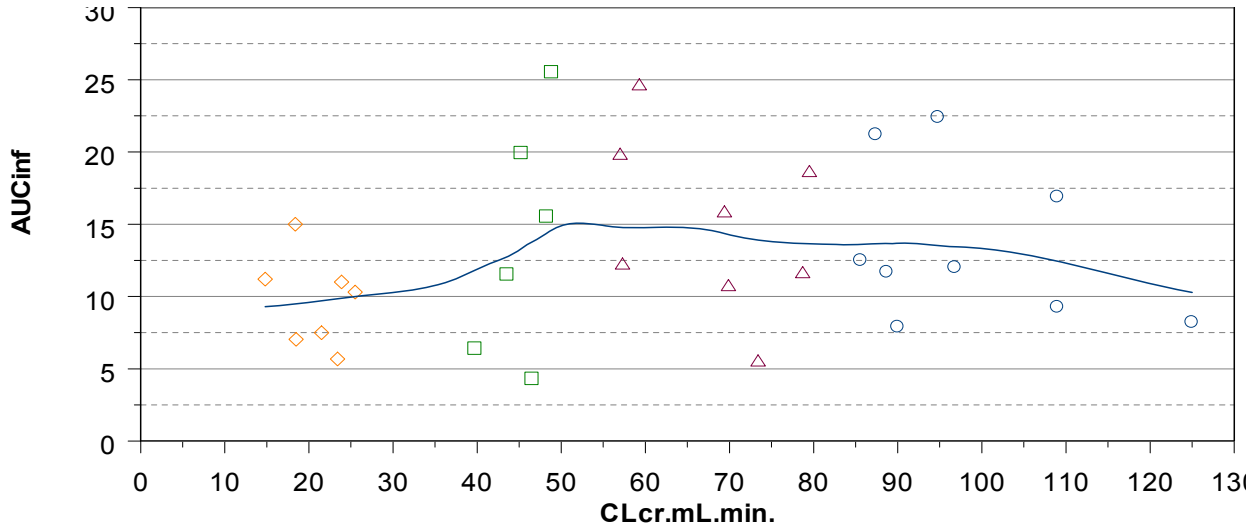
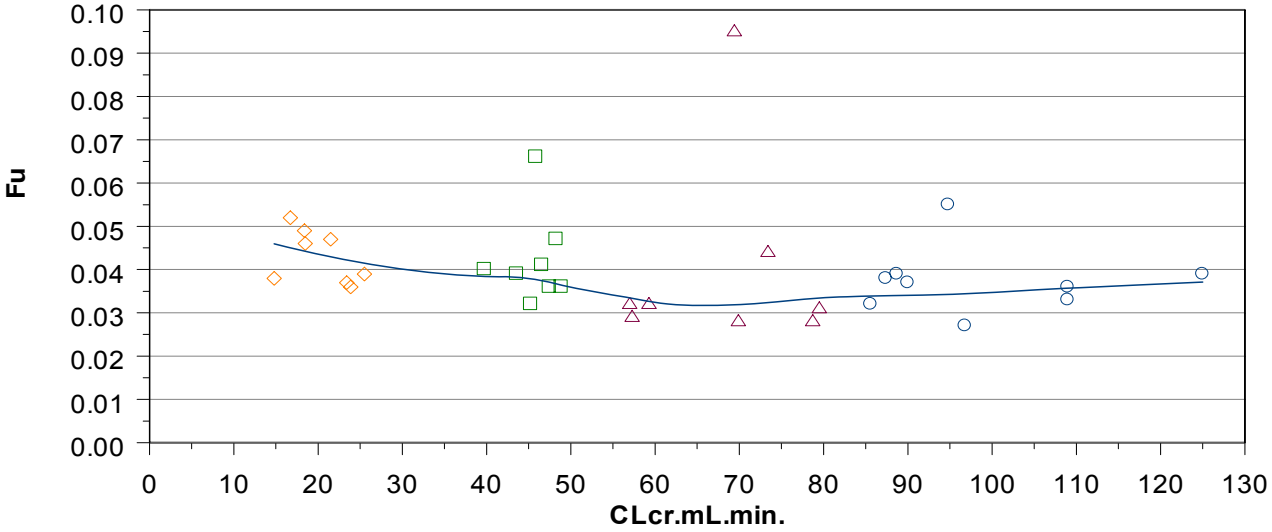


Figure 94 Asenapine Free Fraction vs. Creatinine Clearance



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

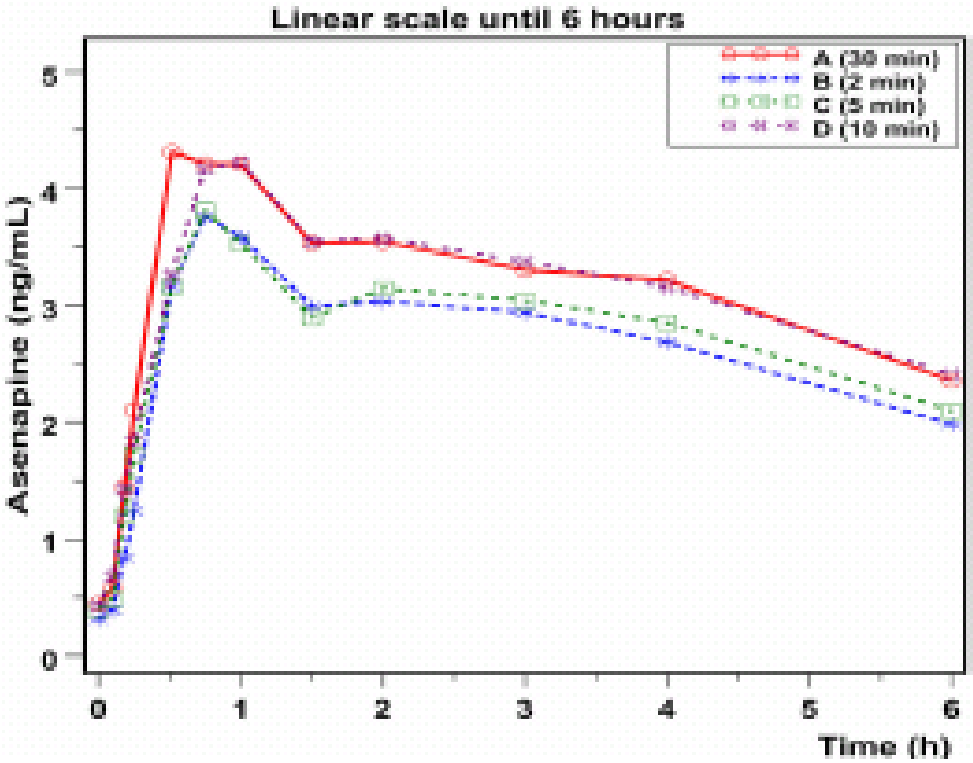


Figure 96 Asenapine Mean Steady-State 0 - 24 hour Concentration vs. Time Profiles when Water is taken at Various Times after Drug Administration – Study 25537

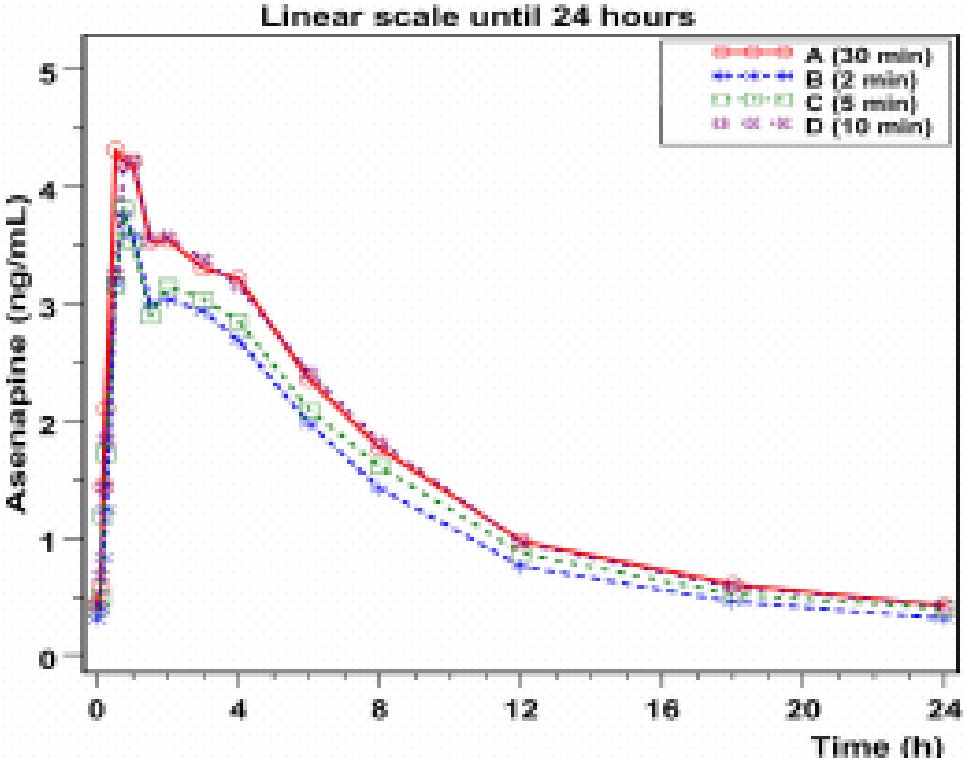


Table 114 Effect of Water at Varying Times on Asenapine and Desmethyl-aseanpine Pharmacokinetics after Asenapine 10 mg Sublingually – Study 25537

	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

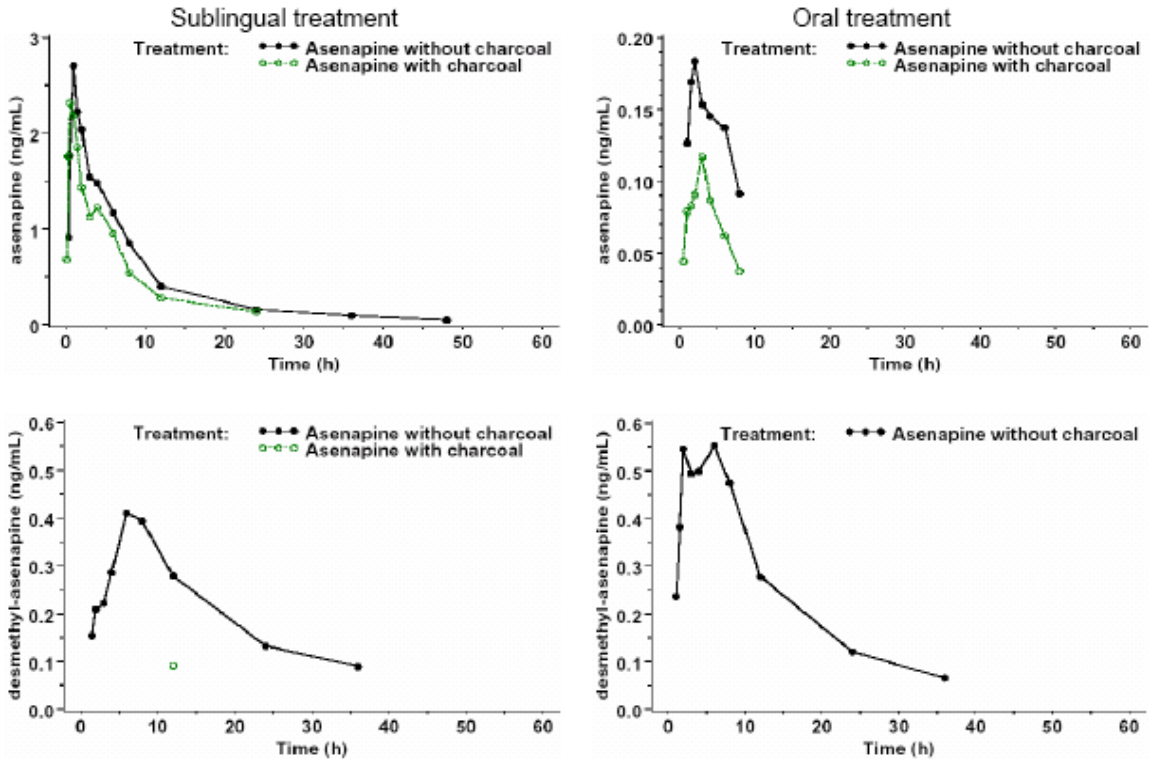
Study 25540 was an open label, randomized, parallel design single dose study in 16 healthy male volunteers to investigate the effect of concurrently administered activated charcoal to prevent gastro-intestinal absorption and to effect asenapine and desmethyl-asenapine pharmacokinetics after sublingual 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)
	t½ (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)
	t½ (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

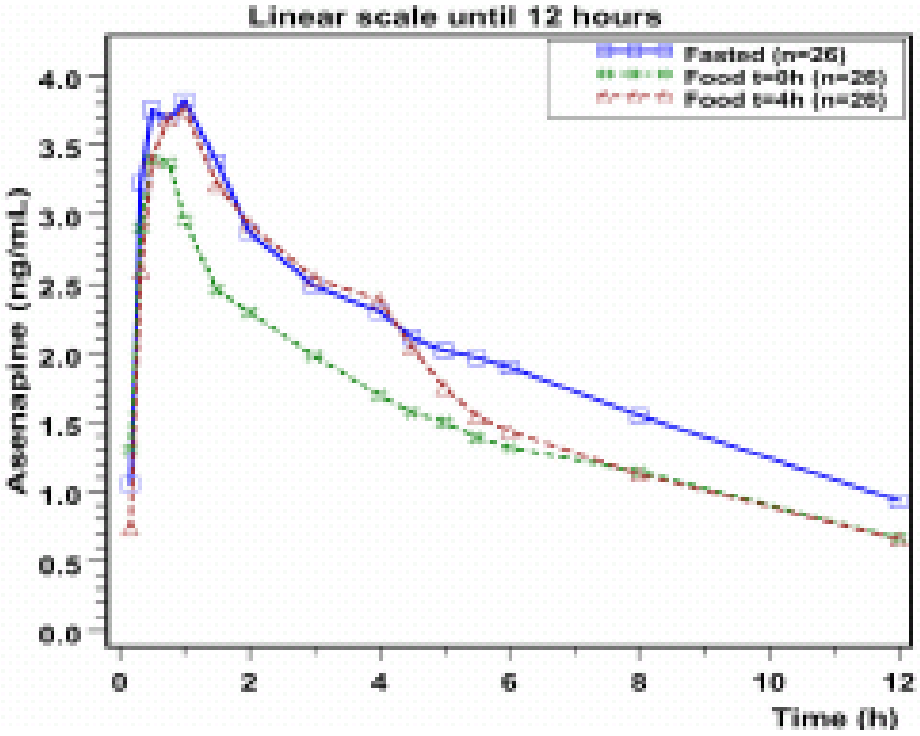


Figure 99 Effect of Food Administration on Desmethyl-Asenapine Mean Concentration vs. Time Profiles – Study 41029

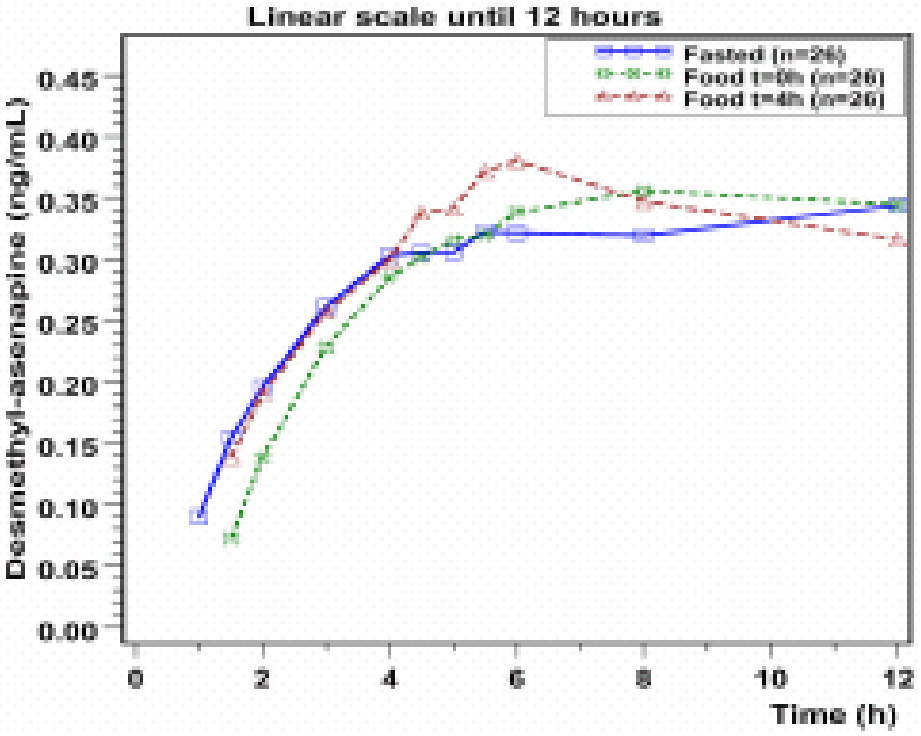


Figure 100 Effect of Food Administration on Asenapine Semi-log Mean Concentration vs. Time Profiles – Study 41029

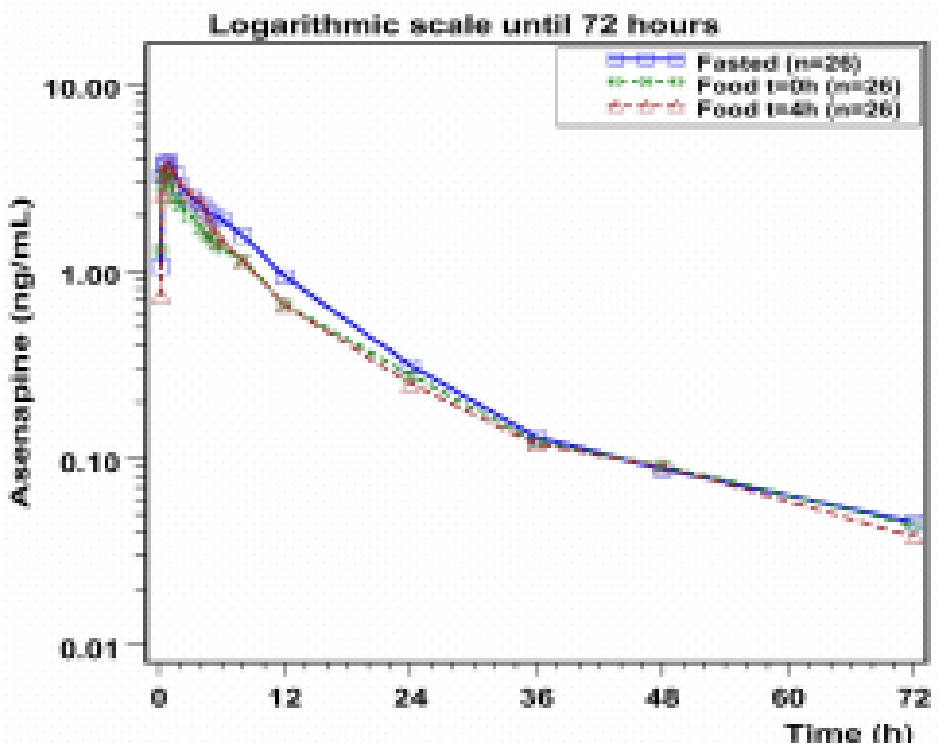


Figure 101 Effect of Food Administration on Desmethyl-Asenapine Semi-log Mean Concentration vs. Time Profiles – Study 41029

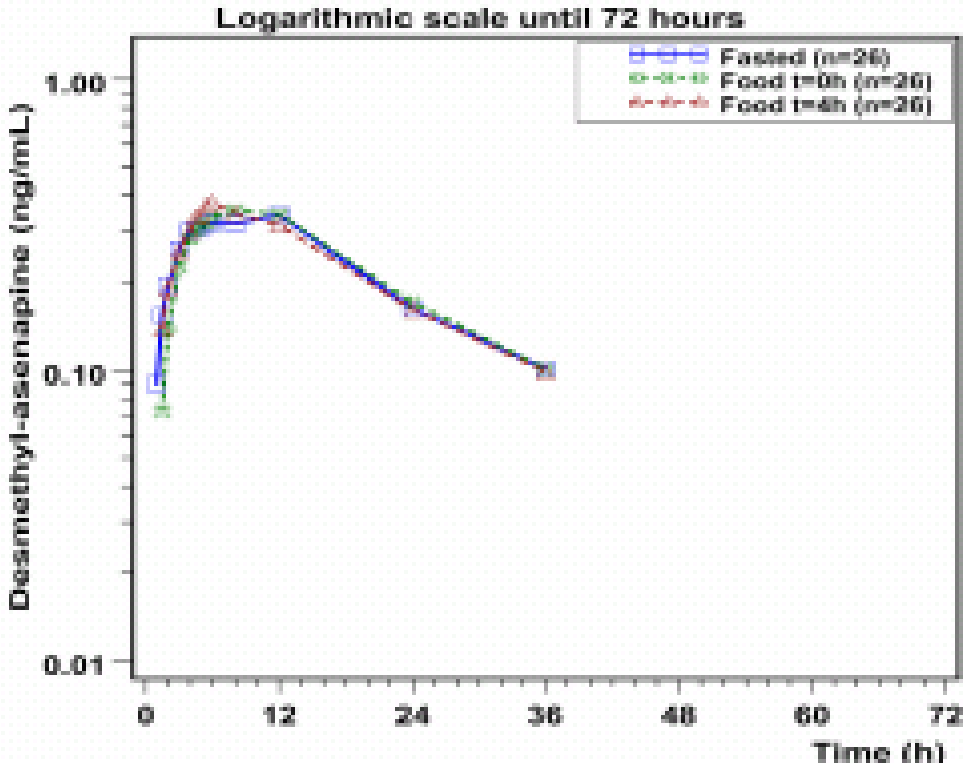


Table 116 Effect of Food on the Pharmacokineticsof Asenapine and N-Desmethyl-Asenapine after a Single Dose of Asenapine 5 mg Sublingually – Study 41029

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

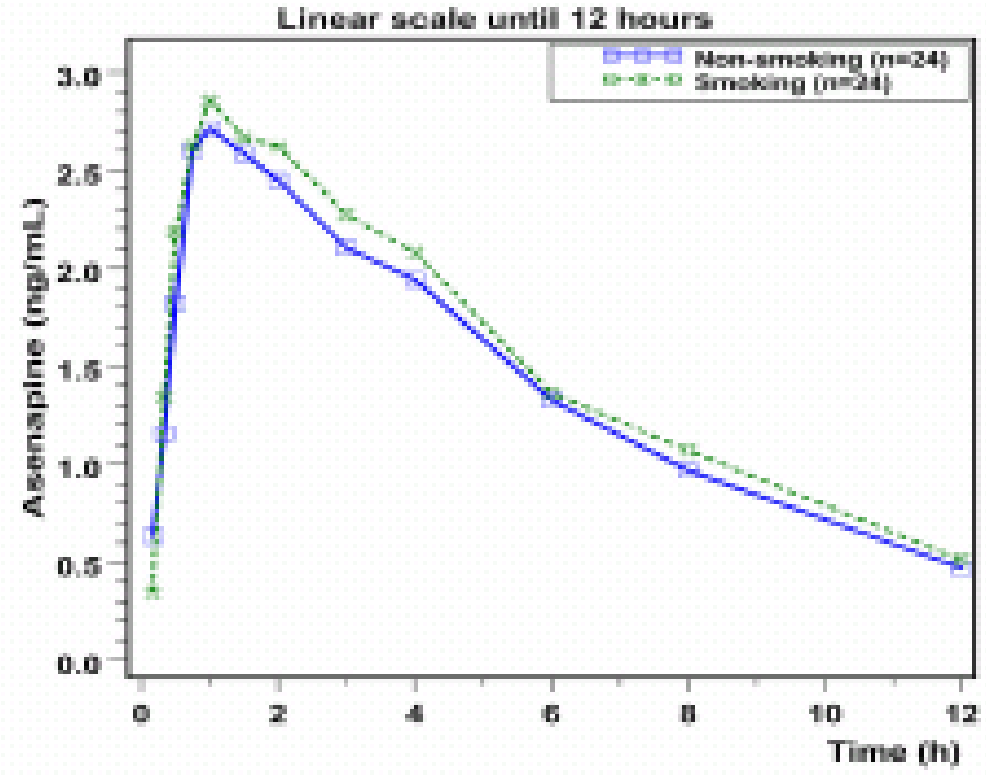


Figure 103 Mean Concentration vs. Time Profiles of Desmethyl-Asenapine in Chronic Smokers While Smoking and Not Smoking - Study 25545

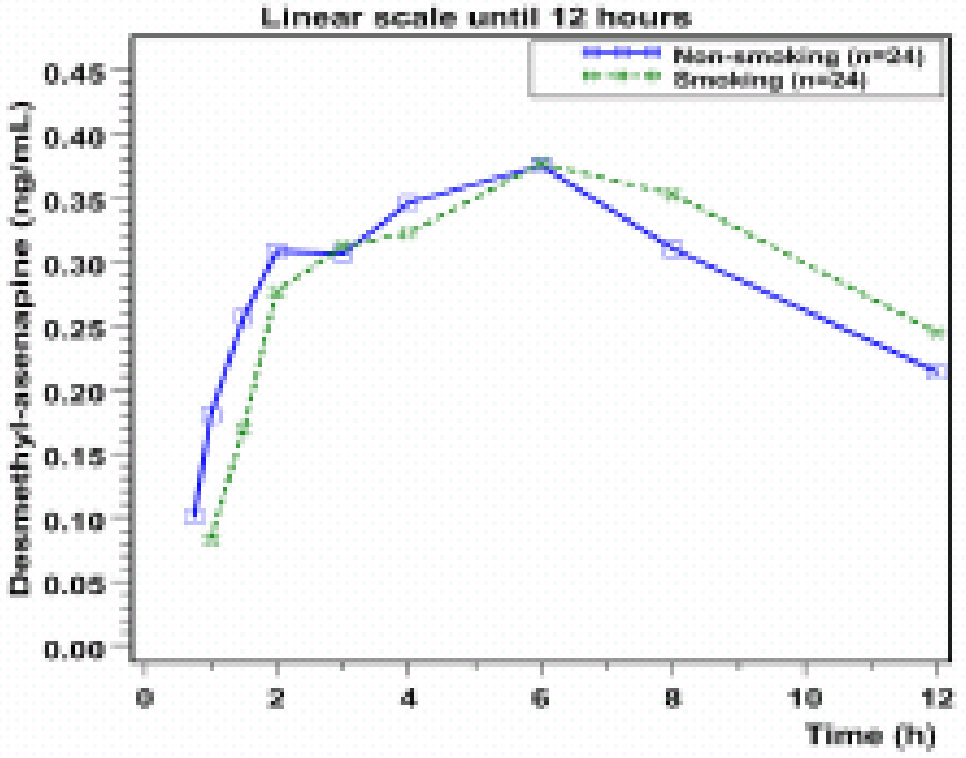


Table 117 Effect of Smoking a Cigarette on Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics in Chronic Smokers – Study 25545

	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 x 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.	–
t½ (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

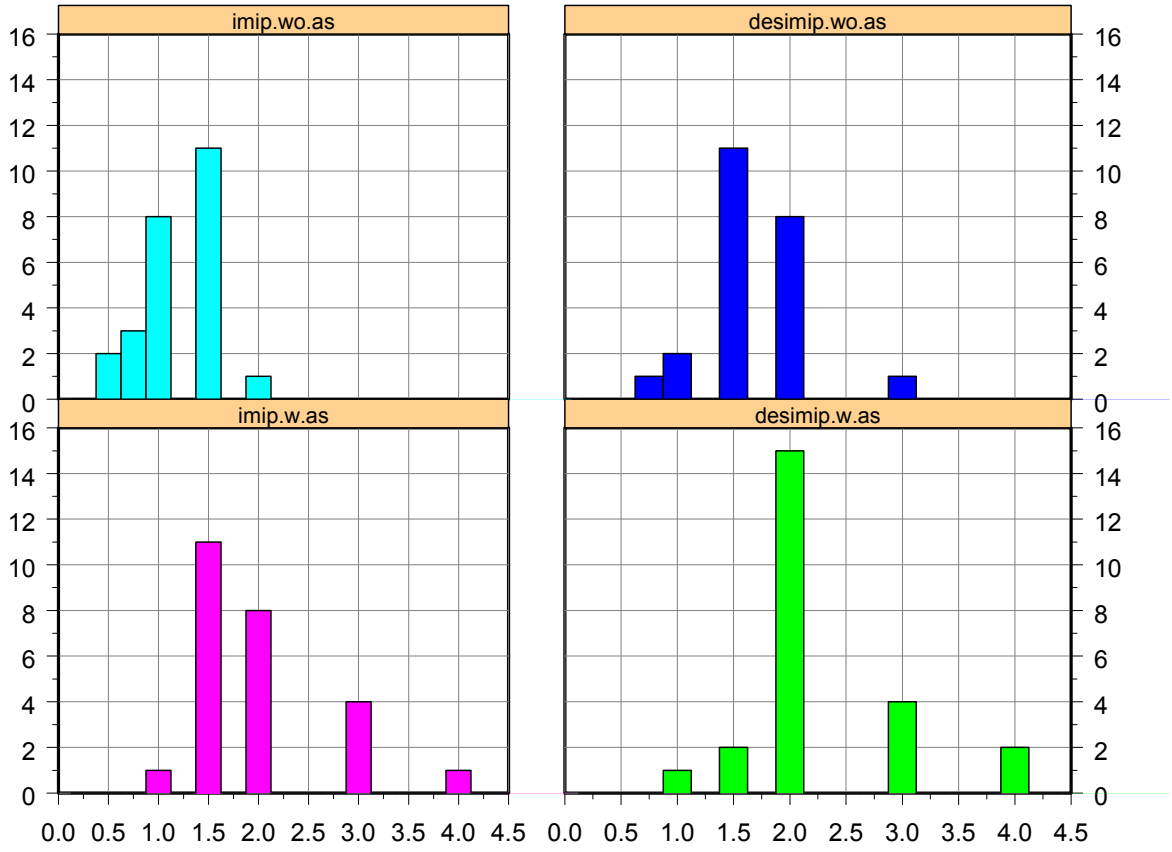
Analyte	Imipramine					Desipramine				
Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)
Parameter (unit)	Imipramine	Asenapine + Imipramine	Imipramine	Asenapine + Imipramine		Imipramine	Asenapine + Imipramine	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			
	Day 7			Paroxetine 20 mg PO QD	
	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

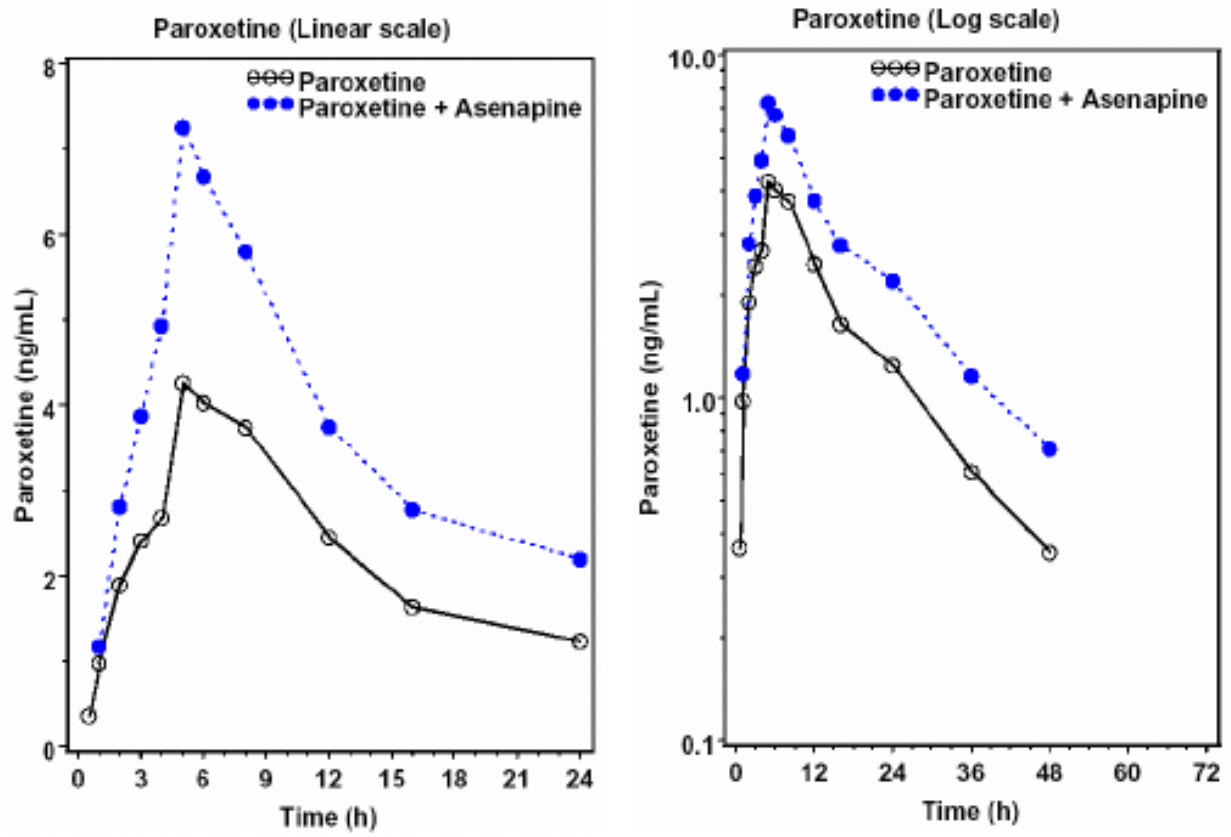


Table 123 Effect of Asenapine 5 mg SL BID on the Pharmacokinetics of Paroxetine 20 mg – Study 25525

	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).

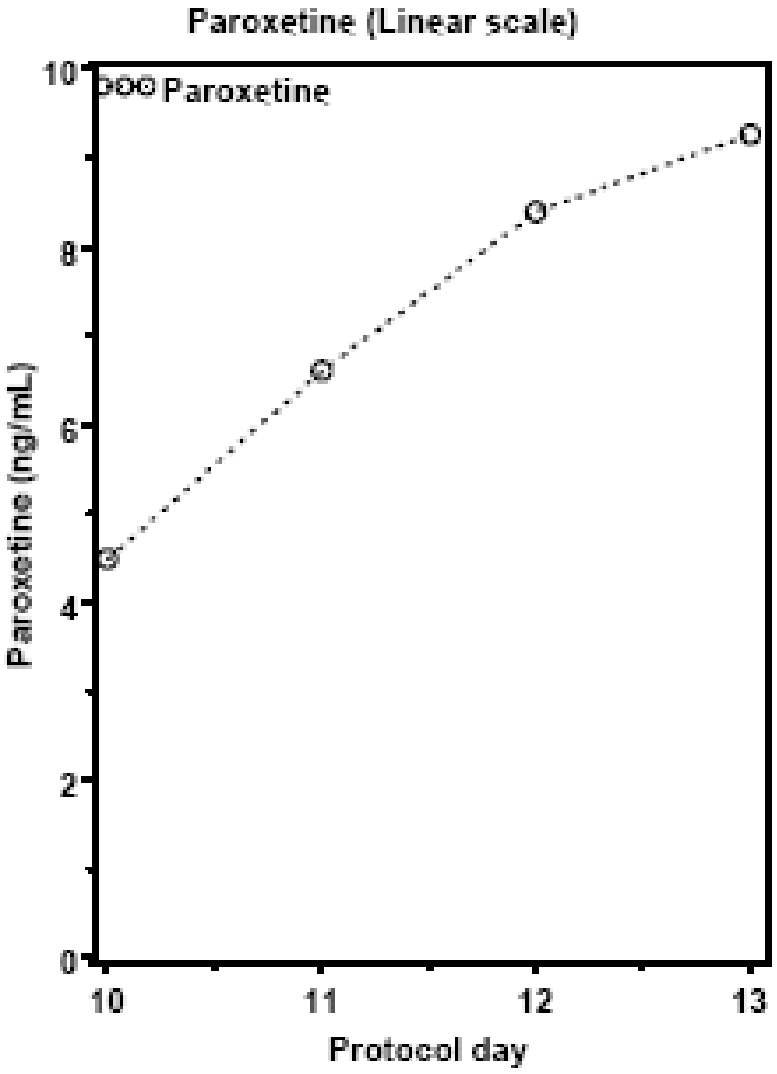
According to the sponsor,*"bioanalysis indicated that dextromethorphan interferes with the desmethyl-asenapine assay and as dextromethorphan was given 48 h before asenapine dosing in the second period this might be the explanation as washout from asenapine in first dosing period was long enough."*

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

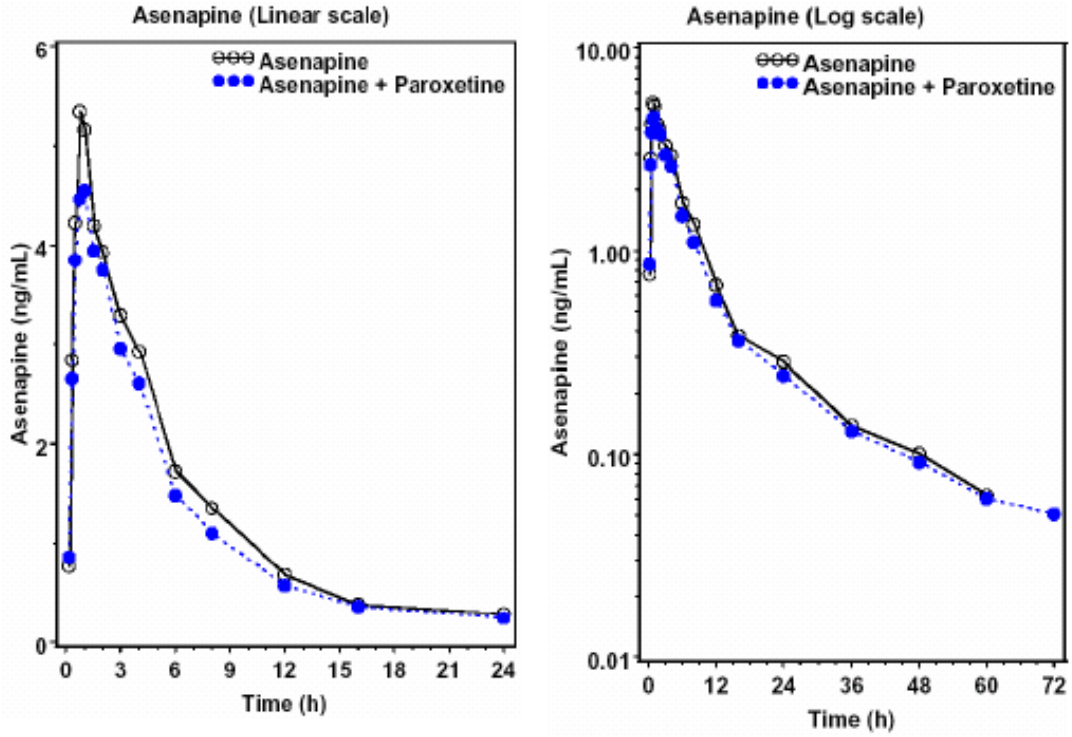


Figure 108 Single Dose Concentration vs. Time Profiles of Desmethyl-Asenapine after Asenapine 5 mg SL in the Absence and Presence of Paroxetine 20 mg qd in CYP2D6 EMs and PMs after a single 30 mg dose of Dextromethorphan – Study 25525

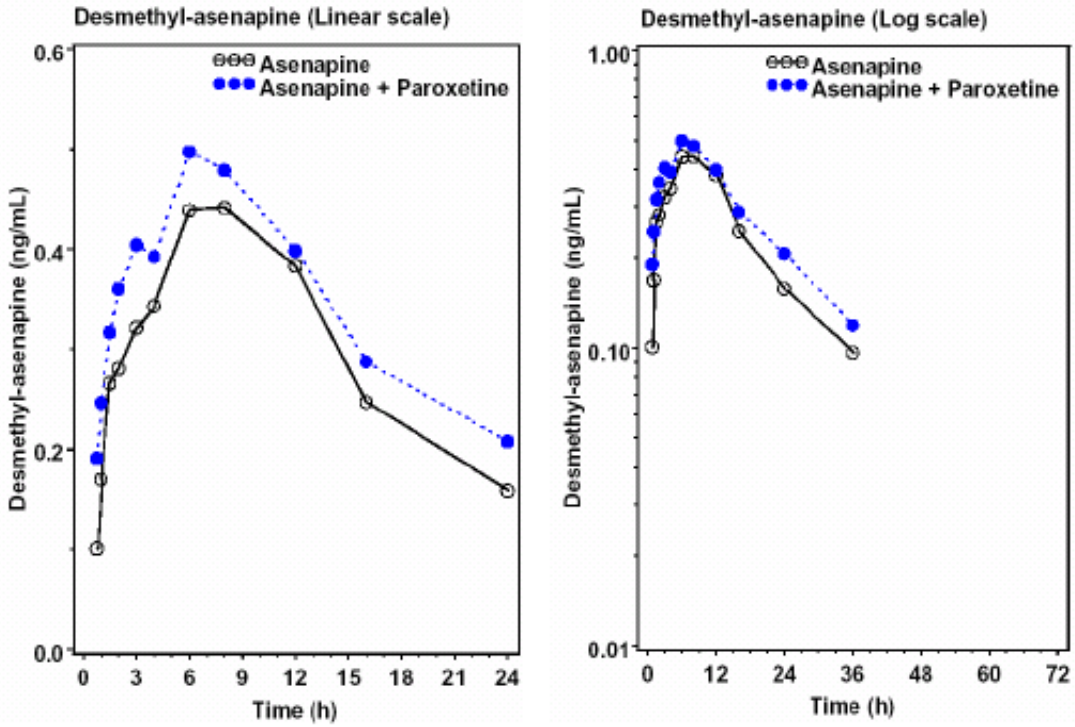


Table 125 Effect of Paroxetine 20 mg qd on the Pharmacokinetics of Asenapine 5 mg SL BID in Study 25525 Arm: [B] Asenapine vs. Asenapine + Paroxetine

	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.

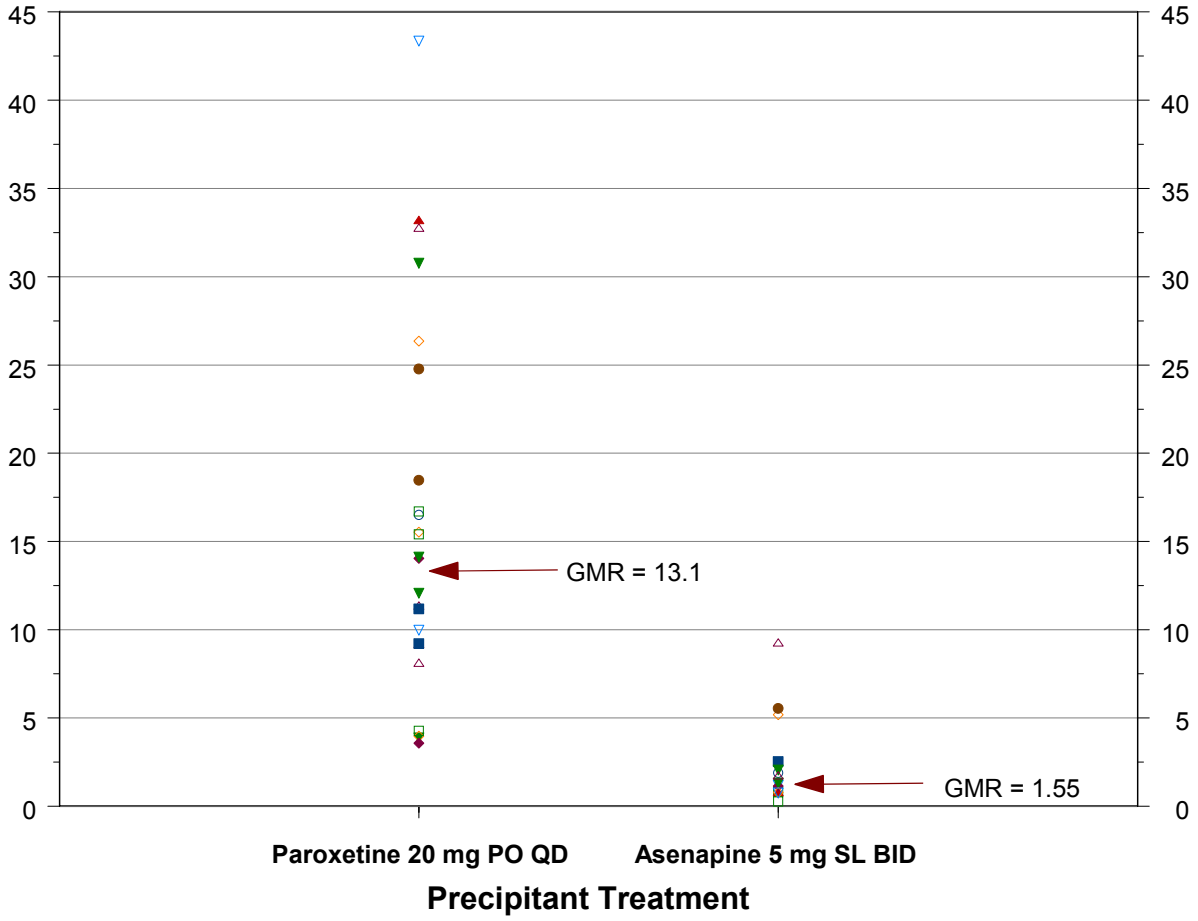
To demonstrate why comparing DX/DM ratios is flawed we need to remember that with inhibition the numerator DX will decrease and denominator DM will increase so the estimate of the degree of inhibition will be compounded consequently this is an invalid way of comparing the relative degree of inhibition 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

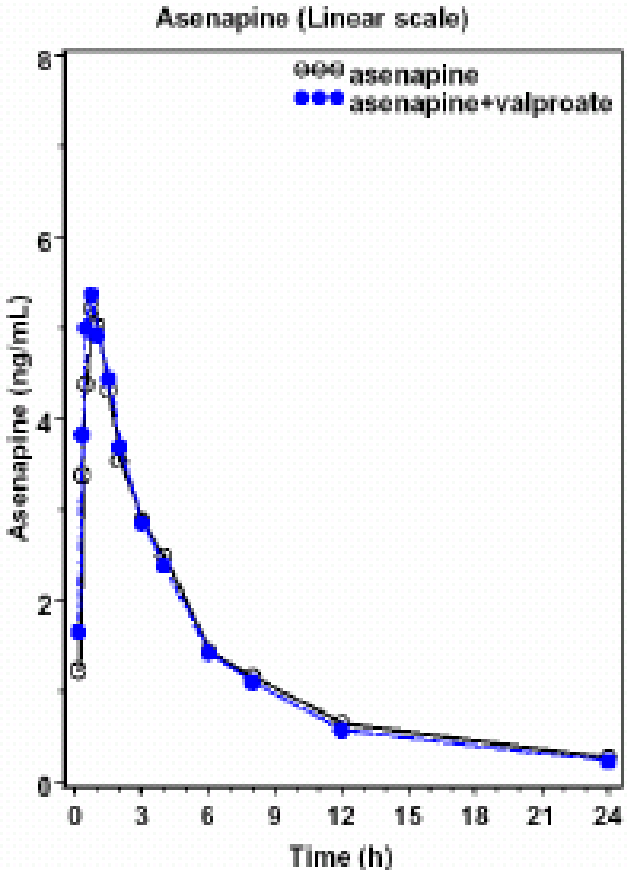


Figure 111 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Valproate – Study 25527

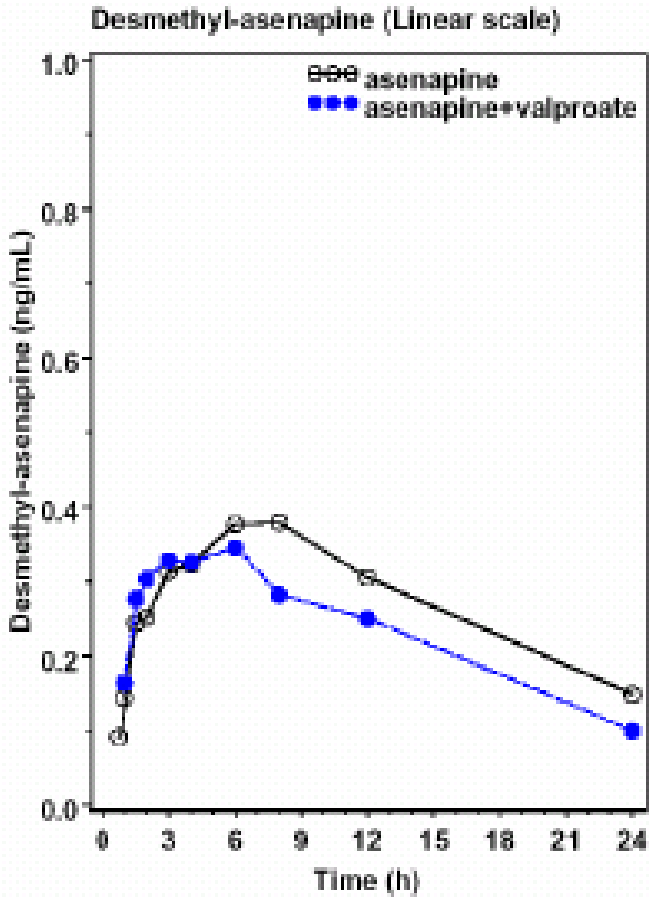
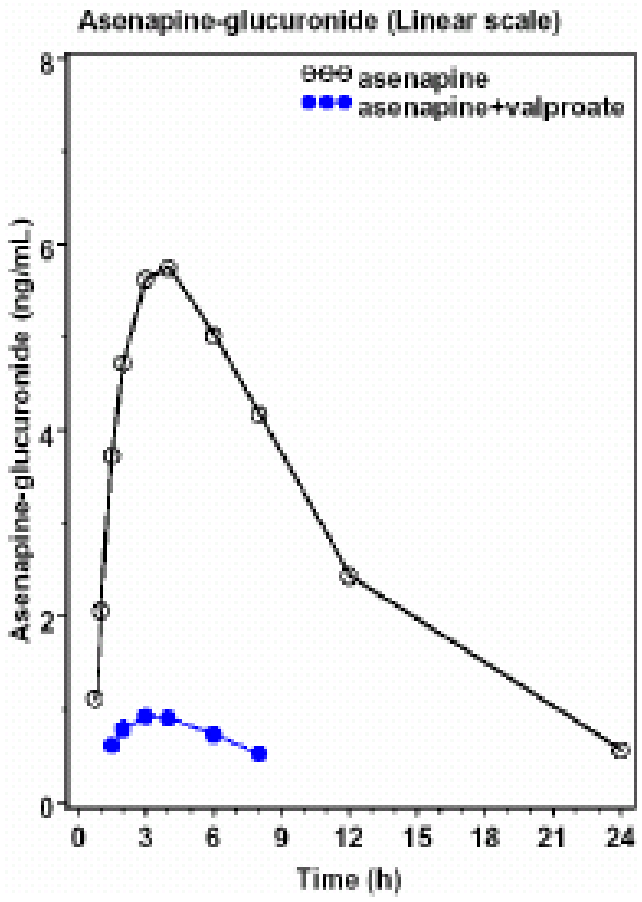


Figure 112 Mean Asenapine Glucuronide Concentration vs. Time Profiles in the Absence and Presence of Valproate – Study 25527



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

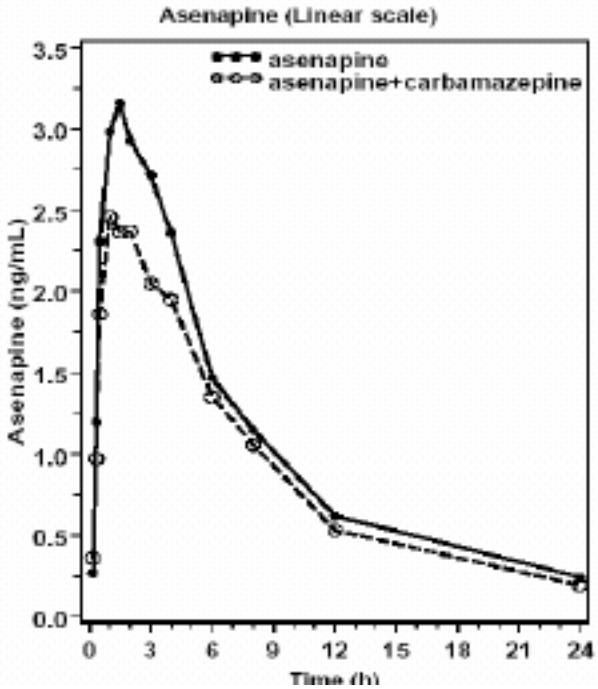


Figure 114 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Carbamazepine – Study 25528

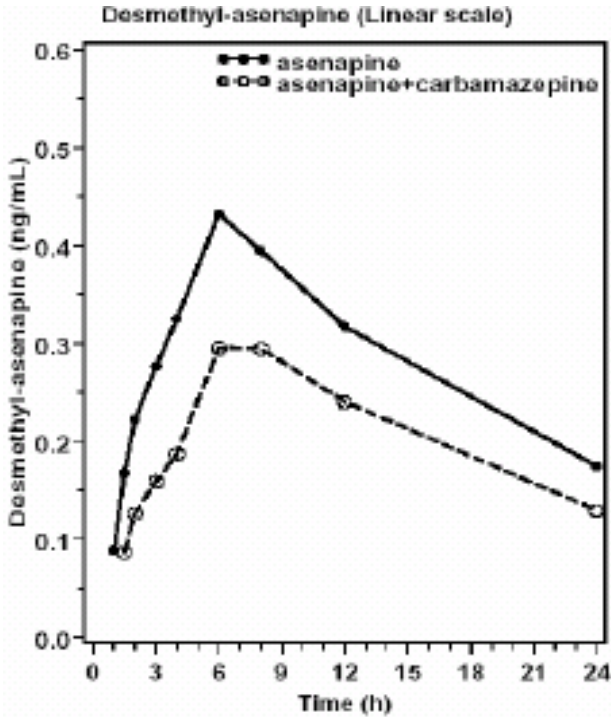


Figure 115 Mean Asenapine Glucuronide Concentration vs. Time Profiles in the Absence and Presence of Carbamazepine – Study 25528

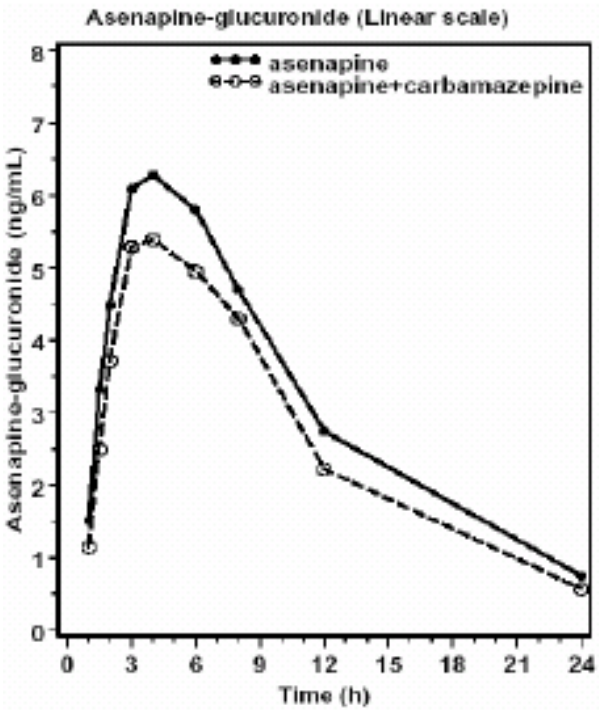


Table 134 Asenapine, Desmethyl-Asenapine, & Asenapine Glucuronide 5 mg SL SD PK Parameters in the Absence and Presence of Carbamazepine 400 mg PO BID – Study 25527

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

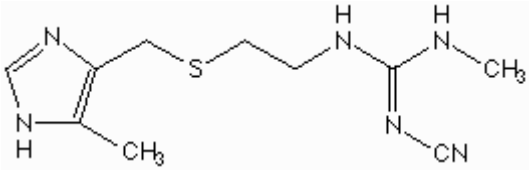


Table 136 to Table 138 show the effect of cimetidine on positive controls for P450 isozyme activity, there is a mean 34% decrease in CYP1A2 activity, a mean 75% decrease in CYP2D6 activity, and a mean 25% decrease in CYP3A4 activity.

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

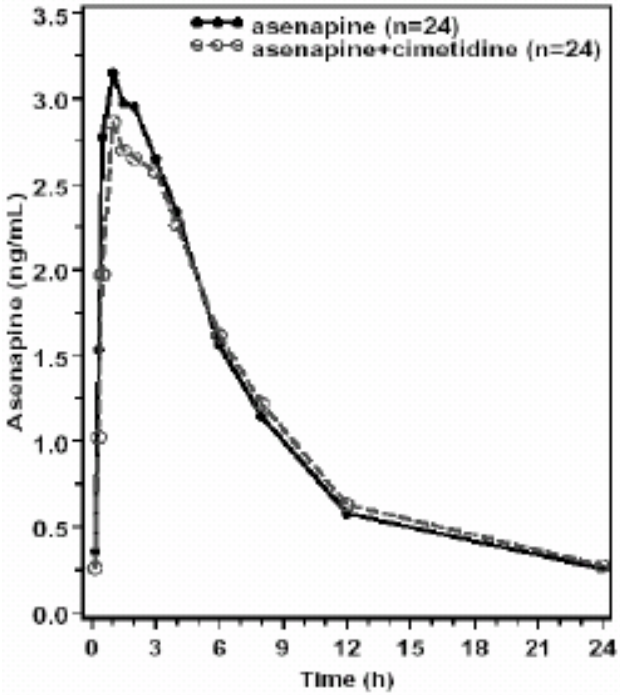


Figure 118 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Cimetidine – Study 25529

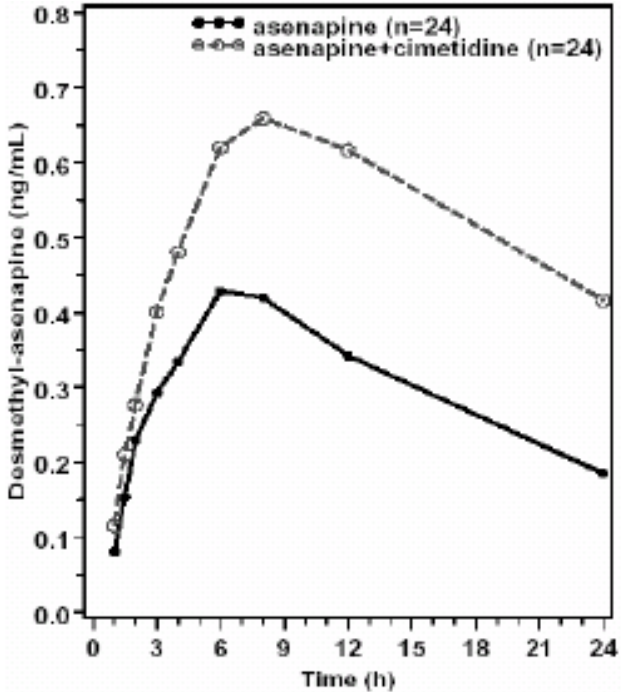


Figure 119 Mean Asenapine Glucuronide Concentration vs. Time Profiles in the Absence and Presence of Cimetidine – Study 25529

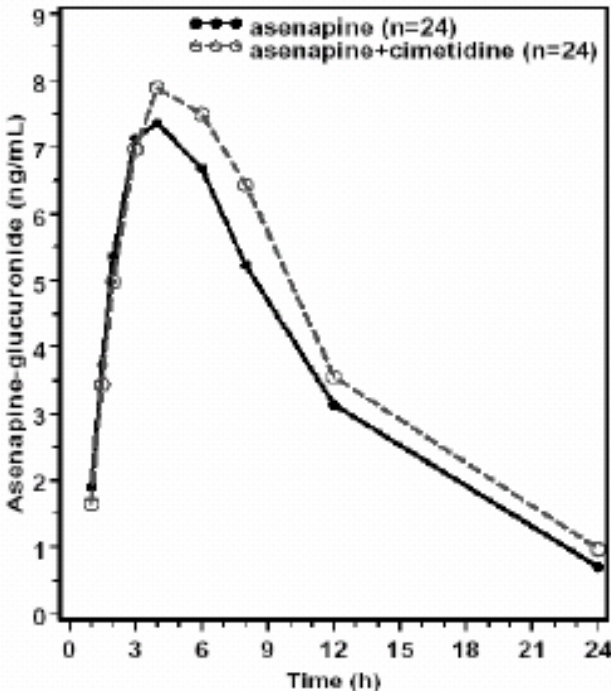


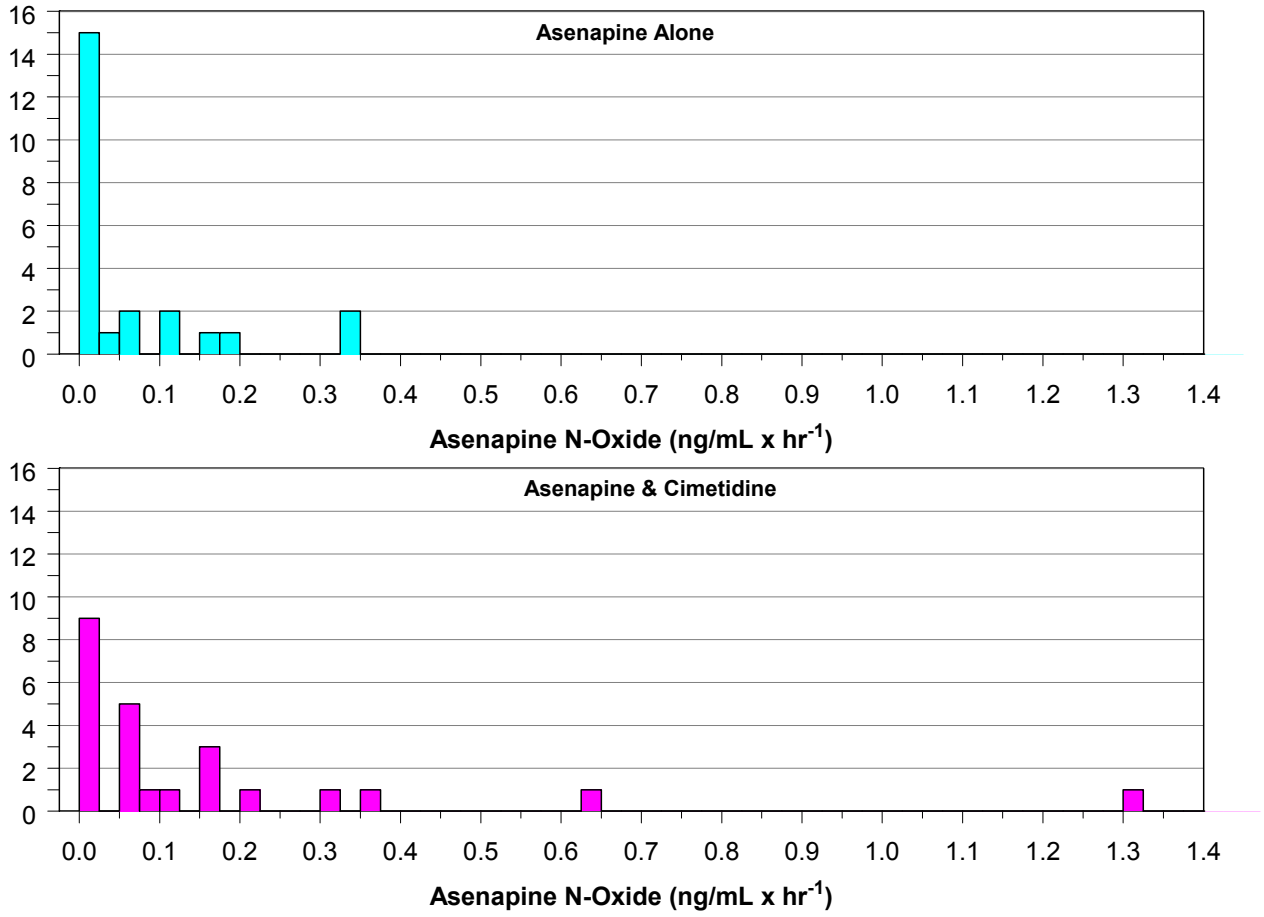
Table 139 Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide 5 mg SL Single Dose PK Parameters in the Absence and Presence of Cimeitdine 800 mg PO BID – Study 25527

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	—
t½ (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	Assessment 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	-19 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.
T**reatment 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.

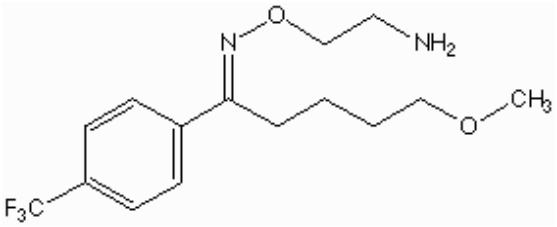
The inhibitory effect of fluvoxamine on CYP1A2 during treatment was assessed as follows:

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



<u>Results:</u>

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

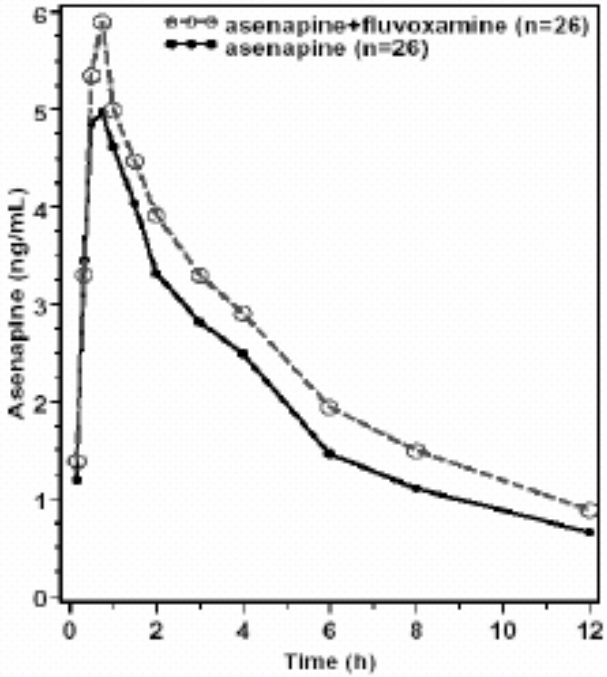


Figure 123 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Fluvoxamine – Study 41033

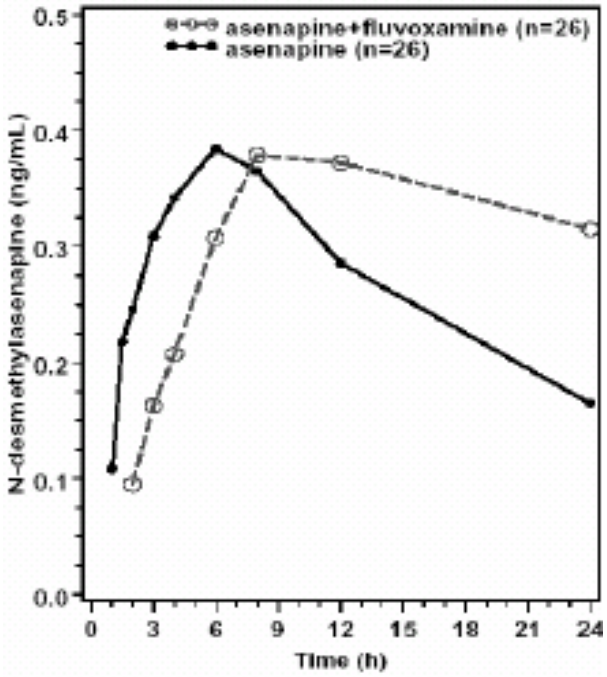


Figure 124 Mean Asenapine 11-O-Sulfate Concentration vs. Time Profiles in the Absence and Presence of Fluvoxamine – Study 41033

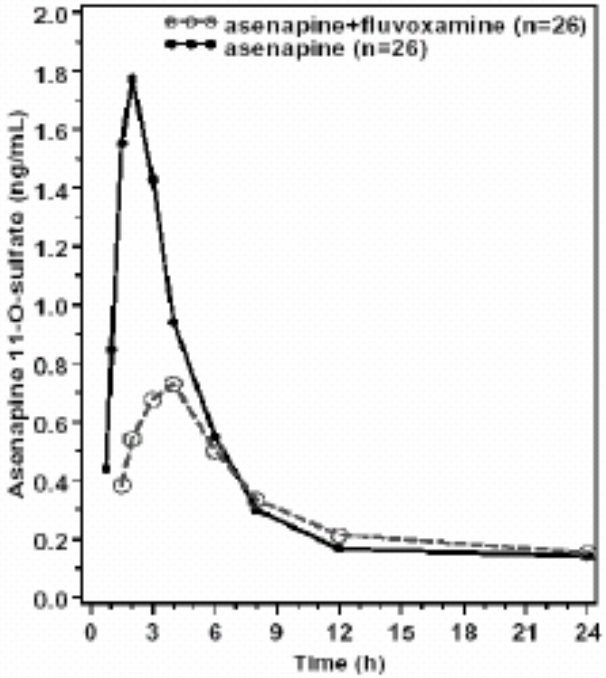


Table 142 Asenapine, Desmethyl-Asenapine, and Asenapine 11-O-sulfate 5 mg SL Single Dose PK Parameters in the Absence and Presence of Fluvoxamine 25 mg PO BID – Study 41033

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 x 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 x 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				
t½ (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:

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

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 H20	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

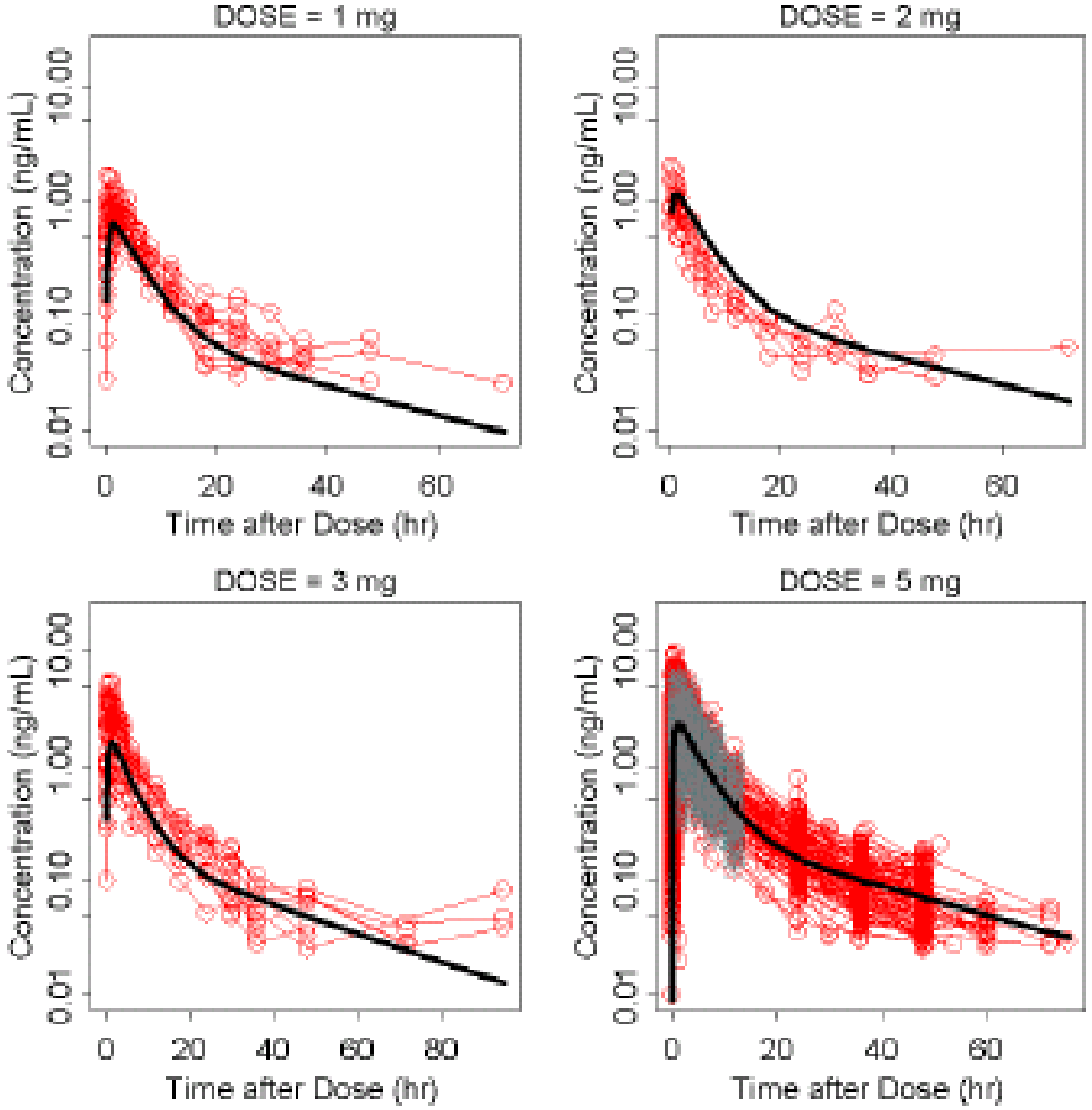
INT000656682

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]

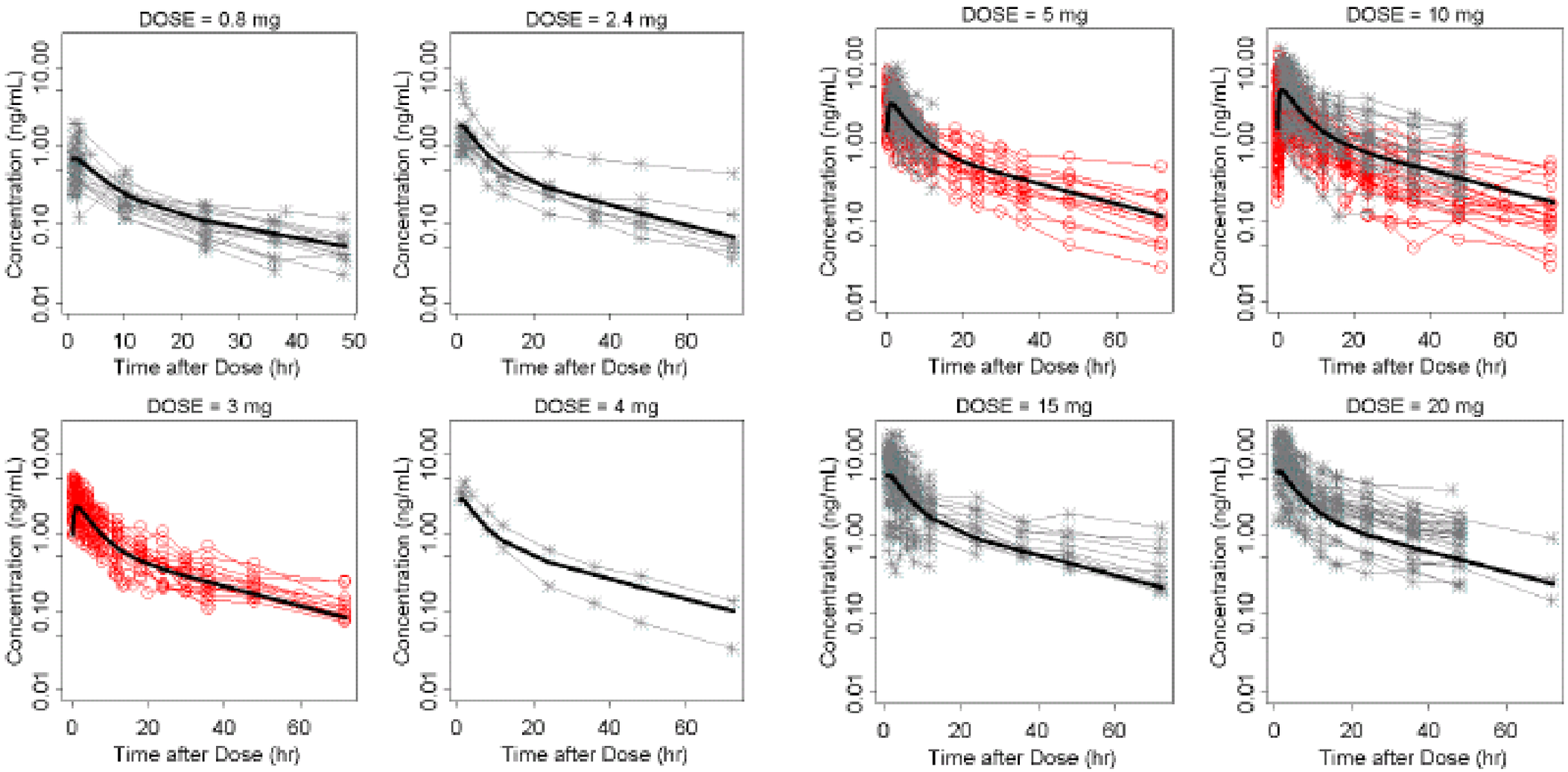
[9] Potential followup issue to be discussed with medical division as necessary.

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



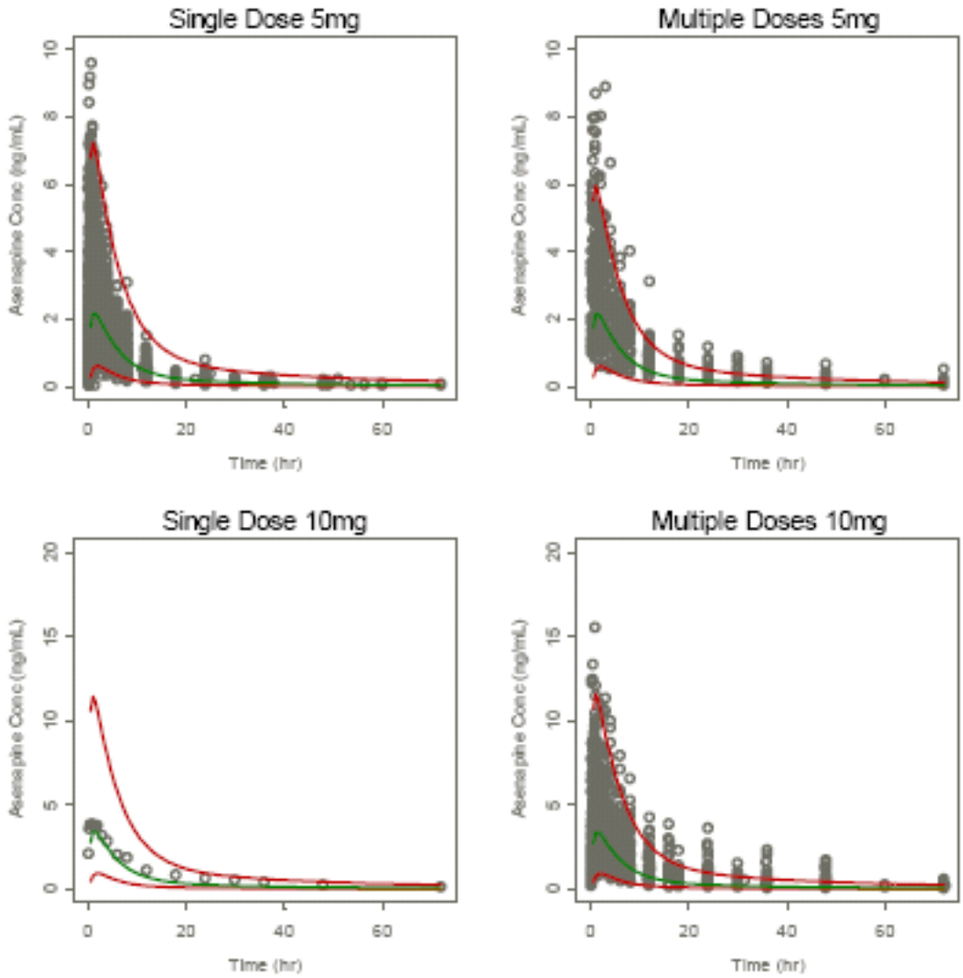
Red circles represent the observed asenapine concentrations from healthy volunteers; gray asterisks represent the observed asenapine concentrations from patients with schizophrenia. Solid lines represent the typical individual (population) predictions obtained from the final base model.

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



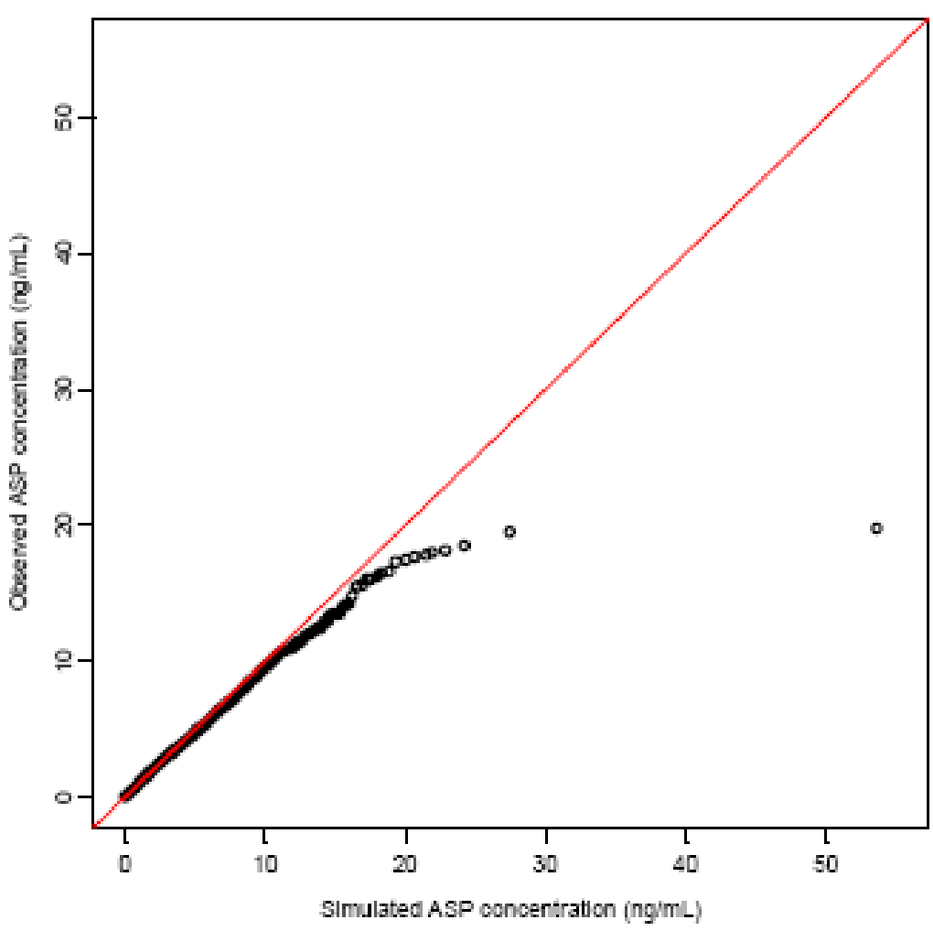
Red circles represent the observed asenapine concentrations from healthy volunteers; gray asterisks represent the observed asenapine concentrations from patients with schizophrenia. Solid lines represent the typical individual (population) predictions obtained from the base model.

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.

5.5.8.2 Phase II and Phase III Efficacy Studies

Validation of the pop PK model developed using the phase I and II data was done utilizing data from the phase II and III acute efficacy studies. The sponsor's description of this validation process follows:

'The final population pharmacokinetic model described above <in the previous section> was utilized, without modification, in this analysis to simulate asenapine concentration data to create unconditional prediction intervals (UPI). The UPI is an uncertainty interval that reflects model predicted variability at the individual observation level. The UPI was used to assess whether the observed data were consistent with the population PK model developed previously. Consistency between the model and the data can be determined by comparing the percentage of observations below or above the UPI distribution percentiles (e.g., a 90% UPI should contain 90% of the observed data). Since the UPI addresses data at the observation level, residual variability (as well as between patient variability) is included in its calculation. The term 'unconditional' is utilized in the name of this prediction interval to indicate that uncertainty in the residual variability estimate is incorporated within the interval unlike the prediction interval typically computed for regression analyses. Since a closed form expression for the UPI is not available for nonlinear mixed effects models, it is computed using simulation. To this end, a parametric bootstrap procedure was implemented, which is described below.

Each simulation dataset contained 1000 subjects and 500 replicates of simulated dataset per dose were generated to create unconditional prediction intervals. The simulations consisted of the following three steps.

1. Simulation Data Shell Generation: Using Splus 6.2, 1000 subjects records were created with missing DV for steady state. Time after dose in hours as a predictor variable were created ranging from 0 to 48 hours in an increment of 0.5 hours for every subject. As black race on ke was a significant covariate, uniform random numbers were used to generate 34% (observed black race population proportion in Phase 2/3 datasets) of black race patients among the 1000 subjects in the shell dataset.

2. Simulation: Using PERL scripts, the NONMEM output of the Phase 1/2 was parsed and multivariate normal random sampling was performed with mean of parameters estimates and variance of the variance-covariance matrix (N=500). Then each sample parameter vector was replaced into the NONMEM script and changed estimation into simulation with a different seed resulting in a simulated dataset for all 500 replicates.

3. Post Processing: All the simulated concentrations were combined and at each time point 5th, median, and 95th percentiles were calculated. The unconditional prediction intervals based on the previous population PK model were generated to assess similarities/differences in the results from the Phase 2/3 studies versus the Phase 1/2 studies.'

A listing of the studies utilized is shown in Table 151 and demographic characteristics are shown in Table 152. Although the sampling was not intensive Table 151 shows that sampling was adequate and better than is usually seen.

Figure 129, Figure 130, Figure 131, and Figure 132 on the following pages show observed asenapine concentrations from phase II and III studies overlaid on simulated 90% confidence intervals based on the phase I / II pop PK model. Figure 129 shows all phase II and phase III data from the acute efficacy studies by dose. Figure 130 shows data by dose and indication. Figure 131 shows data from the thorough QT study, and Figure 132 shows data from each individual acute efficacy study by indication and dose.

Again maximal peak concentrations appear to be around 20 ng/ml however inspection of the datafile reveals a maximum concentration of 9.99 ng/ml with a dose of 10 mg and on two concentrations at a dose of 20 mg with the highest reported concentration being 2.64 ng/ml. In addition, there are listings for lithium and valproate concentrations and the data definition file includes these in the phase I/ II data sets also even though these drugs were not coadministered in the phase I and II studies modeled.

Table 151 Phase II and III Acute Efficacy Studies included in Population Pharmacokinetic Modeling

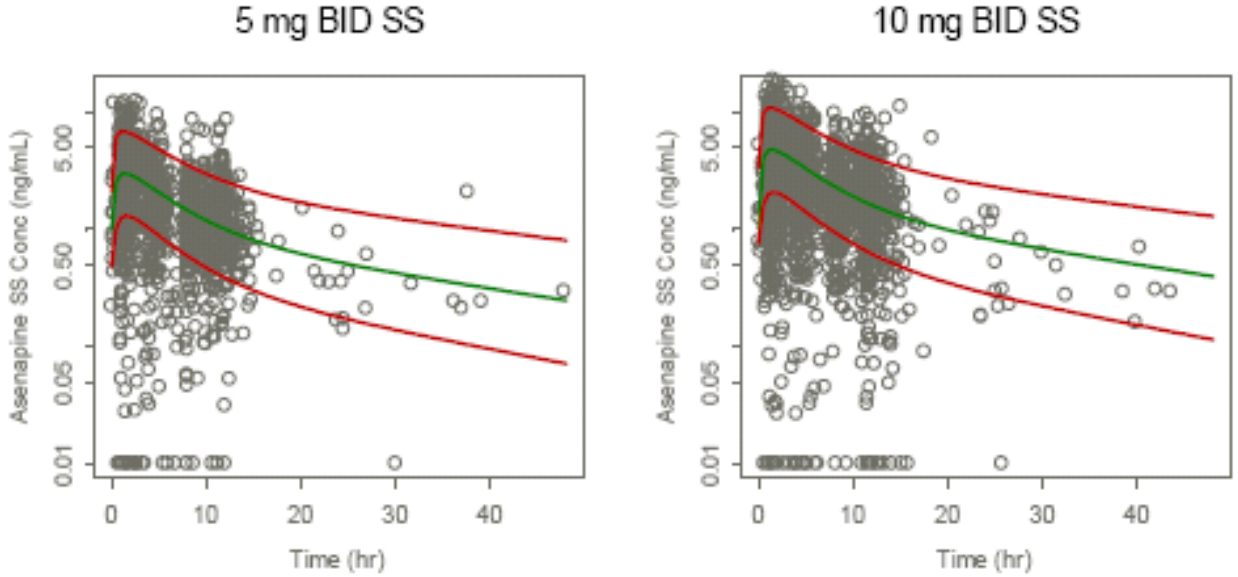
Study # (Phase)	SD / MD	Study Title	Subject Population	Treatment	Analytic Method	LLOQ (ng/mL)	PK Sampling Times
041004 (2b)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine, risperidone and placebo in acute exascerbation of schizophrenia	Acute Schizophrenia	Day 1: 1 mg BID Day 2: 2 mg BID Day 3: 3 mg BID Day 4: 4 mg BID Day 5-42: 5 mg BID	GC-MS	0.020	***Days 0, 7 & 21:*** 1-2 hours before AM dose. ***Day 7:*** 1-3, 4-6, and 8-12 hours postdose. ***Day 42:*** postdose
041021 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,olanzpaine, and placebo in acute exascerbation of schizophrenia	Acute Schizophrenia	5 or 10 mg BID up to 42 days	LC-MS	0.025	***Screening. Day 14:*** predose, 1-3, 4-6, 8-12 hours. ***Day 28:*** 1-8 hours. ***Day 42:*** Within 24 hours postdose.
041022 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,olanzpaine, and placebo in acute exascerbation of schizophrenia	Acute Schizophrenia	5-10 mg BID up to 42 days	LC-MS	0.025	***At screening. Day 14:*** predose, 1-3, 4-6, 8-12 hours. ***Day 28:*** 1-8 hours. ***Day 42:*** Within 24 hours postdose.
041023 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,haloperidol, and placebo in acute exascerbation of schizophrenia	Acute Schizophrenia	5 or 10 mg BID up to 42 days	LC-MS	0.025	***At screening. Day 14:*** predose, 1-3, 4-6, 8-12 hours. ***Day 28:*** 1-8 hours. ***Day 42:*** Within 24 hours postdose.
A7501004 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,olanzpaine, and placebo in inpatiens with an acute manic episode	Acute Mania	5-10 mg BID for 21 days	LC-MS	0.025	***Day 1, 7, 14 and 21:*** predose. ***Day 7:*** 1-3, 4-6, 8-12 hours postdose.
A7501005 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,olanzpaine, and placebo in inpatiens with an acute manic episode	Acute Mania	5-10 mg BID for 21 days	LC-MS	0.025	***Day 1, 7, 14 and 21:*** predose. ***Day 7:*** 1-3, 4-6, 8-12 hours postdose.

Table 152 Population Demographic Characteristics for Categorical Variables from Phase II/III Population PK Studies[a] [N (%)]

Study	N	Gender		Race				Alcohol Consumption		Smoking Status	
		Male	Female	White	Black	Asian	Other	Yes	No	Yes	No
14	45	36 (80)	9 (20)	21 (46.7)	20 (44.4)	0 (0)	4 (8.89)	0 (0)	45 (100)	40 (88.9)	5 (11.1)
21	187	135 (72.2)	52 (27.8)	94 (50.3)	81 (43.3)	8 (4.28)	4 (2.14)	186 (99.5)	1 (0.5)	133 (71.1)	54 (28.9)
22	79	59 (74.7)	20 (25.3)	39 (49.4)	34 (43)	1 (1.27)	5 (6.33)	79 (100)	0 (0)	57 (72.2)	22 (27.8)
23	199	129 (64.8)	70 (35.2)	123 (61.8)	49 (24.6)	21 (10.6)	6 (3.02)	199 (100)	0 (0)	118 (59.3)	81 (40.7)
4	67	32 (47.8)	35 (52.2)	43 (64.2)	21 (31.3)	1 (1.49)	2 (2.99)	67 (100)	0 (0)	51 (76.1)	16 (23.9)
5	79	51 (64.6)	28 (35.4)	56 (70.9)	19 (24.1)	0 (0)	4 (5.06)	79 (100)	0 (0)	63 (79.7)	16 (20.3)
Total	656	442 (67.4)	214 (32.6)	376 (57.3)	224 (34.1)	31 (4.73)	25 (3.81)	610 (93)	46 (7.0)	462 (70.4)	194 (29.6)

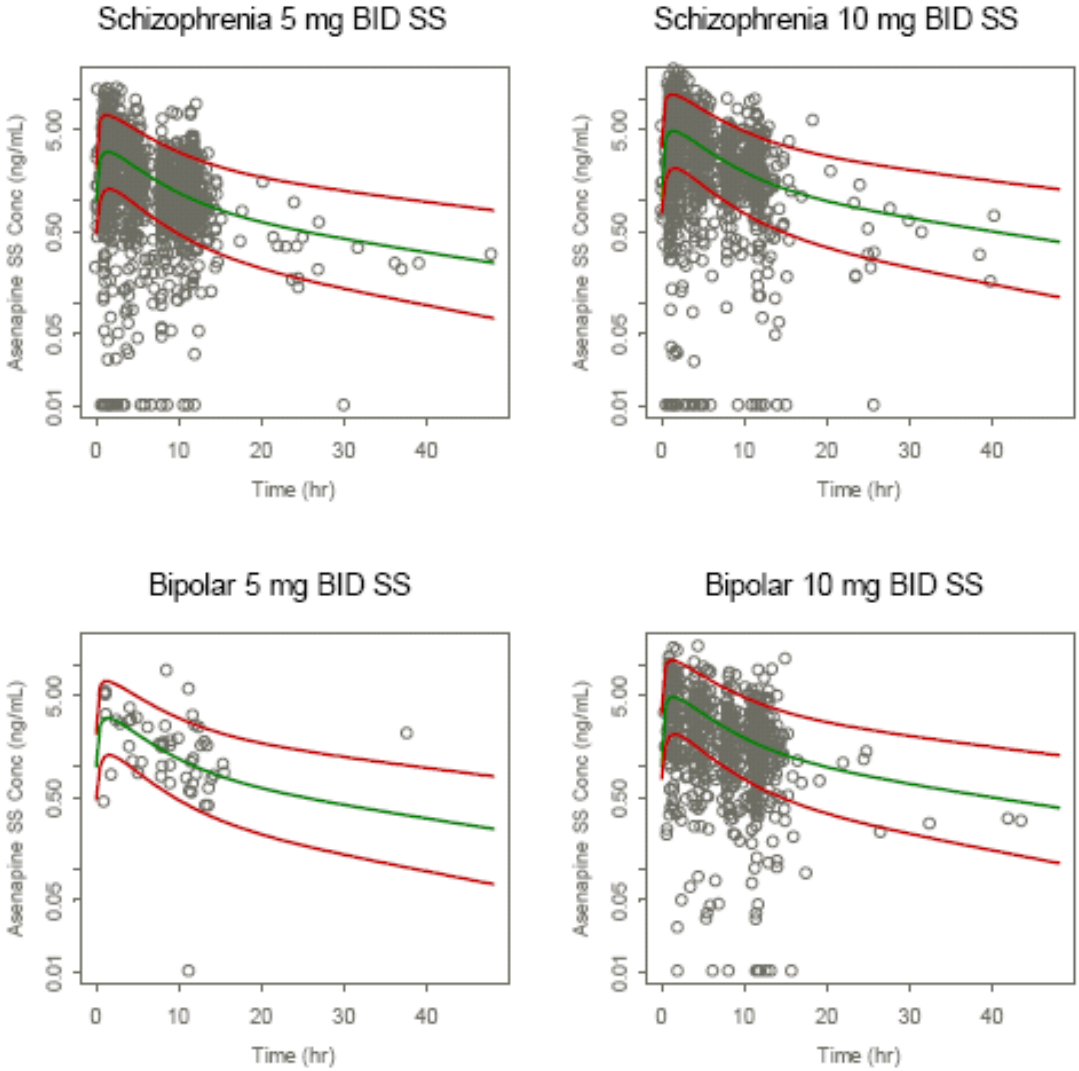
a Based on data at screening

Figure 129 Observed Asenapine Concentrations from All Phase 2/3 Studies by Dose Overlaid on Unconditional 90% Prediction Interval



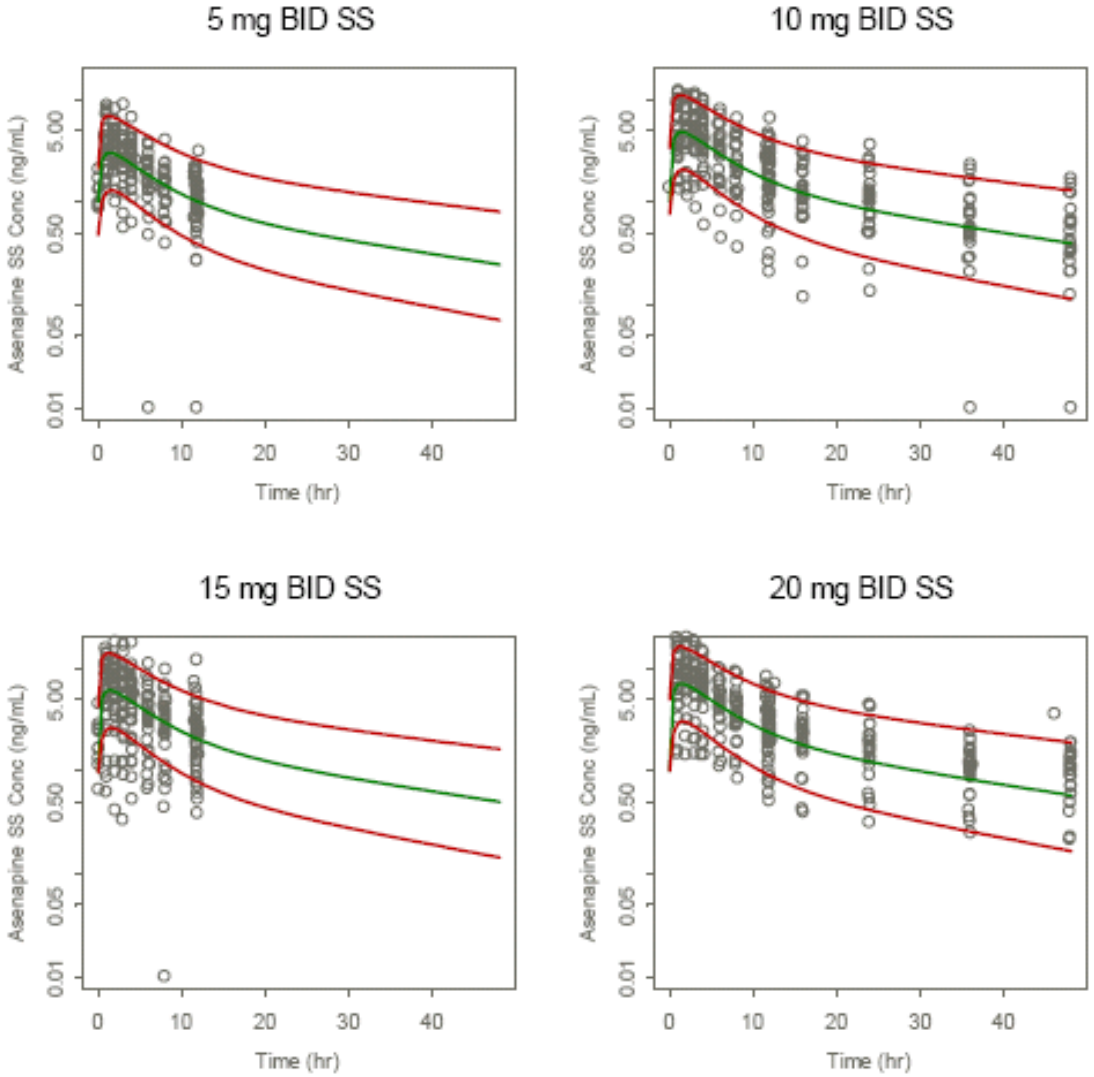
Grey circles represent the observed asenapine concentrations; red lines represent the 95th and 5th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

Figure 130 Observed Asenapine Concentrations from Phase 2/3 Studies by Indication and Dose Overlaid on Unconditional 90% Prediction Interval



Grey circles represent the observed asenapine concentrations; red lines represent the 95th and 5th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

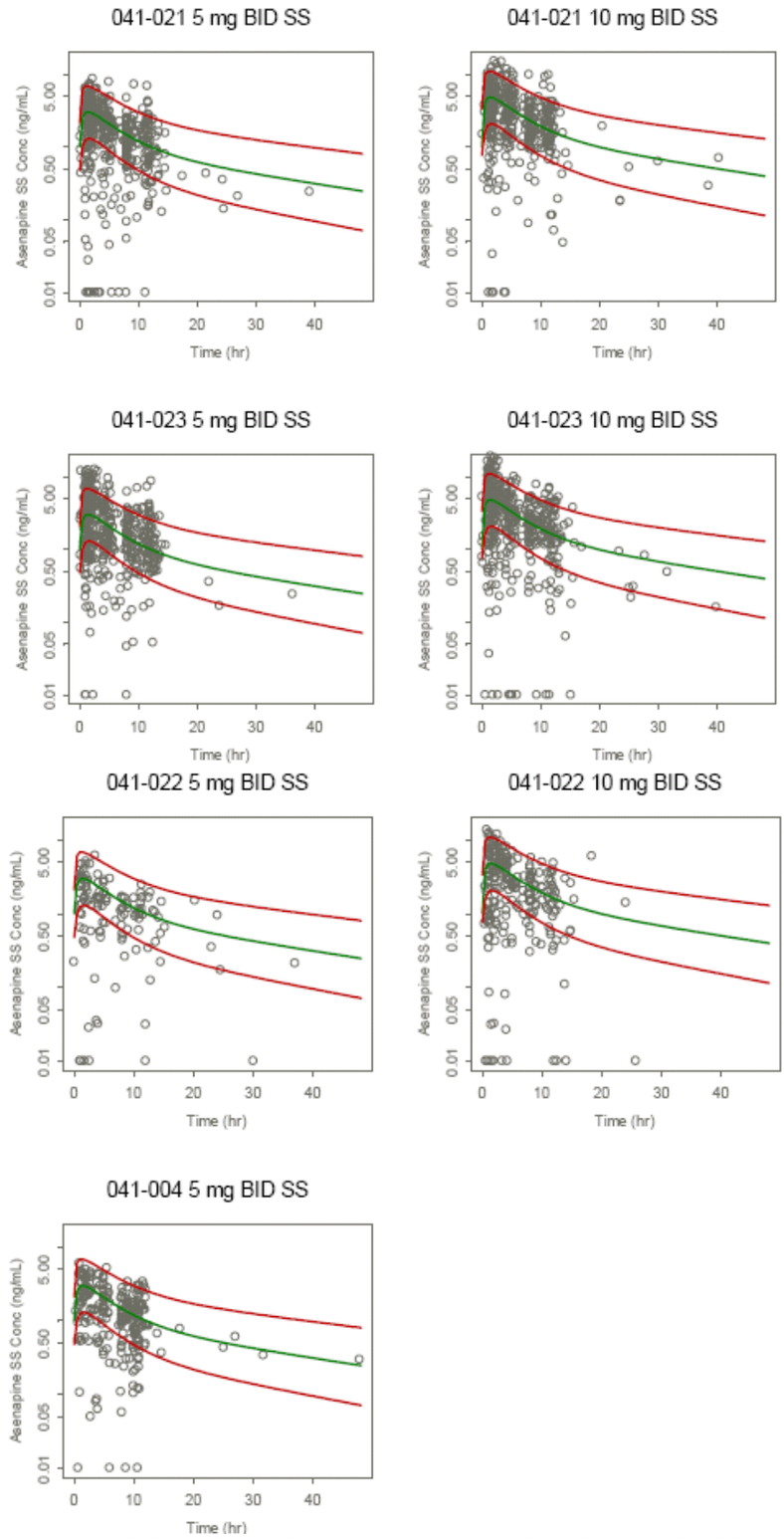
Figure 131 Observed Asenapine Concentrations from the Thorough QTc Study Overlaid on the Unconditional Prediction Interval for Model Validation - Study A7501001



Grey circles represent the observed asenapine concentrations; red lines represent the 95th and 5th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

Figure 132 Observed Asenapine Concentrations from Individual Phase 2/3 Studies Overlaid on Unconditional 90% Prediction Interval by Indication, Study, and Dose

Phase II / III Efficacy Studies in Schizophrenia



Phase II / III Efficacy Studies in Acute Mania

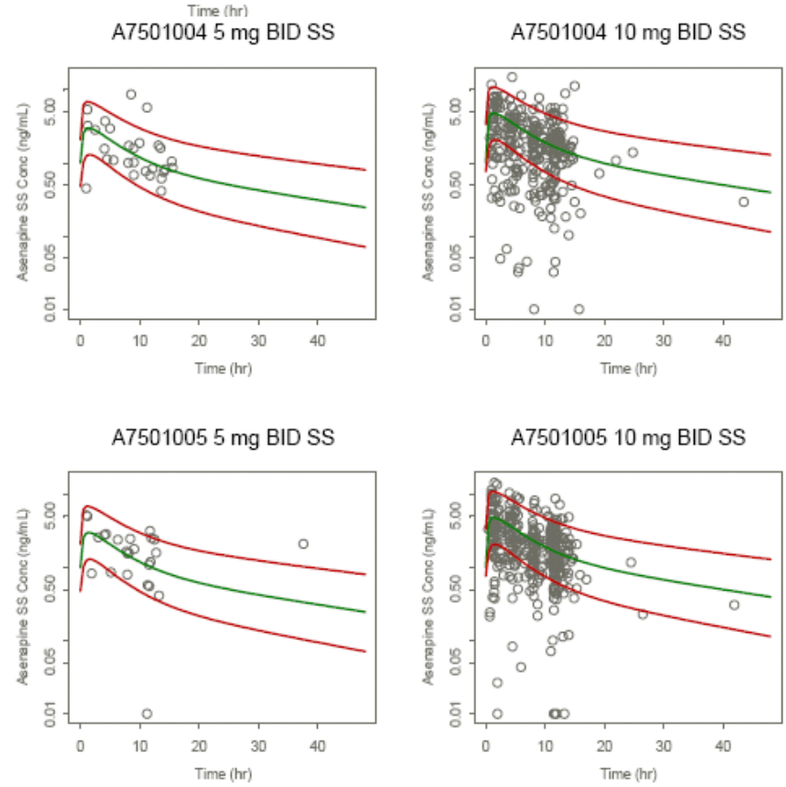


Table 153 shows the percent of the observations above and below the predicted median, 5th, and 95th, percentiles for the phase II / III studies. It's clear that the model overpredicts however, the large percent of concentrations that are below the 5th percentile and are even zero suggests that this may be in part due to noncompliance although it's also likely that a large percentage of this is due to the effect of smoking that has not been adequately captured in the model. In addition, the underprediction of variability, especially on the high end may indicate that not all covariates have been adequately identified.

Table 153 Percent (%) of Observations from Phase II/III Population PK Studies Above and Below the 5th, Median, and 95th Percentiles for the Simulated Unconditional Prediction Intervals

Study Number	5 mg				10 mg			
	Below 5th	Below Median	Above Median	Above 95th	Below 5th	Below Median	Above Median	Above 95th
A7501001 (Phase 1 in Patients)	4.8	40.9	59.1	3.9	9.3	44.9	55.1	8.6
All Phase 2/3	20.1	57.3	42.7	6.5	22.9	58.4	41.6	5.7
All Schizophrenia	20.6	57.9	42.1	6.5	21.9	56.5	43.5	6.0
All Bipolar	7.4	42.6	57.4	7.4	24.7	61.4	38.6	5.3
041-021	18.1	54.2	45.8	3.6	20.1	58.0	42.0	5.6
041-023	19.0	53.5	46.5	13.2	19.7	53.2	46.8	7.7
041-022	29.3	72.4	27.6	0.8	29.3	60.8	39.2	3.4
041-004	23.9	65.7	34.3	3.2	–	–	–	–
A7501004	3.6	50.0	50.0	7.1	28.2	61.3	38.7	4.9
A7501005	11.5	34.6	65.4	7.7	21.8	61.4	38.6	5.6

5.6 Pharmacodynamics

5.6.1 PK/PD

5.6.1.1 Biomarker - PET Studies

Two PET studies after oral administration of asenapine were conducted in 1989 and 1990, and two studies after sublingual administration of asenapine were conducted in 1996 and 1997.

Little binding to D_2 receptors and no binding to D_1 receptors was detected at Tmax after 10 mg oral doses of asenapine in studies 86033 and 25503.

After sublingual administration of a single 100 mcg dose in study 25510, and multiple doses of asenapine 300 mcg in study 25516, low levels of binding to dopamine D_2 receptors in the caudate nucleus and putamen were detected.

Based upon the observed plasma concentrations and binding values, and assuming a simple Bmax model, this reviewer estimated that Cmaxs of around 3 – 9 ng/ml are needed to achieved 90% D_2 receptor blockade. Based on the phase I pharmacokinetic studies this appears to be achievable with doses of 5 – 10 mg SL BID in young healthy male volunteers.

5.6.1.1.1 Oral Administration

In 1989 and 1990 the sponsor conducted PET studies of orally administered 10 mg doses of asenapine to determine the receptor binding to D_2 and D_1 receptors respectively. In study 86033, conducted in 1989, asenapine 10 mg was administered to 2 healthy male volunteers and D_2 binding by ^{11}C - raclopride in the putamen and cerebellum was measured at 2 hours and 5.5 hours post dose. No binding was detected at 5.5 hours post - dose although at 2 hours post - dose binding was 24%.

According to the introduction section of this study report 1.5 mg 5 mg, 10 mg, and 15 mg PO BID dosing for 14 days resulted in dose dependent increases in transaminases in the 5 – 15 mg dose groups in 3 of 6 subjects, (see Figure 223 in Appendix §**Error! Reference source not found.**). This was a safety study and plasma samples for pharmacokinetics were not obtained. In addition hepatotoxicity was seen in the dog studies.

In study 25503, conducted in 1990, asenapine 10 mg was administered to 2 healthy male volunteers and D_1 binding by ^{11}C - SCH - 23390 in the putamen and cerebellum was measured at 2 hours and 3 hours post dose. No binding was detected at either time.

5.6.1.1.2 Sublingual Administration

5.6.1.1.2.1 PET Study 25510

Three healthy male volunteers were administered a single dose of placebo on day 1 and asenapine 100 mcg sublingually one week later.

PET ligands to measure binding affinities to D_2 and 5 - HT_{2A} receptors *in vivo* were guided by the pharmacokinetic characteristics of asenapine. Information on the administration of these ligands and the timing of their scans are shown in Table 154Table 154 PET Scans Employed in Study 25510

Table 154 PET Scans Employed in Study 25510

Scan No.	Time of PET Scan	Receptor of Interest	Positron Emitter
PET 1	2.5 hrs post dose	D_2	^{11}C - raclopride
PET 2	4.5 hrs post dose	5 - HT_{2A}	^{11}C - N - Methyl - spiperone (NMSP)

Figure 133 shows the *in vitro* receptor binding affinities for asenapine reported in this study.

Figure 133 Asenapine *In Vitro* Receptor Binding Affinities per Study Report 25510

Receptor	Radioligand	ORG 5222 (K_i in nM)
D_1	[3H]SCH 23390	4
D_2	[3H]spiperone	3.1
D_2	[3H]NPA	0.6
α_1	[3H]prazosin	0.6
α_2	[3H]rauwolscine	7.9
5-HT_{1A}	[3H]8-OH-DPAT	10
5-HT_{1B}	[3H]5-HT (rat)	40
5-HT_{1D}	[3H]5-HT (calf)	79
5-HT_{2A}	[3H]ketanserin	0.06
5-HT_{2C}	[3H]5-HT (pig)	0.08
H_1	[3H]mepyramine	7.9
ACh/m	[3H]QNB	5000

From de Boer et al. 1993

Figure 134 shows the asenapine concentration time profiles and Figure 135 and Figure 136 show the degree of radionuclide receptor binding to D_2 in the putamen and $5HT_{2A}$ in the frontal cortex compared to the cerebellum in the presence and absence of asenapine. From these 3 figures it's easy to see that asenapine peak concentrations of around 110 pg/ml in subject #3 are associated with around 10% binding to $5HT_{2A,}$ and around 25% binding to D_2. This suggests that a concentration of around 1 ng/ml is needed to achieve 75% D_2 binding, and concentrations of 3 ng/ml or more is needed to achieve around 90 % D_2 binding.

Figure 134 Asenapine Plasma C vs.T Profiles in Subjects Undergoing PET Scans – Study 25510

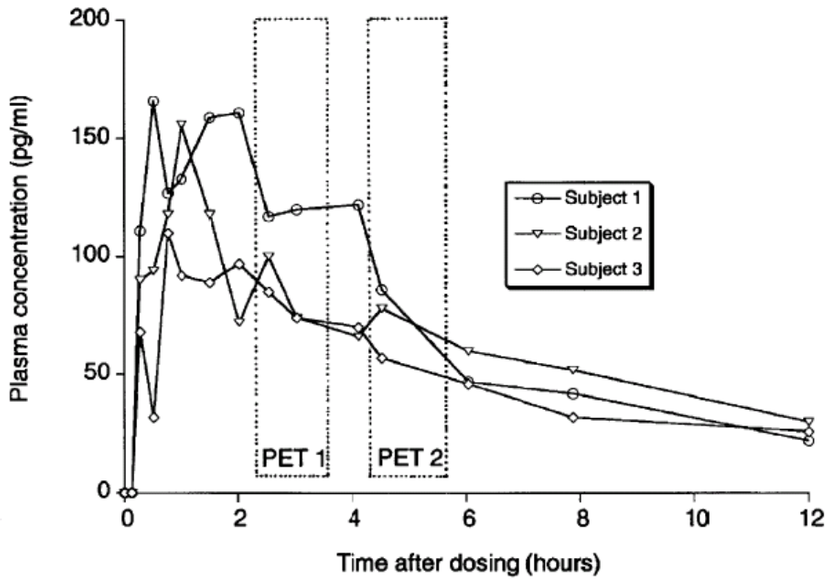


Figure 135 Radionuclide Receptor Binding to $5HT_{2A}$ in the Frontal Cortex and Cerebellum in the Presence and Absence of Asenapine 100 mcg – Study 25510

Figure 4 Regional radioactivity versus time in man (subject 3 in this study), before and 4.5 hours after sublingual administration of 100 µg Org 5222 with the ligand [^{11}C]NMSP. 19

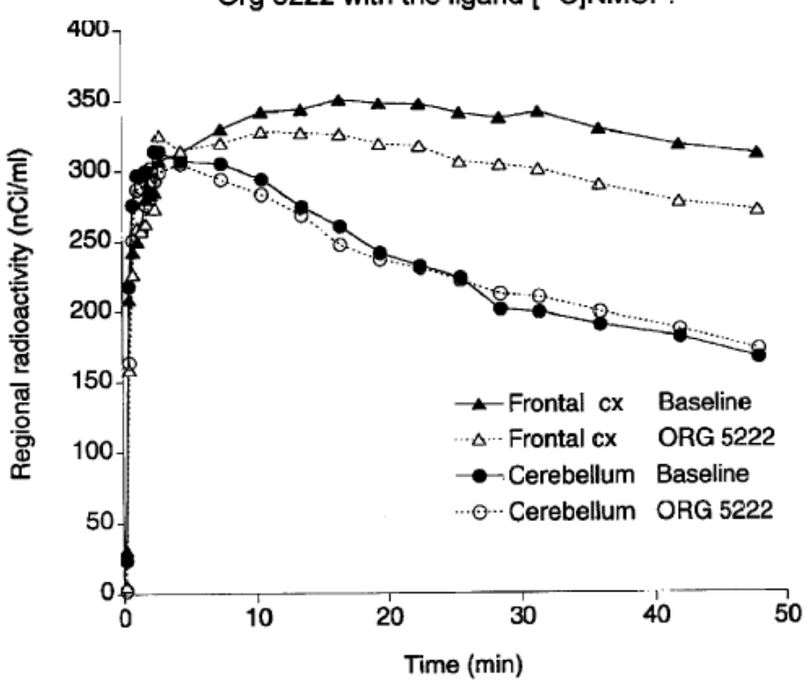


Figure 136 Radionuclide Receptor Binding to D_2 in the Putamen and Cerebellum in the Presence and Absence of Asenapine 100 mcg – Study 25510

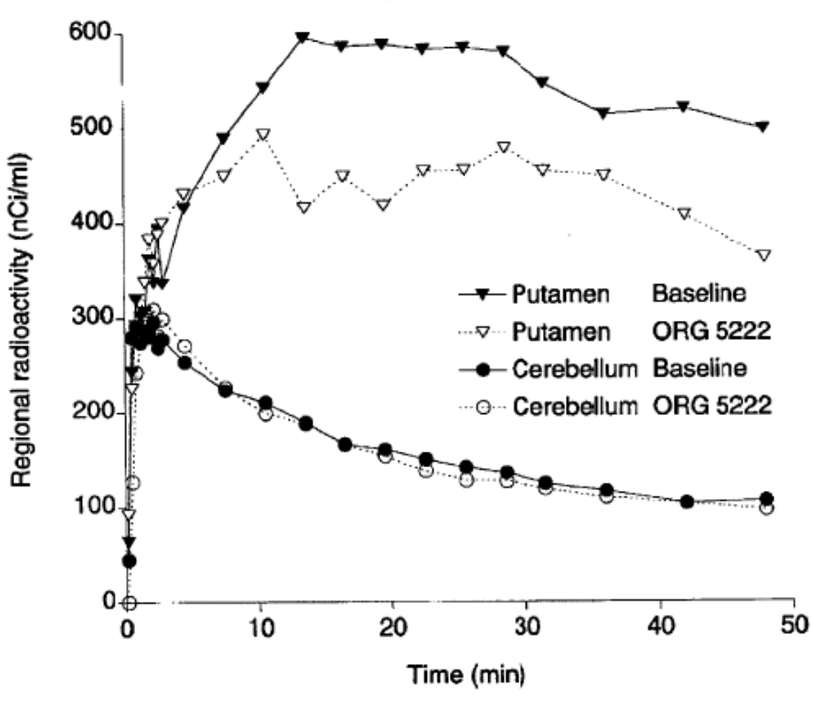


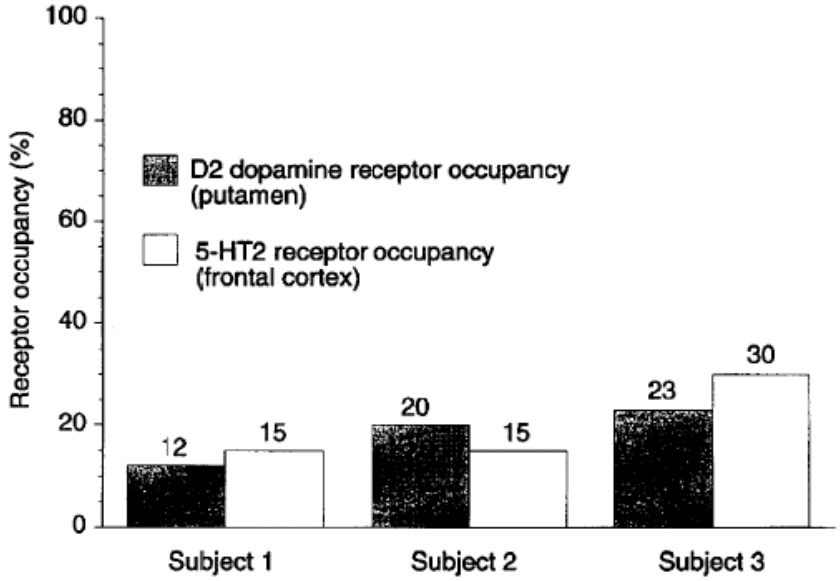
Figure 137 and Figure 138 show the actual pharmacokinetic metrics and the sponsor's calculated % binding to D_2 and $5HT_{2A}$ associated with these metrics in these 3 subjects.

Figure 137 Asenapine Pharmacokinetic Metrics from Healthy Volunteers in PET Ligand Binding Study 22510

Subject #	AUC_{0-12} (pg·h/mL)	$AUC_{0-\infty}$ (pg·h/mL)	CL/f (l/h)	C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)
1 (1st occasion)	570*	785	127	140	0.75	4.5
2	776	1028	97	156	1	5.7
3	609	850	118	110	0.77	6.8
1 (2nd occasion)	905	1023	98	166	0.5	3.9
Mean	715	922	110	143	0.8	5.2
S.D.	155	123	15	24	0.2	1.3

* AUC given is AUC_{0-8} ,because at t=12 the concentration was below the lower limit of quantification.

Figure 138 Asenapine D_2 and $5HT_{2A}$ Receptor Binding in Healthy Volunteers after Asenapine 100 mcg SL in PET Ligand Study 22510



Based upon these values and assuming a simple Bmax model we can estimate that Cmaxs of around 3 – 9 ng/ml are needed to achieved 90% D2 receptor blockade, (see Table 155).

Table 155 Reviewer's Estimation of Cmax needed for 90% D_2 Binding based on Study 25510 Data

Subject	Cmax (pg/ml)	% D2 Binding	Ki_{app} (pg/ml)	Estimated Cmax needed for 90% D_2 Binding[a]	
				(pg/ml)	(ng/ml)
1	140	12	650	6000	6
2	156	15	1000	9000	9
3	110	23	375	3500	3.5

a Reviewer's estimate based on simple Bmax model.

Based on the results of multiple dose PK study 25542, (conducted June 2004 – Aug 2004 at doses of up to 15 mg BID SL for safety), as well as multiple other PK studies this suggests a dose of around 5 - 10 mg SL BID is needed and in smokers the dose may possibly need to be even higher.

Even at the time of this this PET study this dose should have been predictable, not only based on the pharmacokinetics from this PET study, study 25510, but also based on the pharmacokinetics from an earlier study, study 25509 conducted from November 1994 to April 1995 with single sublingual doses of 100 mcg. Table 156 shows the individual peak concentrations seen in this study.

Table 156 Peak Concentrations with Single Sublingual Dose of Asenapine 100 mcg - Study 25509

Subject	Tmax (hours)	Cmax (pg/ml)
53	3	75.2
54	3	76.1
55	1	85.6
56	1	85.6
57	1	98.1
58	1	100.9
59	2	83.8
60	1	68.7
Average	–	84.2 ± 11.1 (13.2)

Assuming linear kinetics a 100 fold higher dose of 10 mg should product average peak concentrations of 8400 pg/ml, (8.4 ng/ml) with a range of 6.9 – 10.1 ng/ml. This is consistent with a dosage of 10 mg daily assuming no decrease in bioavailability.

The sponsor's conclusion from this PET study was that doses greater than 100 mcg were needed, and in the introduction to their follow - up confirmatory PET study, 25516, states that this data suggested an efficacious dose range of only 400 – 800 mcg.

5.6.1.1.2.2 PET Study 25516

PET study 25516 was intended both to be a confirmatory study and to follow the time course of asenapine caudate nucleus and putamen D_2 receptor occupancy in 7 healthy male volunteers over a 24 hour period after 4 doses of asenapine 300 mcg SL BID.

shows the observed mean plasma concentrations and mean observed % D_2 occupancy in the Putamen and Caudate Nucleus over a 24 hour period after dosing with asenapine.

Table 157 Asenapine Plasma Concentrations and Mean D_2 Occupancy in the Putamen and Caudate Nucleus over Time – Study 25516

Time (hours)	n	Mean Plasma concentration Org 5222 (pg/ml)	Putamen Occupancy (%)	N. Caudatus Occupancy (%)
2	4	217.7	31	29
3.5	2	166.2	25	31
6	6	108.9	16	18
12	6	54.5	5	7
24	6	30.2	5	3

Using a simple Bmax model and these values, this reviewer calculates a concentration of 5 ng/ml is needed to achieve 90% D_2 receptor occupancy with asenapine which is similar to what this reviewer calculated with the data from study 25510. The sponsor also used a Bmax model (model 1) as well as an exponential model. However the sponsor instead of using a Bmax of 100% used Bmax's of 97% (based on the PET ligand itself) and a target D_2 occupancy of 61% based on reports with clozapine. It appears that they chose this 61% as their maximum target based on this study and PET study reports for other atypical antipsychotics where subtherapeutic doses were used. However it does not appear that they corrected for time postdose in these studies. Consequently they estimated a dose of only 600 – 800 mcg as shown in Table 158.

To this reviewer is seems readily apparent that these would be inefficacious doses based both on the maximum binding and the expected binding over a 12 hour dosage interval.

Table 158 Sponsor's Estimated D2 Receptor Binding with Two Proposed Biferpunox Dosages – Study 25516

Org 5222 [µg]	Estimated Plasma Level, (2h post-dosing) [pg/ml]	Model 1, 97 %			Model 1, 61 %		
		2 h	12 h*	24 h*	2 h	12 h*	24 h*
600	430	45	19	7	38	16	6
800	580	52	22	8	42	18	6

* Values were calculated from the receptor occupancy at 2 hours, assuming a receptor binding half-life of 8.1 hours.

5.6.1.2 PK / PD Modeling and Simulation

On September 28, 2001 Pharsight, on contract to Organon, issued a modeling and simulation report, INT00039259, for dose-finding.

According to the report:

'The revised objectives of Aim 1 were:

- Predict mean week 6 Last Observation Carried Forward (LOCF) PANSS change from placebo for the ongoing study (041-013)[1], and the uncertainty around these predictions (including uncertainty and variability).

- The underlying predicted mean LOCF PANSS true dose response curve for Org5222 and the uncertainty around that prediction.

- Simulations giving the predicted likelihood of the treatments in study 041-013 being significantly different from placebo.

- An evaluation of the effect of dropout on the LOCF predictions.

- Predicted doses of Org5222 corresponding to clinically used doses of atypical antipsychotics.'

To achieve this Pharsight did the following:

- Developed population pharmacokinetic models for 4 antipsychotics in addition to asenapine
- Fit models to D2 occupancy vs. plasma concentration data
- Simulated D2 receptor occupancy time profiles with steady-state dosing and performed a covariate analysis
- Developed a model to convert BPRS scores to PANSS scores for inclusion in the PK/PD model
- Developed a pharmacodynamic link model for the influence of D2 occupancy biomarker on PANSS score
- Explored other Potential Co-Factors
    - Evaluated the potential of a Bell (or U) shaped dose response
    - Developed a mixed effects model to incorporated the influence of dropouts on PANSS scores
- Developed a Final Model
- Simulated the effect of asenapine under conditions used in study 41013 at doses of 1.6 mg and 2.4 mg BID

5.6.1.2.1 Development of Population Pharmacokinetic Models for 4 Antipsychotics in addition to Asenapine

The following pharmacokinetic data was used per the report:

'Pharmacokinetic data for Org5222 was provided by Organon. A three-compartment population pharmacokinetic model provided by Organon as the most suitable model was used for Org5222 pharmacokinetics. For Olanzapine, Risperidone, Ziprasidone and Quetiapine, public domain regulatory

[1] DB PBO controlled fixed dose study of Asenapine 1.6 mg and 2.4 mg SL BID.

documents including the Summary Basis of Approval (SBA's), Advisory Committee documents, and clinical expert reports were used. A thorough literature review was also performed and provided additional information about these compounds, as well as information on the pharmacokinetics of Haloperidol.'

The final pharmacokinetic models and parameters used in the modelling are shown in Table 159. It's interesting that the sponsor used a 3-compartment model for asenapine here but a 2 compartment model in the Pop PK analysis.

Table 159 Sponsor's Table 5 Population mean PK parameters used in simulations, and associated fractional SEs.

Compound	Haloperidol	Olanzapine	Asenapine	Risperidone	Ziprasidone
Model	1 compartment	1 compartment	3 compartment	2 compartment	1 compartment
Ka (h^{-1})	0.36 (26%)	0.54 (30%)	2.31	2.19 (6%)	0.147 (5%)
Cl (L/h)	26 (10%)	20.6 (4.5%)	159 (11%)	5.64 (4%)	31.5 (5%)
Vc (L)	672 (8%)	1121 (12%)	1080 (18%)	75 (3%)	105 (10%)
Vp (L)			4340 (16%)	73 (3%)	
V3 (L)			846 (16%)	2.64 (4%)	
Q1 (L/h)			29.6 (56%)		
Q2 (L/h)			311 (56%)		
F (%)	60 (13%)	*	*	*	60 (15%)
Reference	YF Cheng et al, 1987	SBA, page A 63	Internal report	Expert report, page 134	Drug label
Comments	Corrected for average study population of 74% men, 64% smokers			active moiety (risperidone + 9-OH-risperidone)	Ka derived from tmax

*parameters are corrected for F (i.e. CL/F, V/F, etc.)

5.6.1.2.2 Fit of D2 Occupancy vs. Plasma Concentrations

The sponsor fit the following models to the data:

- Linear
- Emax
- Quadratic
- Cubic
- Quartic
- Sine Functions (Fourier Series)
- Splines

For the Emax model both a common Emax model was fit as well as individuals Emax models for each drug. Parameter estimates for the common Emax model are shown in Table 160, and parameter estimates for individual drug Emax models are shown in Table 161.

Table 160 Sponsor'sTable 7 Parameters of model with common Emax

	Value	SE
Emax	93%	1.8
	EC50	
Haloperidol	0.548	*0.106
Org5222	0.437	*0.082
Olanzapine	6.75	*0.127
Risperidone	4.78	*0.112
Ziprasidone	13.3	*0.173

* SE of logs

Table 161 Sponsor's Table 6. Parameters of model with separate Emax for each compound

Drug	Emax	SE	EC50	SE
Haloperidol	92.0	4	0.532	*0.16
Olanzapine	87.5	3	5.29	*0.14
Org5222	101.8	6	0.528	*0.14
Risperidone	91.2	3	4.43	*0.14
Ziprasidone	98.0	10	15.4	*0.29

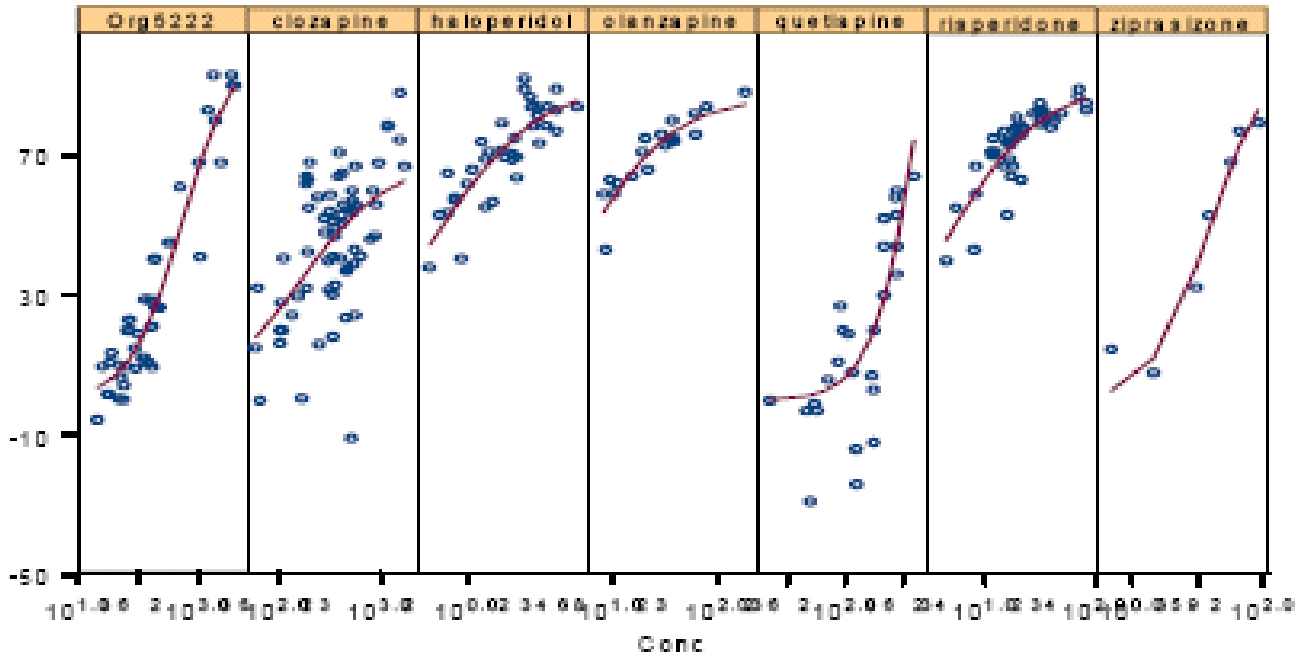
*SE of logs

According to the sponsot both models gave reasonable fits as assessed graphically, and the precision of all parameter estimates was high.

The final model selected was the separate Emax model for each compound.

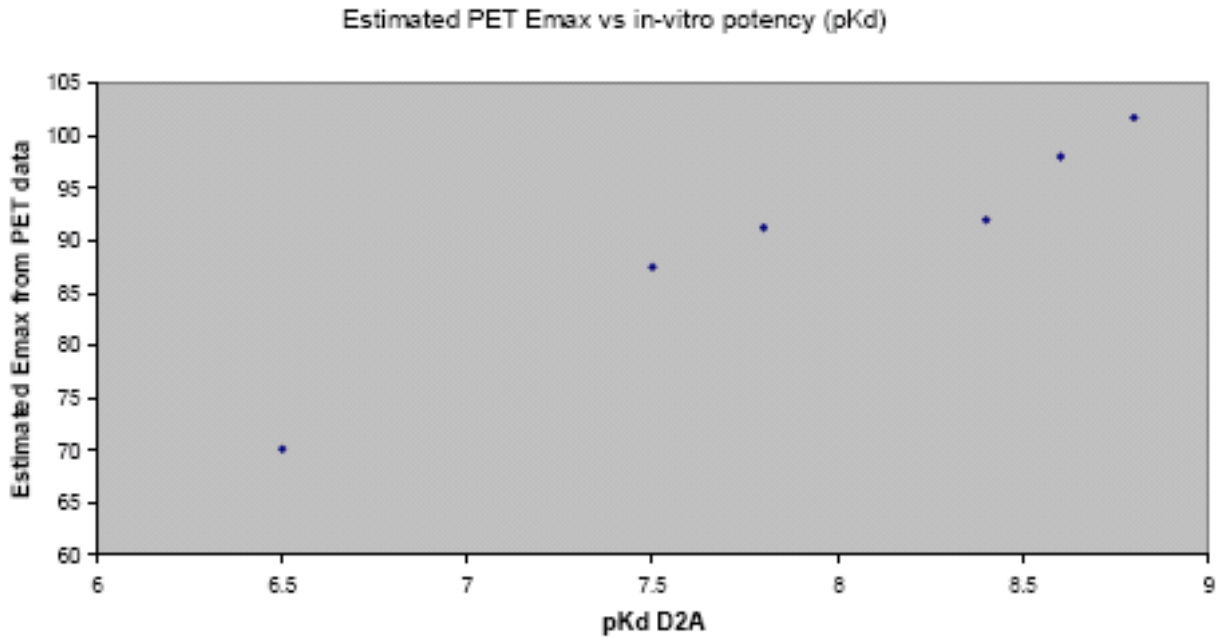
The sponsor's fits of individual Emax models to data for the various drugs is shown in Figure 139.

Figure 139 Sponsor's Figure 2 of the fit of separate Emax models to drug concentration / D2 occupancy data for antipsychotics.



Since the Emaxs in Figure 139 are less than 100%, it's possible the sponsor limited the fit to the data range. However, Figure 140 indicates that this apparent Emax might also be due to the binding affinity relative to the radioligand or another ligand.

Figure 140 Sponsor's Figure 3 Emax from fitting of concentration-D2 occupancy data, plotted against in-vitro receptor affinity estimates.



In either event, both the sponsor's Emaxs and EC_{50}s shown in Table 162 are apparent values are suspect.

Table 162 Sponsor's Table 3 Parameters from fitting of Emax model to PET data.

Drug	Clozapine	Haloperidol	Olanzapine	Org5222	Quetiapine	Risperidone	Ziprasidone
Emax	70.1	92.0	87.5	101.8	75.1	91.2	98.0
EC_{50}	136	0.532	5.29	0.528	301	4.43	15.4

Table 163 shows a comparison of relative *in vivo* EC_{50}s to *in vitro* Kds. The table shows the best concordance with asenapine and haloperidol, and worse concordance with clozapine and quetiapine which did not have adequate coverage of the the entire binding range. However, as these are corrected values which can't be checked and as the relationship with Risperidone isn't available the reliability of this analysis is unknown.

Table 163 Sponsor's Table 4. Comparison of relative EC50s derived from human in-vivo PET data to relative Kds derived from in-vitro data. Haloperidol is used as the reference.

Drug	Clozapine	Haloperidol	Olanzapine	Org5222	Quetiapine	Risperidone	Ziprasidone
Relative PET EC_{50}*	258	1	10	1	17	1200	0.5
Relative Kd	79-100	1	8-10	0.4-0.8	3-4	–	0.6-8

*Corrected for molecular weight and plasma protein binding.

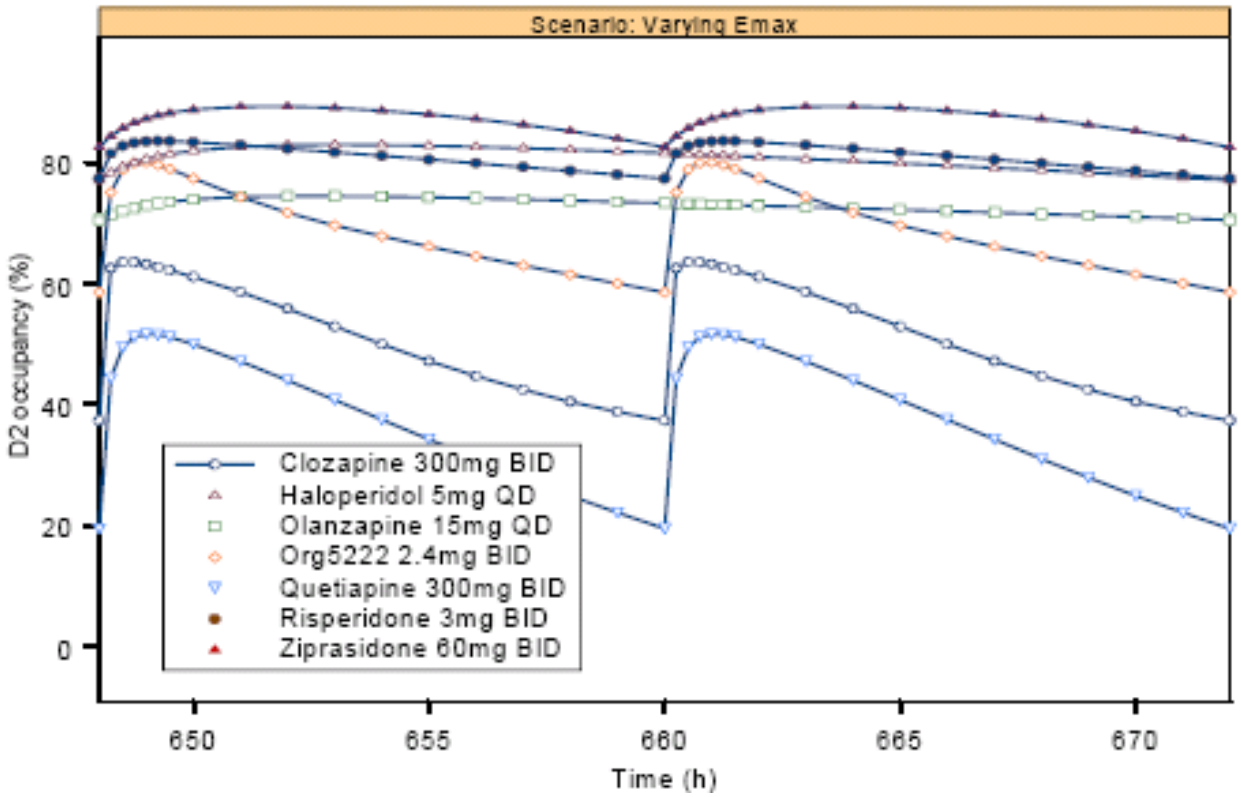
The sponsor to an extent came to a similar conclusion as shown by the following and excluded clozapine and quetiapine data from further analysis.

'After discussions with the project team and with Dr Kapur, the consensus was that clozapine and quetiapine, with their far lower receptor affinity, may not be similar to the other atypical antipsychotics, and that it is currently impossible to say whether they truly have a lower Emax, and thus act at far lower occupancies than other atypicals, or whether this is an artefact of the PET methodology. Thus, as these differences make data from clozapine and quetiapine difficult to interpret, it was decided not to include data from these drugs in the final analyses. It was decided to examine two scenarios regarding the Emax in the final analysis, one where a common estimate was achieved across compounds, and one which allowed separate estimates to be used for all compounds, see Section 10.2.'

5.6.1.2.3 Simulation of D2 Cccupancy vs. Time Profiles and Covariate Analysis

Figure 141 shows predicted Mean D_2 occupancy at steady-state based on their estimated metrics. The D2 occupancy is likely low except for ziprasidone. Consequently, excluding clozapine and quetiapine whose binding metrics are likely off by large amounts the extent of D2 occupancy over the entire dosage interval is in the range of 70% – 90% and is likely higher. Based on this figure alone an asenapine dose of 2.4 mg BID is subtherapeutic.

Figure 141 Sponsor's Figure 4 Predicted mean D2-occupancy – time profiles for antipsychotics given in commonly used dosage regimens. Separate Emax values estimated for each compound.



5.6.1.2.3.1 Convariate Analysis

The sponsor also performed a covariate analysis using data from study 41002.

In addition to a center effect, the following covariates were investigated, for the main endpoint LOCF PANSS week 6, and the effect on time of dropout.

Smoking; Age; Sex ;Weight; Race; Prior olanzapine drug use; Prior risperidone drug use; Prior haloperidol drug use ;Any prior psycholeptic use ;Prior anti-epileptic drug use; Prior anti-Parkinson drug use; Prior anti-analeptic drug use.

The sponsor made the following conclusions: 'In short, none of the above had any major impact on either the absolute PANSS score and, more importantly, none were associated with a clear treatment by covariate interaction. That is, the size of the treatment effect was reasonably consistent across the various levels of each covariate.

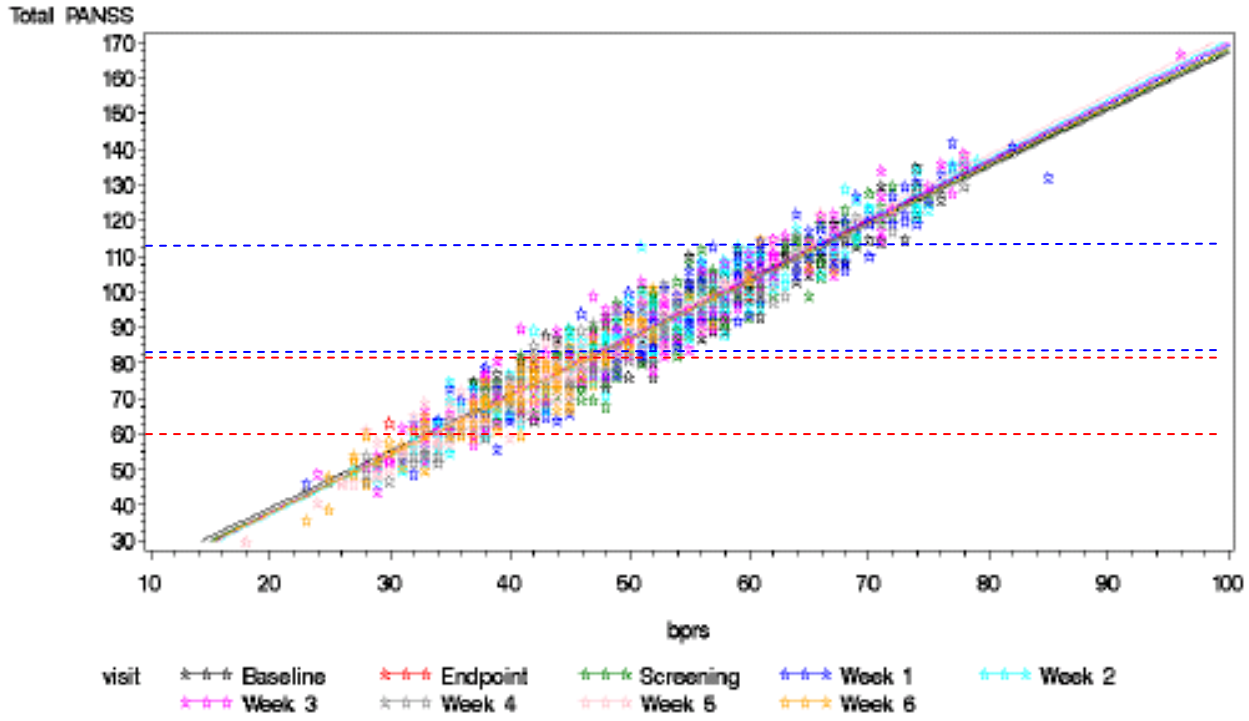
In the analysis looking at time of dropout, there was no evidence that any subgroup were significantly more likely to stay in or withdraw from the study. This result must be taken with caution, as subtle effects may be difficult to detect with this relatively small sample size.'

However, no store can be placed in these conclusions as the maximum dose used in study 41002 was only 0.8 mg BID which is clearly an inadequate dose.

5.6.1.2.4 Conversion of BPRS Scores to PANSS Scores

The sponsor also examined the relationship of Total PANSS score and BPRS so that they could use data from trials that did not have PANSS scores. Figure 142 shows the correlation of Total PANSS scores with BPRS scores although the relationship might seem to be quite good to get a true idea of the acceptability the variability at a single BPRS score needs to be assessed. Consequently, we can see that a BPRS score of 52 at week 2 can mean a PANSS score of between 82 and 112 a spread of 30 units. Since that is the typical degree of change over time in a typical efficacy study it appears that this conversion may not be sufficiently reliable. Although this is the maximum difference we can also see that for the six week data at a BPRS score of 41 the range in PANSS scores is still 20 units.

Figure 142 Plot of Total PANSS score vs. BPRS for All Data by Duration of Treament.



5.6.1.2.5 Pharmacodynamic Link Model of PANSS vs. D2 Occupancy

Full details of the model development, are included by the sponsor in Appendix 3 of the report. The investigation of the modelling resulted in the following conclusions by the sponsor:

- A transformation of the predictor variable was appropriate.
- A cubic polynomial fit the data well.
- Only placebo controlled data would be used.
- A weighting based on the sample size was appropriate.

The transformation of the %D_2 scale used was Log (100-%D_2). This made the scale more concordant with parametric modelling.

The relationship between the treatment effect and %D_2 receptor occupancy was modelled as a cubic polynomial, as shown below.

$$Y = \beta_0 + \beta_1 X + \beta_2 X^2 + \beta_3 X^3 + \xi$$

Where:

Y = Response = change from placebo, week 6 PANSS LOCF value.
X = Log (100 – %D_2) = Log transformed (100 – Mean %D_2 Receptor Occupancy)

The data and model prediction with 95% Confidence Interval is shown in Figure 10. Each symbol represents a treatment arm in a clinical study. The change from placebo for this treatment arm observed in the study is plotted against the (transformed) expected %D_2 receptor occupancy for the corresponding drug and dose level. Clearly, as %D_2 receptor occupancy increases, clinical effect (change from placebo) increases.

Figure 143 Sponsor's Figure 10 Mean PANSS LOCF at 6 weeks versus D2 occupancy Overlaid with Mean model prediction and 95% CI

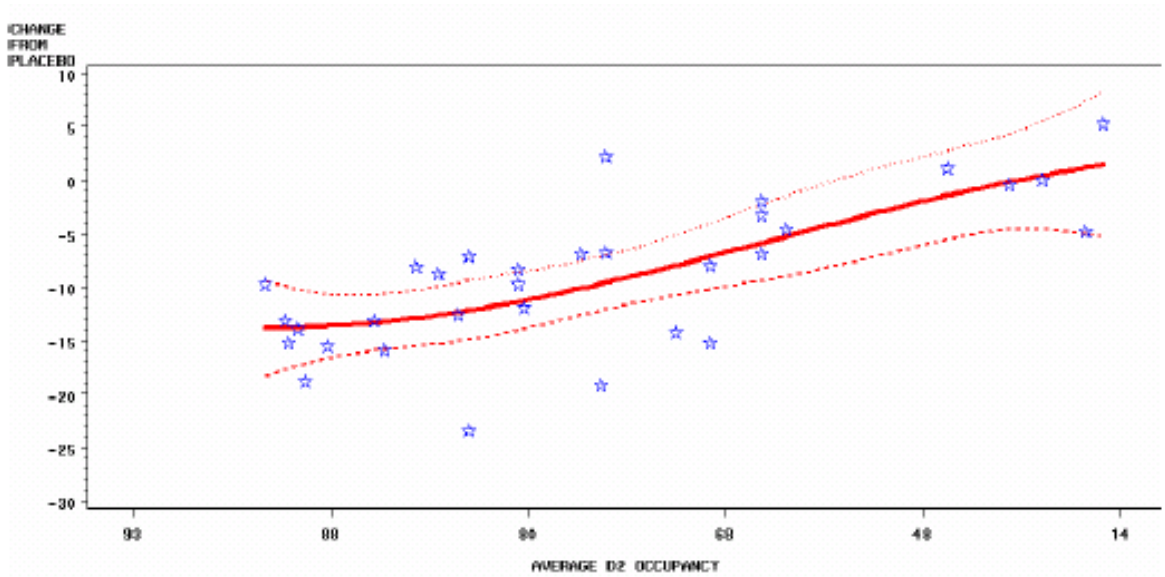
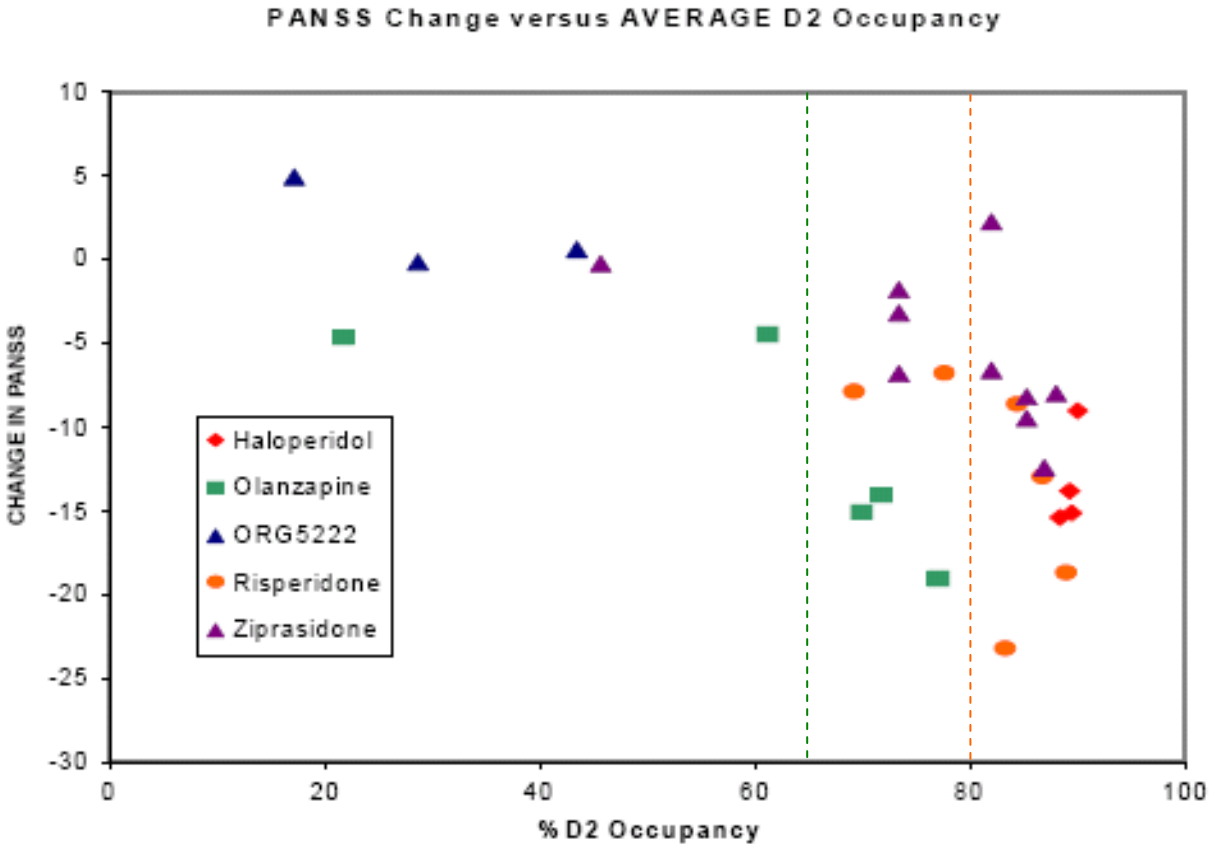


Figure 141 shows the sponsor's plot for Change in PANSS vs. predicted mean D2 occupancy. Interpretaion of this graph must be done cautiously, as we don't know for which data points the PANSS scores were estimated based on BPRS and thereby may introduce excessive variability. Also the D2 occupancy is a mean value and is based on predictitions. In spite of this the graphs indicates that a mean D2 occupancy of greater than 80% is likely needed to achieve a clinically significant change in PANSS score based on 3 of the 4 active controls. Figure 143 demonstrates this even more clearly as below 80% D2 occupancy the variability is excessively high.

Figure 144 Sponsor's Figure 7 Observed clinical response (PANSS LOCF change from placebo), plotted against the mean predicted D2 occupancy for each dose level.



5.6.1.2.6 Exploration of Other Potential Co-Factors

5.6.1.2.6.1 U-Shaped Dose Response

This was allowed initially but then rejected.

5.6.1.2.6.2 Mixed Effect Model of Drop-outs on LOCF

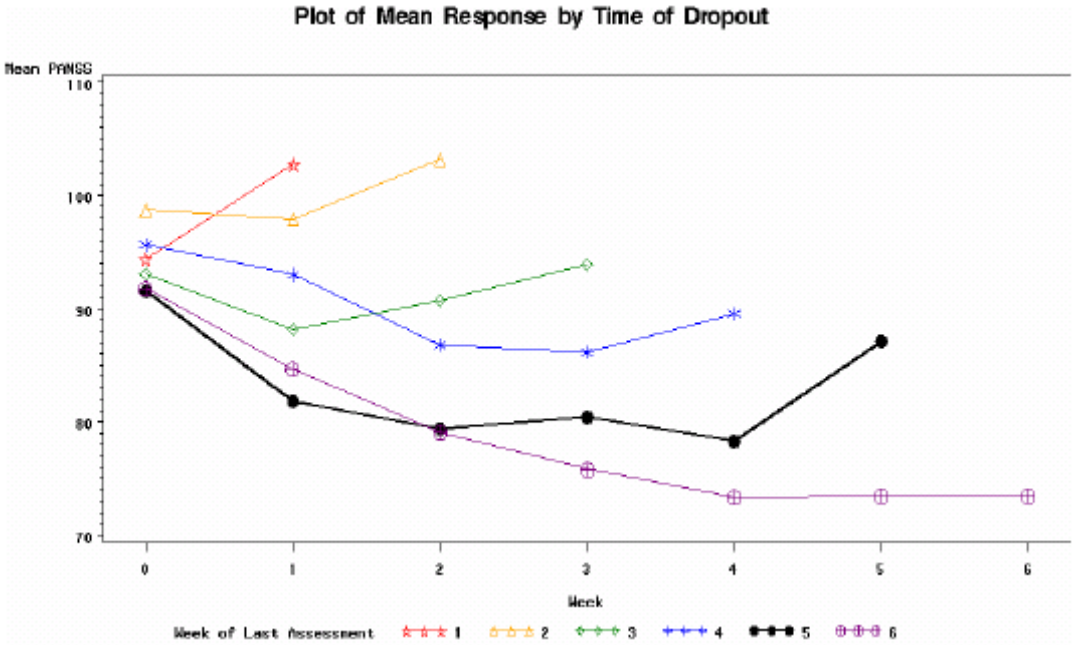
This was explored but eventually dropped from the model. The lack of a relationship may have been due to evaluating the effect on LOCF rather than OC, due to an inadequate model, or other reasons. The sponsor's discussion follows:

'Dropout is a very important factor during clinical studies of antipsychotics. The level of dropout is generally high in this area, ranging from 9% to 91 % in the analysed studies, over a 6 week study duration. To try to avoid bias because of the high and often treatment related dropout, PANSS scores are

mostly analysed as Last Observation Carried Forward (LOCF) values. The interaction between dropout and LOCF PANSS scores is complex. On one hand, data from study 041-002 indicate that patients with higher or increasing PANSS scores tend to drop out earlier in the study (Figure 8), which likely reflects drop out due to lack of sufficient efficacy.

A mixed effects model was applied to the relationship between D_2 occupancy and LOCF PANSS scores. Using this model, a highly significant relationship between dropout and LOCF PANSS change from baseline could be detected. However, the effect of dropout on the change from placebo in LOCF PANSS was not significant. This may be due to the high variability in the placebo effect, which increases over time in some studies, but decreases in others. Thus, even as the PANSS score at a given week may influence dropout, there may be no clear correlation between dropout and LOCF PANSS that is not better explained by differences in D_2 occupancy.

Figure 145 Sponsor's Figure 8 Mean PANSS scores at weeks 0-6 of study 041-002, grouped by the week of dropout



Initially, it was also assumed that a relationship exists between PANSS scores or change in PANSS and likelihood of dropout. However, after further examination this was not found to impact the results, as shown above in Section 6.7.'

5.6.1.2.7 Modeling and Simulation

In summary the final model included:

- POP PK models of several individual antipsychotics as shown in Table 159, excluding clozapine and quetiapine
- Emax models of D2 occupancy vs. plasma concentration for each individual antipsychotic as shown in Table 161
- A pharmacodynamic link model of PANSS vs. D2 Occupancy as shown in §5.6.1.2.5.

5.6.1.2.7.1 Simulation of Study 041-013

Pharsight TrialSimulator TS2.1 was used for simulations. According to the sponsor The simulation used the following algorithm:

"Response" is defined as Change from Placebo in LOCF PANSS Score at Week 6.

Effect is defined as log transformed (100 – %D_2 occupancy).

1) Fit the model of Response versus Effect.

2) From the PK-PET model, the mean and SD of %D_2 occupancy were derived for an N=60 study, for each Org5222 dose level.

3) Sample from the above distribution, to obtain 1000 replicates of the %D_2 occupancy for each dose.

4) For each replicate, obtain from equations 4 and 5 the expected mean and SD of Response corresponding to that specific Effect (derived from %D_2 occupancy).

5) Sample once from distribution from 4) to obtain Response for each replicate.

6) For each replicate, sample an N=60 study, based on mean from 5), and SD of 20. This reflects variability at the subject level.

7) Obtain estimate of Response from each N=60 study, and summarise responses across all 1000 replicates. This provides the distribution of results incorporating model uncertainty, D_2 uncertainty and study uncertainty.

8) For each replicate in 5), simulate 1000 corresponding placebo data, each with expected mean zero, and SD 20. Empirical power calculated by simple t-test of mean and SD from 5) versus simulated placebo. Significance level set at $p < 0.05$.

Figure 146 shows the expected D2 distribution with an asenapine dose of 1.6 mg BID and its' predicted effect on difference in PANSS score from Placebo. From the graph this appears to result in a mean D2 occupancy rate of ~60% and a difference from placebo of a change in PANSS of -5 from baseline. Extrapolating visually, a D2 occupancy rate of greater than 80% is need for a change of -10 which is low for an active agent.

Figure 147 shows the distribution of simulated mean responses (Change in LOCF PANSS score) with the asenapine doses of 1.6 g BID and 2.4 mg BID employed in study 41013 assuming a scenario with the Same Emax and average D2 occupancy and incorporating the combined model and interindividual uncertainty. It's clear that at these doses that the predicted response included a difference in PANSS score of zero.

Table 164 shows the sponsor's mean predicted response and the 95% confidence limits for the doses employed in study 41013 for all 4 scenarios, and Table 165 shows the sponsor's predictions of the success of study 41013 for each of the 4 scenarios. Overall the chance of success from study 41013 is estimated as only 50% and with the most likely scenario the chance of success is only slightly greater than 1 in 3. Thus modeling indicates that this was a poor business decision.

Figure 146 Sponsor's Figure 11 Expected Mean Fit and Distribution of D2 occupancies and Corresponding Effects on PANSS, following Asenapine 1.6 mg SL BID

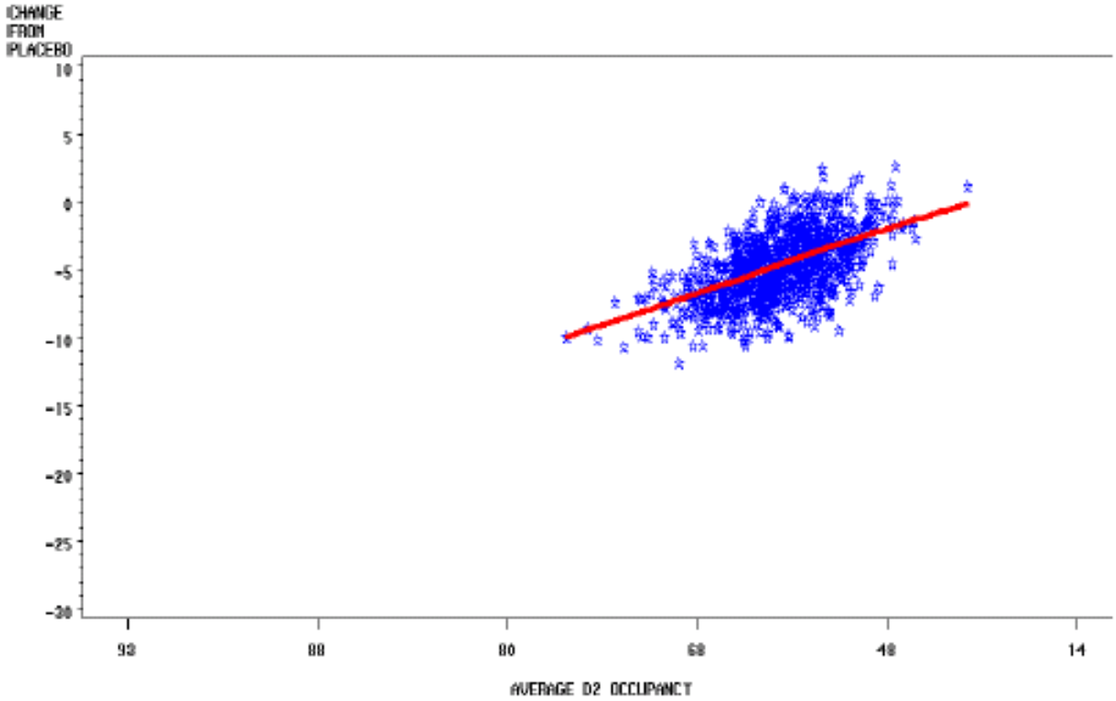


Figure 147 Sponsor's Figure 12 Distribution across 1000 simulated replicates showing predicted mean LOCF PANSS change from placebo after administration of 1.6 and 2.4mg Org5222 b.i.d to 60 subjects. Distribution incorporates model uncertainty and interindividual variability.

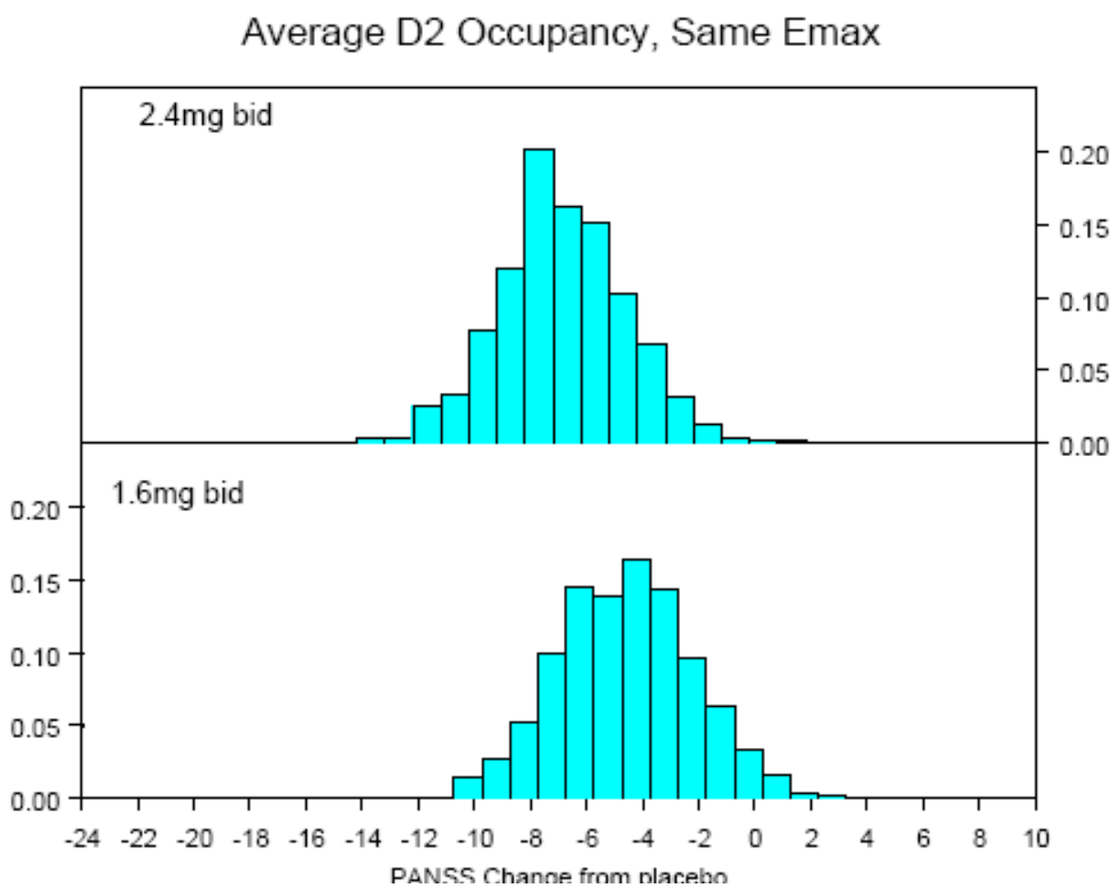


Table 164 Sponsor's Predicted mean PANSS LOCF change from placebo at 6 weeks for Org5222 given at the doses of 1.6 and 2.4mg in study 041-013 for 4 different simulation scenarios.

Scenarios	Assumptions		Dose (mg)	Mean	Confidence Limits	
	Emax	Average or Mean D2 Occupancy			Lower 95%	Upper 95%
1	Same Emax	Average	1.6	-4.6	3.2	-13.2
			2.4	-6.8	2.2	-15.2
2	Same Emax	Max	1.6	-6.7	0.9	-15.1
			2.4	-9.0	-0.3	-17.3
3	Different Emax	Average	1.6	-5.1	3.4	-14.2
			2.4	-8.1	1.7	-16.8
4	Different Emax	Max	1.6	-8.5	-0.2	-17.3
			2.4	-10.7	-0.7	-19.6

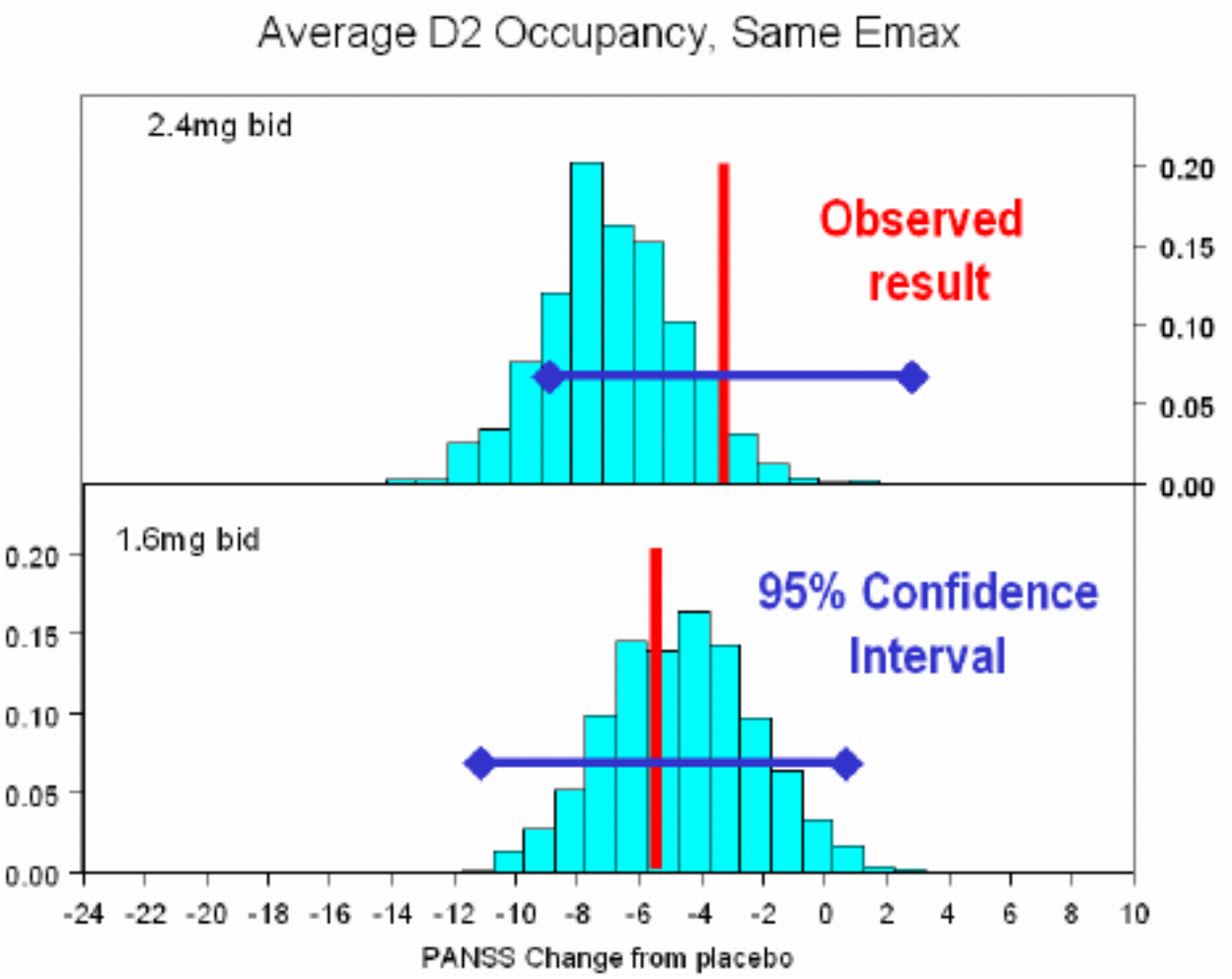
Table 165 Sponsor's Table 11. Predicted likelihood of showing a significant difference from placebo for each of the two doses in study 041-013, for the four different simulation scenarios.

Scenarios	Assumptions		Dose (mg)	Likelihood of Success
	Emax	Average or Mean D2 Occupancy		
1	Same Emax	Average	1.6	27%
			2.4	46%
2	Same Emax	Max	1.6	44%
			2.4	67%
3	Different Emax	Average	1.6	33%
			2.4	58%
4	Different Emax	Max	1.6	60%
			2.4	81%
Overall Average				52%

5.6.1.2.7.2 Validation

Figure 148 shows the actual results from study 41013 and the 95% CI overlaid on the predictions based on the most likely scenario clearly showing the failure of the study and the inability to differentiate from placebo for both doses. Consequently this is a poor test of the validity of the model.

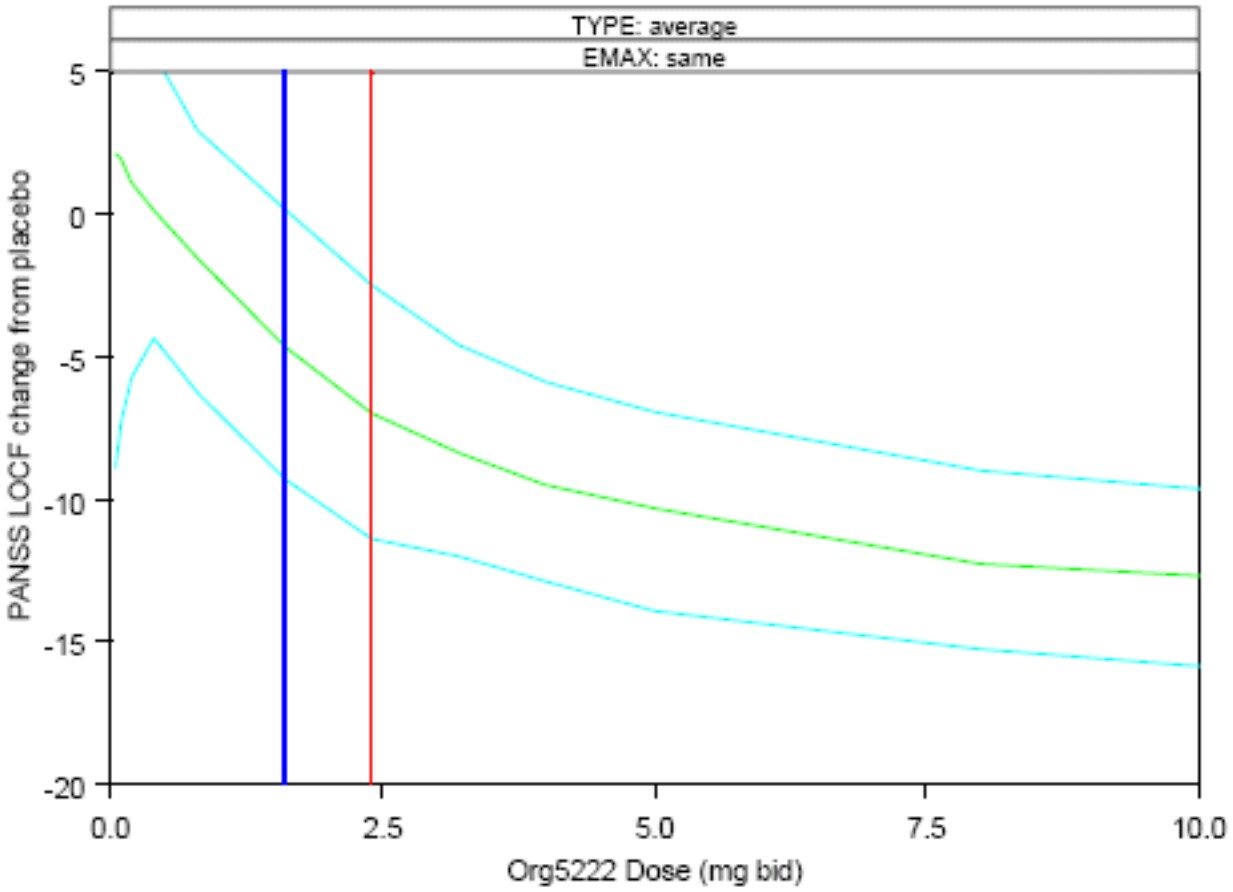
Figure 148 Sponsor's Figure 14 Actual results from study 041-013 shown with estimate and 95% CI, in comparison to distribution across 1000 simulated replicates showing predicted mean LOCF PANSS change from placebo.



5.6.1.2.7.3 Dose Prediction

Figure 149 shows the exposure response curve of the difference from Placebo in change in LOCF PANSS score vs. dosage, with the simulated 95% confidence interval indicating that a dose of 5 – 10 mg BID is needed for a clinically significant response. However the overlay of the response seen with the 1.6 and 2.4mg doses indicate that the 2.4 mg should have definitely differentiated from placebo, however in actuality it didn't. Consequently, the model is clearly flawed in some manner.

Figure 149 Sponsor's Figure 13 Dose response curve showing the predicted mean PANSS LOCF change for placebo vs dose of Org5222. Predictions for Scenario 1: Average D2 occupancy, same Emax, are shown. The green line represents the mean predicted response while the light blue lines represent the 5th and 95th percentiles. The vertical lines indicate the response seen with the 1.6 and 2.4 mg doses.

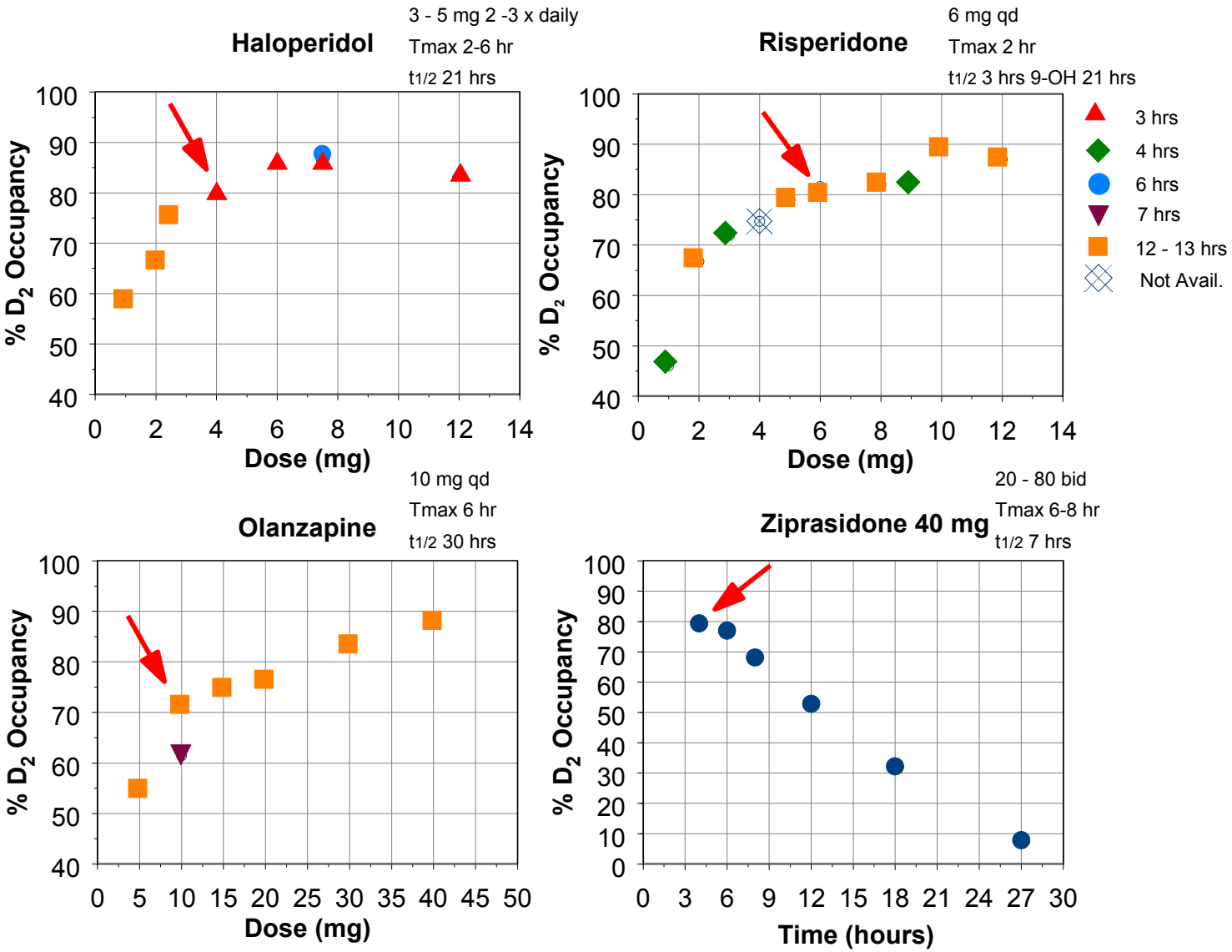


5.6.1.2.8 Reviewer's Dose Estimates Based on Analysis of PET Studies

Figure 150 shows graphs of average D2 receptor cccupancy by dose and time post administration for the four antipsychotics that did not have low apparent Emaxs. For 3 of the 4 drugs typical clinical doses result in 80% receptor occupancy. Since there is variability, peak receptor occupancy may be closer to 85% - 90% in many individuals.

As previously stated in §5.6.1.1.2.1 and §5.6.1.1.2.2 that respectively reviewed PET studies 25510 and 25516, fitting an Emax model to the asenapine D2 occupancy data indicates that a peak concentration of 3 – 9 ng/ml is needed to achieve 90% occupancy and that extrapolation of the data available at the time of the study indicates that a daily dosage of 10 mg is necessary to achieve this assuming dose linearity.

Figure 150 D2 Receptor Occupancy by Dose and Time of Administration for Four Antipsychotics



5.6.1.2.8.1 Conclusions

In summary, the modeling and simulation did not result in a better dose estimate than simply fitting and Emax model to the PET data and eyeballing doses needed to achieve these concentrations. However, the quantitative estimations of having a positive or failed study under various scenarios would be quite useful for business decisions, although additional model refinement is clearly needed as shown by the poor predictability of the current model.

Source: Clinical Summary

There are 63 trials in the asenapine schizophrenia and bipolar mania clinical development programs that were conducted with the sublingual formulation of asenapine as of the database cut-off of 15 January 2007. The safety information from the completed Phase 2/3 trials was analyzed in five cohorts. As of the January 15, 2007 database cutoff date, there were 11 deaths in the all asenapine group, 1 death in the placebo group, and 3 deaths in the olanzapine group.

One subject in the long-term schizophrenia trial (study 25517) died from aspiration during a *seizure*. The subject, a 33 year old Caucasian female had received asenapine 5-10 mg for one month during the study and was discontinued due to a *seizure*. Three months later, she had another seizure that resulted in death. This death is not included in the tables and listings because it occurred more than 30 days after the last dose. The most common adverse event leading to death was suicide (6 asenapine 5-10 mg b.i.d. [0.3%], 2 olanzapine [0.2%]). In addition, there were 2 drug overdoses that led to death, 1 in the asenapine 5-10 mg b.i.d. group (accidental overdose) and 1 in the olanzapine group (overdose) neither of the overdose cases was due to asenapine overdose. One subject died of cardiac failure in an ongoing trial

The most common cardiac AEs were bradycardia (3.6%) and tachycardia (2.8%) A 27 year old male Caucasian healthy volunteer (study 25506), collapsed 15 minutes after the end of a 30 minute intravenous infusion of asenapine (0.7 mg). Just prior to collapse, the subject reported feeling dizzy and unwell and then fell back on the bed. The event was reported as *asystole*; however, this event was considered to be due to neurally mediated reflex bradycardia. The subject recovered.

A 22 year old Caucasian male (resting heart of 58 bpm), received a 30 mg oral dose of asenapine in study 25501. Approximately 2.5 hours after the dose, the subject sat up in bed and felt dizzy and nauseated. The ECG telemetry strip showed heart rate slowing and an *8.7 second pause. This was followed by heart block with nodal bradycardia*, which spontaneously converted to sinus rhythm. He had another episode 2 hours later. Both episodes resolved spontaneously without intervention while the subject remained in the supine position

Vomiting, *syncope*, hypotension were experienced by a 23 year old female (study 25504), following asenapine (4 mg dose) on Day 13, which led to discontinuation from the study (considered related to study drug). Subject recovered the same day. Grand mal *convulsion* occurred in a 59 year old male (study 25505), following asenapine (2 mg dose) on Day 6, which led to discontinuation from the study. Subject recovered the same day. According to the investigator, the grand mal convulsion was due to hyponatraemia (sodium: 114 mmol/L) secondary to polydipsia and was not related to study drug (see Section 2.7.4.2.1.5.7 on hyponatraemia).

In the long-term schizophrenia study 25517, ECGs were performed at Screening, Weeks 3, 6, 24, and endpoint, and the tracings were read by a central laboratory. Analyses included interval changes from baseline (descriptive statistics), categorical changes, outlier analysis, and post-baseline markedly abnormal changes in morphology. The most frequently reported ECG related AE in the asenapine group (1.2%) was Electrocardiogram QT corrected interval prolonged (0.6% in the olanzapine treatment group).

Reviewers Comment: QT prolongation was also noted in clinical studies. Seizures can be expected in this population due to lowering of seizure threshold due to drug, polydipsia/substance abuse. However, syncope/asystole and an 8.7 sinus pause were noted in young healthy subjects.

Oral ORG 5222 (1-50 mg/kg) administered to conscious dogs induced dose-dependent negative inotropic and positive chronotropic effects, accompanied by shortening of the PR interval, less marked hypotensive effects and dose-dependently prolonged QTc. The QRS interval was shortened but only at the higher dose. Moderate orthostatic hypotension was observed on tilt which was accompanied by marked and dosedependent tachycardia. Behavioral excitation was observed at dose levels from 2.5 mg/kg onwards. Sublingual administration of ORG 5222 (0.01-1 mg/kg) induced dose dependent tachycardia in the absence of negative inotropy and hypotension. QTc was only markedly prolonged by the highest dose used which also lengthened QRS. A similar moderate orthostatic hypotension was seen upon tilt but the accompanying tachycardia was considerably less than after oral administration. Sublingually given Org 5222 caused minor and transient behavioral excitation at the highest dose only, but induced long lasting tranquilization especially at the mid and high doses.

Reviewer's Comment: Non clinical data are suggestive of dose-and concentration dependent QT prolongation.

3.2 PRECLINICAL INFORMATION

Source: nonclinical summary

ORG 5222, tested at 0.1, 0.3, and 1 μM concentrations using HEK-293 cells transfected with HERG produced statistically significant and concentration-dependent decreases in hERG current amplitude (30.9 ± 4.3%, 51.2 ± 5.7%, and 69.8 ± 5.8%, respectively) when compared to vehicle control. The IC50 for ORG 5222, the concentration computed from the concentration-response relationship at which 50% of total current was suppressed, was 0.3 μM.

The results of a study in isolated canine Purkinje fibers indicate that asenapine induced mainly decreases in action potential duration, in particular on APD_{50}. These effects were associated with a decrease in the plateau of action potential involving mainly calcium channel current. Decreases in action potential duration were dose-dependent and were more pronounced under low stimulation rate (0.33Hz) than under normal stimulation rates (1Hz). N-desmethylasenapine induced comparable effects (decreased action potential duration, particularly APD_{50}) but at approximately 10 times higher concentrations.

FDA Analysis: The Point Estimates and 90% CI Corresponding to the Largest Upper Bounds for Asenapine by Dose Group

Treatment	N	Time, h	Mean ΔΔQTcF, ms	90% CI, ms
Asenapine 5 mg b.i.d.	30	3	5.0	-1.5, 11.4
Asenapine 10 mg b.i.d.	27	2	10.5	4.5, 16.5
Asenapine 15 mg b.i.d.,	33	3	8.7	3.0, 14.4
Asenapine 20 mg b.i.d.,	29	4	4.9	-1.9, 11.6

An exposure-response analysis conducted by both the sponsor and FDA reviewers showed that asenapine prolonged the QTcF interval in a concentration-dependent manner (described in section 5.2.1.2). The model predicted mean ΔΔQTcF at a mean C_{max} of 10.6 ng/mL, which corresponds to an asenapine dose of 20 mg b.i.d., is 6 ms (8 ms, 90% upper confidence limit). Asenapine 20 mg b.i.d., the maximum tolerated dose in patients with schizophrenia, provides a 2-fold increase in exposure over the highest clinical dose (10 mg b.i.d.) and adequately covers the plasma concentrations observed in phase 2b/3 clinical studies (Figure 1). We note, however, that subjects with severe hepatic impairment have 7-fold increase unbound AUC. The magnitude of QT prolongation in these subjects is not known.

Because asenapine belongs to a pharmacological class of compounds associated with QT/QTc prolongation, the sponsor used quetiapine 375 mg b.i.d. as the positive control. The magnitude of quetiapine effects on the QTc interval is not well characterized. In this study, the difference from placebo in LS mean time-matched QTcF change from baseline at T_{max} was 7 ms (90% CI: 1, 13) on Day 10 and 10 (90% CI: 3, 17) ms on Day 16. The exposure-response relationship for quetiapine was similar to the observed relationship in Study R076477-SCH-1014 in NDA 21,999 (Table 13). Therefore, assay sensitivity with quetiapine could be established.

4.2.7.3 Safety Analysis There were no deaths reported in this trial. Three subjects experienced serious adverse events- a 51-year-old man, experienced severe atrial fibrillation on Day 1 after receiving a 5 mg dose of asenapine. He required hospitalization and was withdrawn from the trial. A 40-year-old woman, experienced a change in intensity of sinus tachycardia from mild to moderate on Study Day 9, and she was hospitalized. She was receiving quetiapine 375 mg b.i.d.. Study drug was discontinued and she was withdrawn from the trial. A 38-year-old woman experienced the adverse event of severe schizoaffective disorder 1 day after completing screening and starting to taper off her antipsychotic medication. Nine subjects, including 2 who experienced serious cardiac adverse events, discontinued from the trial due to adverse events. One of these subjects discontinued from the trial due to laboratory abnormalities (elevated LFT). Five discontinued due to psychiatric adverse events . The adverse events, other than oral adverse events (dry mouth, dysgeusia), experienced by 3 or more asenapine-treated subjects and reported for a higher percentage of asenapine-treated subjects than quetiapine- or placebo- treated subjects were somnolence, restlessness, anxiety and dizziness, constipation and fatigue, akathisia, gait disturbance, nasal congestion, loose stools, and dysarthria.

5.6.1.3 Effect on QTc

Asenapine prolonged QTc.

There were four study reports associated with the sponsor's evaluation of the effect of asenapine on QTc and they are listed in Table 166. Three of these study reports were located under eCTD section 5.3.5.4 (Reports of Efficacy and Safety Studies [Indication] – Schizophrenia – Other Study Reports), that this reviewer was advised not to examine.

Table 166 Study Reports Associated with the Sponsor's Evaluation of QTc

Study Report #	Study Report Title	Report Date
A7501001	A Double-Blind, Parallel, Multicenter Study to Assess the Effect of Asenapine, Quetiapine (Seroquel®), and Placebo on the QTc Interval in Patients With Schizophrenia	June, 2005
754-0046	Exposure-Response Analysis to Assess the Effect of Asenapine, Quetiapine (Seroquel®), or Placebo Administration on the QTc Interval in Patients with Schizophrenia	31 May 2006
INT00036960	Exposure-Response analysis to assess the Effect of Asenapine Administration on the QTc Interval in Patients with Schizophrenia (Phase 3 ACTAMESA study)	May, 2007
INT00036719	Population pharmacokinetic analysis using Phase 2/3 asenapine concentration data from patients with schizophrenia or bipolar disorder	May, 2007

The QT team performed the QT review and this may be found in the DFS file. Consequently this section of this review takes the most important graphs and tables from that review[11] and adds additional critiques when warranted. It should be noted that the QT review contains the sponsor's background information on clinical safety (with respect to cardiac effects) and preclinical *in vivo* and *in vitro* evaluations of cardiotoxicity, all of which are consistent with clinically significant arrhythmigenic potential.

Independent analyses by the QT team include selected data in Table 168, plus Figure 152 and Figure 153. Otherwise the QT team incorporates the sponsor's analyses into their review. This reviewer found that the manner in which the QT team wrote their review did not clearly indicate when analyses and discussions were taken directly from the sponsor's reports and when the QT did independent analyses and made independent assessments. In fact it is not even clearly stated that that report 754-0046 was reviewed and that figures were taken from that report.

Study A7501001 was a double-blind, placebo and active controlled parallel design, multicenter PK/PD study to assess the effect of asenapine on the QTc interval in male and female patients with schizophrenia.

Treatments are shown in Table 167. The study was designed to have 30 completers per group. It's readily apparent from Table 167 that not only is this a parallel design with respect to the test drug and the active comparator but also with respect to placebo which results in additional intersubject variability with respect to subtraction of baseline drug ΔQTc from time matched placebo ΔQTc.

[11] Except for Figure 157and Figure 158 which this reviewer took from the sponsor's study report as the QT review included them as black and white graphics rather than in color.

Table 167 Treatment Groups and Dosing in TQTc - Study A7501001

Group	Drug	Period 1: Target Dose (post Titration)	Period 2: Target Dose (post Titration)
1	Asenapine	5 mg BID 10 days	10 mg BID 6 days
2	Asenapine	15 mg BID 10 days	20 mg BID 6 days
3	Quetiapine	375 mg BID 10 days	375 mg BID 6 days
4	Placebo	BID 10 days	BID 6 days

Table 168 on the following page shows the statistical reviewer's analysis at each time point post-dosing for the various asenapine dosing regimens. The study is clearly positive with a maximum upper limit of the 90% CI for the mean change in ΔΔQTc of 16.5 mSec (i.e. above 10 mSec) at 4 hours after dosing of 10 mg BID. It's noteworthy that the change in ΔΔQTc is greater with proposed clinical dose of 10 mg BID than with the higher doses of 15 mg and 20 mg BID. Although there is a signal for a clinically significant QT effect for asenapine at even 5 mg SL BID.

It's also noteworthy that the sponsor's analysis has an even greater upper limit of 17.5 mSec based on manually read ECGs which are typically considered more reliable than machine read ECGs which I'm assuming was what was used in the statistician's analysis, (see Table 168).

Table 168 Difference in Least Square Means from Placebo of Time Matched Change from Baseline in QTcF (ΔΔQTcF) – Study A7501001

Treatment Day	Treatment Comparison	Statistical Reviewer's Analysis					Sponsor's Analysis of Manually Read ECGs				
		N	Time Post-Dose (hour)	Difference (SE)	Lower Limit 90% CI	Upper Limit 90% CI	N	Time Post-Dose (hour)	Difference (SE)	Lower Limit 90% CI	Upper Limit 90% CI
Day 10	Asenapine 5 mg b.i.d. vs Placebo	30	1	0.9 (4.2)	-6.0	7.9	30	1	0.9	-5.0	6.9
		30	2	2.6 (3.4)	-3.0	8.2	30	2	2.6	-3.3	8.6
		30	3	5.0 (3.9)	-1.5	**11.4**	30	3	5.0	-1.0	**10.9**
		30	4	5.8 (3.0)	0.8	**10.8**	30	4	5.8	-0.2	**11.7**
		30	6	4.1 (3.0)	-0.8	8.9	30	6	4.1	-1.9	**10.0**
		29	8	5.8 (3.4)	0.3	**11.3**	29	8	5.9	-0.1	**11.9**
		29	12	0.8 (3.6)	-5.1	6.6	29	12	0.9	-5.1	6.8
	Asenapine 15 mg b.i.d. vs Placebo	33	1	5.6 (3.7)	-0.6	**11.7**	33	1	5.6	-0.2	**11.4**
		33	2	6.4 (3.4)	0.9	**12.0**	33	2	6.4	0.6	**12.3**
		33	3	8.7 (3.5)	3.0	**14.4**	33	3	8.7	2.9	**14.5**
		33	4	8.0 (3.4)	2.5	**13.6**	33	4	8.0	2.2	**13.8**
		33	6	5.1 (2.5)	0.9	9.2	33	6	5.1	-0.8	**10.9**
		33	8	6.2 (3.2)	0.9	**11.3**	33	8	6.1	0.3	**12.0**
		32	12	1.2 (3.2)	-4.1	6.5	32	12	1.0	-4.8	6.9
Day 16	Asenapine 10 mg b.i.d. vs Placebo	27	1	3.4 (3.3)	-2.0	8.8	27	1	3.4	-3.13.9	**10.0**
		27	2	10.5 (3.6)	4.5	**16.5**	27	2	10.5		**17.1**
		27	3	-0.4 (3.8)	-6.6	5.9	27	3	-0.4	-6.9	6.2
		27	4	9.3 (4.4)	2.0	**16.5**	27	4	9.3	2.7	**15.9**
		26	6	6.0 (3.8)	-0.3	**12.3**	26	6	6.2	-0.4	**12.8**
		26	8	5.0 (4.3)	-2.0	**12.1**	26	8	5.2	-1.4	**11.9**
		26	12	0.2 (4.9)	-7.8	8.3	26	12	0.4	-6.2	7.1
	Asenapine 20 mg b.i.d. vs Placebo	29	1	2.6 (3.5)	-3.2	8.4	29	1	2.6	-3.8	9.1
		29	2	5.2 (3.6)	-0.7	**11.2**	29	2	5.2	-1.2	**11.7**
		29	3	-1.1 (4.3)	-8.1	5.9	29	3	-1.1	-7.5	5.4
		28	4	4.9 (4.1)	-1.9	**11.6**	28	4	5.1	-1.4	**11.6**
		29	6	-1.3 (3.8)	-7.5	4.9	29	6	-1.3	-7.8	5.1
		29	8	-1.8 (4.1)	-8.5	5.0	29	8	-1.8	-8.2	4.7
		29	12	-1.4 (4.6)	-9.0	6.2	29	12	-1.4	-7.9	5.0

Figure 151 shows the positive results for the positive control quetiapine and the similar degree of maximal ΔΔQTc seen with the dosage used.

Figure 151 Sponsor's Table 4 of Manually Read ECG Double-Delta QTcFs for Quetiapine

Table 4: Difference in Least Square Means of Quetiapine from Placebo of Time Matched Change from Baseline in QTcF (Manually Read)

Treatment Comparison	Time Post-Dose (hour)	N	Difference	90% Lower	90% Upper
Day 10					
Quetiapine 375 mg b.i.d. vs Placebo	1	30	2.5	-3.5	8.4
	2	30	6.7	0.8	12.7
	3	30	7.5	1.5	13.4
	4	30	7.9	1.9	13.8
	6	30	2.7	-3.2	8.7
	8	30	10.9	4.9	16.8
	12	30	3.1	-2.8	9.0
Day 16					
Quetiapine 375 mg b.i.d. vs Placebo	1	27	4.1	-2.5	10.7
	2	27	9.9	3.3	16.5
	3	27	6.9	0.4	13.5
	4	27	6.8	0.3	13.4
	6	27	3.1	-3.4	9.7
	8	27	4.9	-1.7	11.5
	12	27	-0.6	-7.2	6.0

Sponsor's Section 11.1.2.01.01.01, pages236-239 of CSR for A750-1001

Figure 152 and Figure 153 are the only independent data analysis that appears to have been performed by the QT team. They show linear-log plots of the linear model of mean ΔΔQTcF vs. drug concentration with a 90% CI for asenapine and quetiapine respectively. In addition, the QT team pharmacometricians divided the reported drug concentrations into 10% quartiles, which is shown at the bottom of the graphs. They then calculated the mean and 90% CI for the ΔΔQTc at the median concentration for each quartile and overlaid this on the linear plot. What is interesting about these are, a) there appears to possibly be a nonlinear relationship in particular with quetiapine that suggests a threshold effect, b) the 90% upper limit for asenapine barely breaks the 10 mSec threshold in contrast to the analysis by time post-dose, whereas it appears more similar quetiapine, c) the upper range of the measured asenapine concentrations only goes slightly above 10 ng/ml (possible 14 ng/ml) whereas Figure 154 on the following page clearly shows that asenapine concentrations clearly go up to 20 ng/ml in this study with a dose of 20 mg SL BID. In addition Figure 155 shows that concentrations of 20 ng/ml were commonly seen with sparse sampling with the phase IIb/III efficacy studies at the maximum studied clinical dose of 10 mg SL BID

Figure 152 Linear Model of ΔΔQTcF vs. Asenapine Concentration Overlaid with Mean QT Prolongation with 90% CIs at the Median-of the 10% Quantiles for Asenapine Concentration

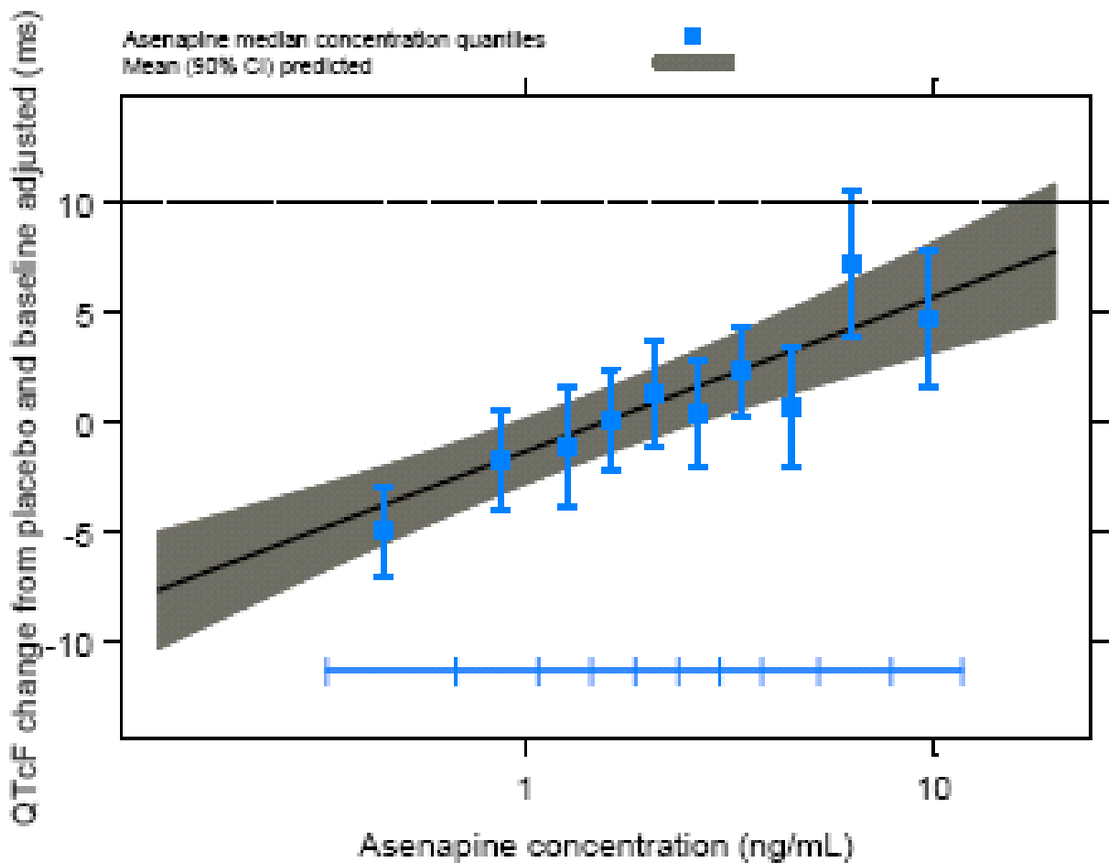


Figure 153 Linear Model of ΔΔQTcF vs. Quetiapine Concentration Overlaid with Mean QT Prolongation with 90% CIs at the Median-of the 10% Quantiles for Quetiapine Concentration.

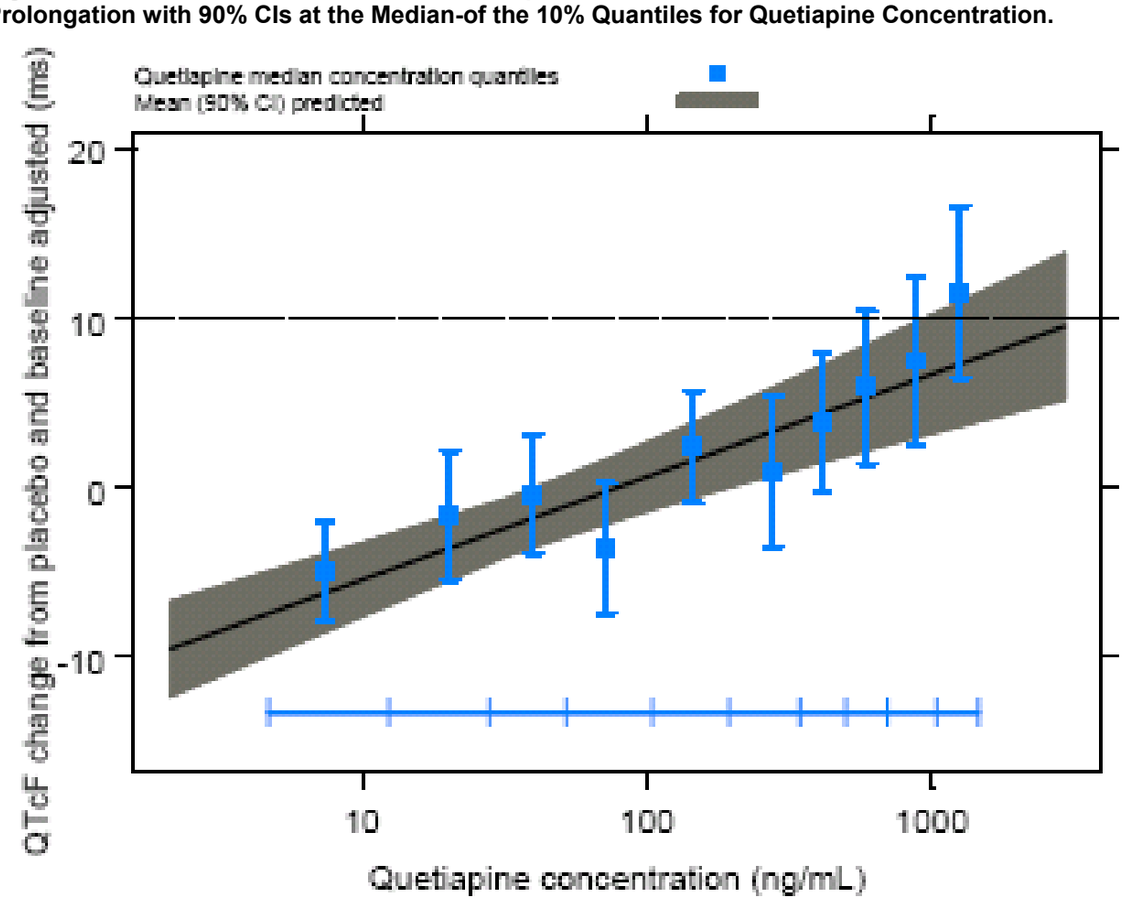


Figure 154 Steady State Asenapine Concentrations with Overlaid Mean Concentration vs. Time Profile Prediction with 90% CIs for Asenapine 20 mg SL BID. Data from Thorough QT study – A7501001

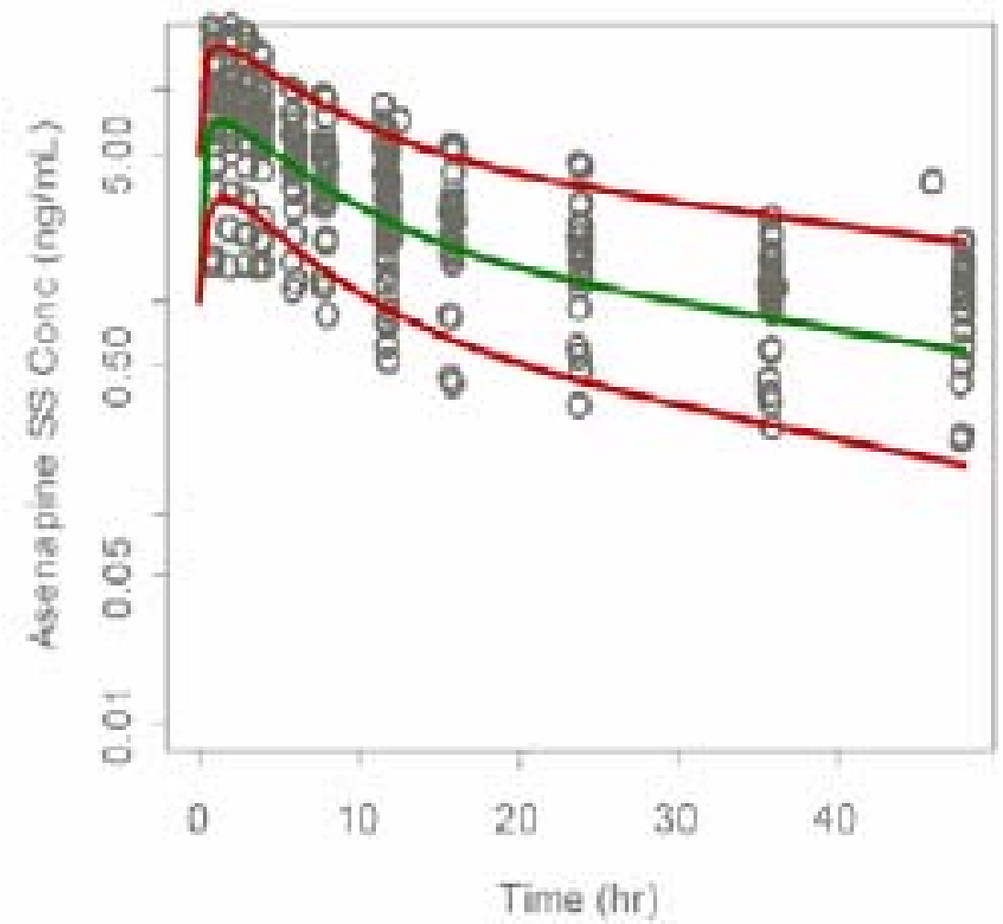
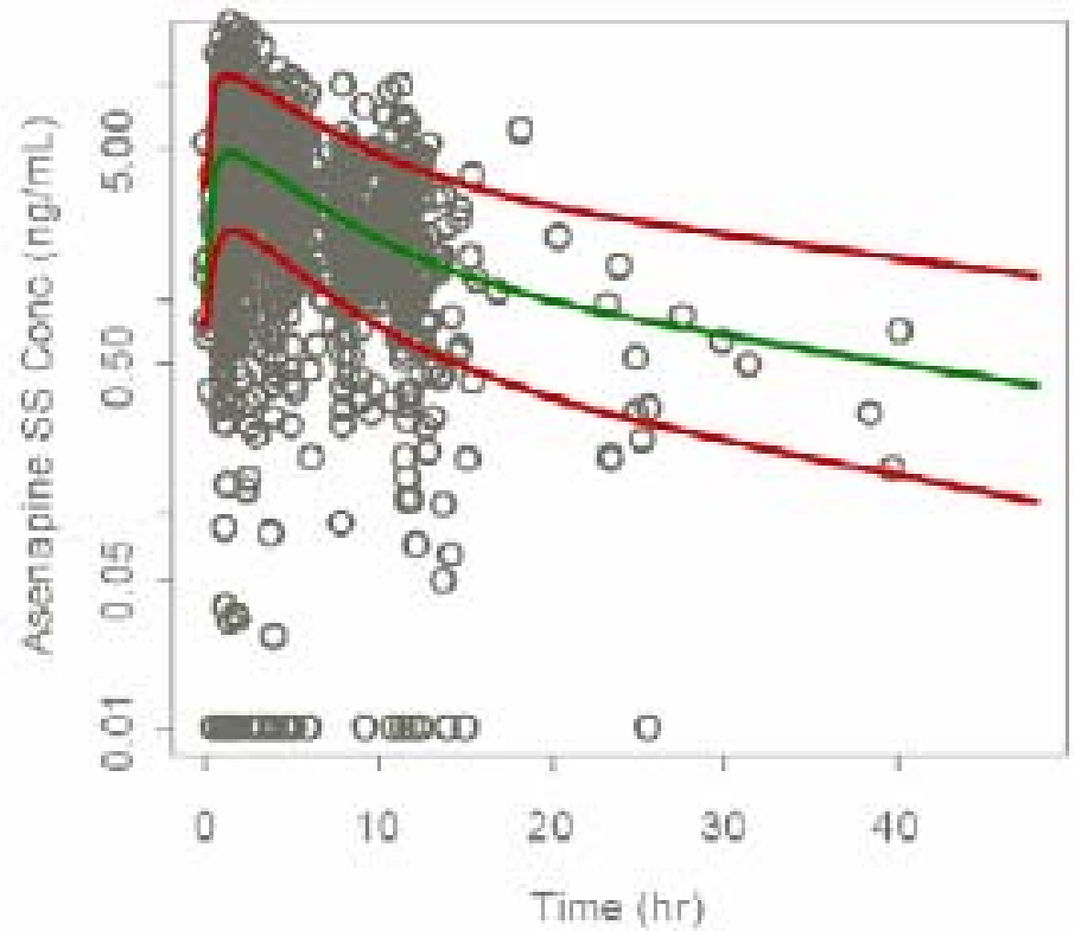


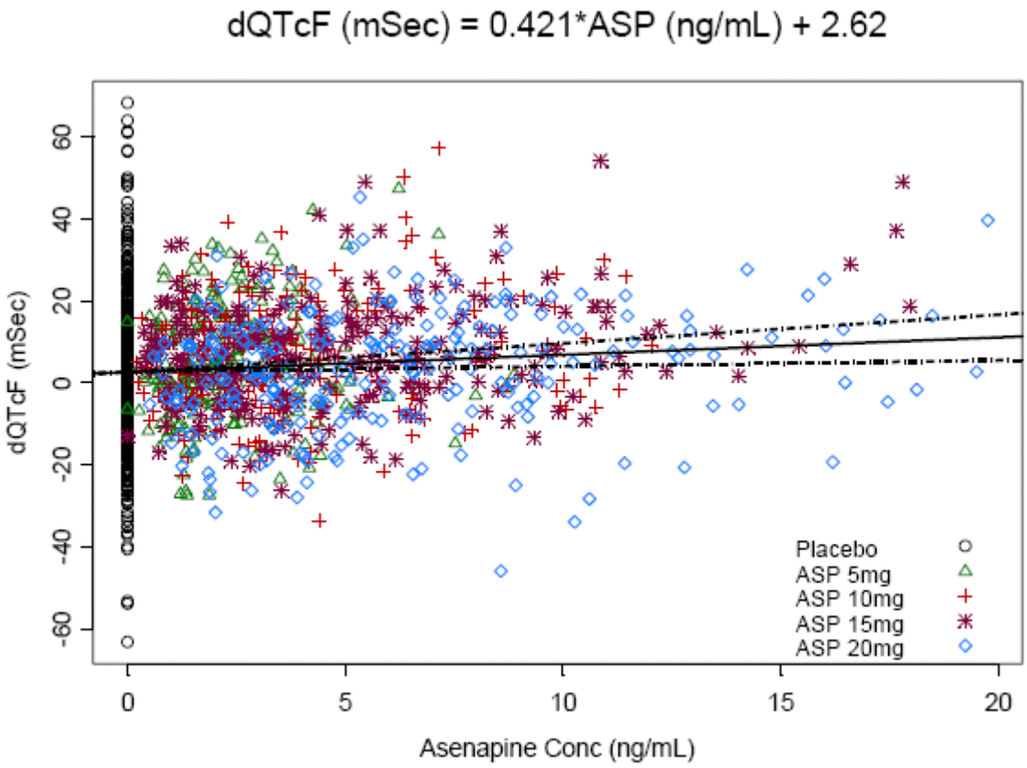
Figure 155 Steady State Asenapine Concentrations with Overlaid Mean Concentration vs. Time Profile Prediction with 90% CIs for Asenapine 10 mg SL BID. Data from TQT and phase IIb/III Studies



Although this reviewer when evaluating the data files submitted for the pop PK study found that there were no asenapine concentrations greater than 10 ng/ml.

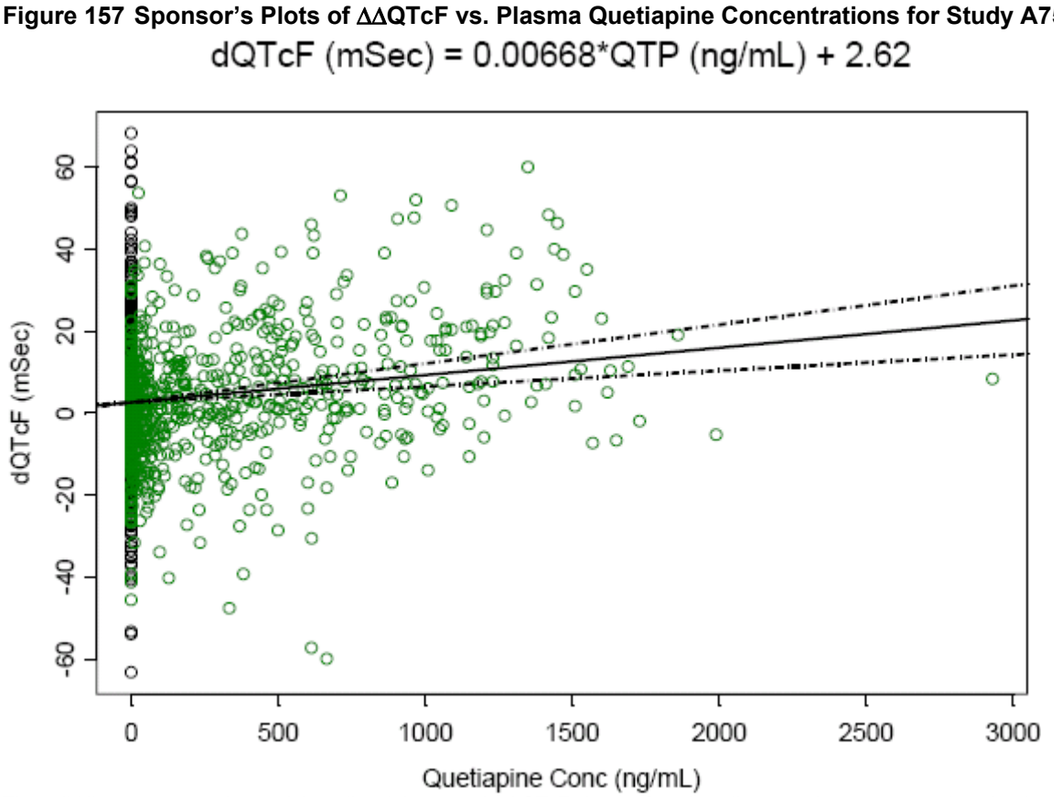
Figure 156 and Figure 158 shows the sponsor's linear models of ΔΔQTcF vs. plasma asenapine and quetiapine concentrations. It's clear that asenapine concentrations do go up to 20 ng/ ml and that most concentrations between 10 and 20 ng/ml are achieved by a dose of 20 mg BID followed by a dose of 15 mg BID, although the mean and upper limits of the CI are much lower than the values seen with the post-administration time dose data. In addition, most Quetiapine concentrations are below 2000 ng/ml at a dose of 375 mg BID which is within the therapeutic dose range of 400 – 800 mg daily. Assuming the highest concentration seen with quetiapine is 2750 ng/ml the maximum dose may result in concentrations of nearly 6000 ng/ml in some individuals. This translates into a ΔΔQTc of over 35 mSec in spite of this quetiapine is not generally considered to have a higher than normal incidence for arrhythigenic potential.

Figure 156 Sponsor's Plot of ΔΔQTcF vs. Plasma Asenapine Concentration for A7501001



The solid line represents the model-predicted time-matched QTcF change from baseline at a given concentration; the dotted lines represent the 95% confidence interval of the model-predicted time-matched QTcF change from baseline; color-coded symbols represent individual patient observations.

Figure 157 Sponsor's Plots of ΔΔQTcF vs. Plasma Quetiapine Concentrations for Study A7501001



The solid line represents the model predicted time-matched QTcF change from baseline at a given concentration; the dotted lines represent the 95% confidence interval of the model predicted time-matched QTcF change from baseline; symbols represent individual patient observations.

Figure 158 shows that when the percent of subjects with changes of 30 – 60 mSec are considered asenapine is no worse than Quetiapine. However when the maximal absolute QTcF is examined women appear to achieve higher QTcFs than males, (see Figure 159). This may be due to lower body mass and higher concentrations in women. This may also help to partly explain the higher ΔΔQTcF seen with the 10 mg SL BID dose, (see Table 169).

Figure 158 Sponsor's Table 6 of Categorical Changes in ΔQTcF by Treatment Group

Table 6: Categorization of QTcF maximum increase from baseline by treatment group

		N (%) of Subjects by Maximum QTcF Increase from Baseline		
Study Day		<30 msec	30-<60 msec	≥60 msec
Treatment	N	n (%)	n (%)	n (%)
Day 1[a] through Day 10				
Placebo	35	27 (77.1%)	6 (17.1%)	2 (5.7%)
Asenapine 5 mg	38	31 (81.6%)	7 (18.4%)	0 (0.0%)
Asenapine 15 mg	38	28 (73.7%)	10 (26.3%)	0 (0.0%)
Quetiapine 375 mg	37	22 (59.5%)	14 (37.8%)	1 (2.7%)
Day 11 through Day 16				
Placebo	32	27 (84.4%)	3 (9.4%)	2 (6.3%)
Asenapine 10 mg	28	20 (71.4%)	8 (28.6%)	0 (0.0%)
Asenapine 20 mg	30	23 (76.7%)	7 (23.3%)	0 (0.0%)
Quetiapine 375 mg	29	20 (69.0%)	9 (31.0%)	0 (0.0%)

Source: 11.1.2.01.01.06
[a] Post dose

Sponsor's Table 38, page 95 of CSR for A750-1001

Figure 159 Sponsor's Table 5 of Categorical QTcFs by Gender and Treatment

Table 5: Categorization of QTcF Data by Gender and Treatment Group

		Number (Percent) of Subjects by Maximum Post-dose QTcF (msec)								
		---------- Males ----------				---------- Females ----------				
		<430	430-<450	450-<500	≥500		<450	450-<470	470-<500	≥500
Treatment	N	n(%)	n(%)	n(%)	n(%)	N	n(%)	n(%)	n(%)	n(%)
Baseline										
Placebo	28	27 (96.4)	1 (3.6)	0 (0.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 5 mg	33	33 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	26 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	12	12 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quetiapine 375 mg	27	27 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 1[a] through Day 10										
Placebo	28	27 (96.4)	0 (0.0)	1 (3.6)	0 (0.0)	7	6 (85.7)	0 (0.0)	1 (14.3)	0 (0.0)
Asenapine 5 mg	33	29 (87.9)	4 (12.1)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	24 (92.3)	1 (3.8)	1 (3.8)	0 (0.0)	12	9 (75.0)	2 (16.7)	1 (8.3)	0 (0.0)
Quetiapine 375 mg	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	10	9 (90.0)	1 (10.0)	0 (0.0)	0 (0.0)
Day 11 through Day 16										
Placebo	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 10 mg	24	21 (87.5)	3 (12.5)	0 (0.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 20 mg	20	20 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	8 (80.0)	1 (10.0)	1 (10.0)	0 (0.0)
Quetiapine 375 mg	22	22 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)

Source: 11.1.2.01.01.05
[a] Post dose

Sponsor's Table 36, page 93 of CSR for A750-1001

In contrast the QT team reports that: *'In the long-term schizophrenia study 25517, ECGs were performed at Screening, Weeks 3, 6, 24, and endpoint, and the tracings were read by a central laboratory. Analyses included interval changes from baseline (descriptive statistics), categorical changes, outlier analysis, and post-baseline markedly abnormal changes in morphology. The most frequently reported ECG related AE in the asenapine group (1.2%) was Electrocardiogram QT corrected interval prolonged (0.6% in the olanzapine treatment group).'*

This was a flexible dose study of asenapine 5 – 10 mg BID vs. Olanzapine 10 – 20 mg QD with randomization in a 3:1 ratio to the lower to higher doses. Dosage adjustments and exposures were similar however EPS was nearly doubled in the asenapine group, elevations in LFTs were lower, by worsening psychosis and dropoutw were worse in the asenapine arms.

The percentage of women treated with asenapine ranged from 13.2% of the asenapine 5/10 mg group (5 of 38 subjects) to 31.6% of the asenapine 15/20 mg group (12 of 38 subjects).

Table 169 Sponsor's Table 15 Summary of subject characteristics: safety analysis group

Characteristic	Placebo	Asenapine BID		Quetiapine 375 mg BID	All Subjects
		5/10 mg	15/20 mg		
N	35	38	38	37	148
Male	28 (80.0%)	33 (86.8%)	26 (68.4%)	27 (73.0%)	114 (77.0%)
Female	7 (20.0%)	5 (13.2%)	12 (31.6%)	10 (27.0%)	34 (23.0%)
Premenopausal	6 (85.7%)	4 (80.0%)	6 (50.0%)	7 (70.0%)	23 (67.6%)
Postmenopausal	1 (14.3%)	1 (20.0%)	6 (50.0%)	3 (30.0%)	11 (32.4%)
Race, n (%)					
Caucasian	16 (45.7%)	12 (31.6%)	18 (47.4%)	11 (29.7%)	57 (38.5%)
Black	13 (37.1%)	19 (50.0%)	18 (47.4%)	21 (56.8%)	71 (48.0%)
Asian	1 (2.9%)	1 (2.6%)	0 (0.0%)	1 (2.7%)	3 (2.0%)
Other	5 (14.3%)	6 (15.8%)	2 (5.3%)	4 (10.8%)	17 (11.5%)
Age	44.8 ± 8.4 19 - 57 [45.0]	42.4 ± 9.5 23 - 57 [43.5]	43.6 ± 7.7 28 - 56 [44.0]	39.6 ± 7.6 26 - 53 [39.0]	42.6 ± 8.5 19 - 57 [43.0]
Weight (kg)	83.8 ± 14.8 52 - 114 [83.6]	82.1 ± 17.4 48 - 127 [81.5]	86.4 ± 14.0 55 - 113 [85.5]	84.9 ± 17.0 56 - 126 [82.7]	84.3 ± 15.8 48 - 127 [83.6]
BMI	27.5 ± 5.0 18 - 35 [27.1]	26.5 ± 4.5 17 - 35 [26.7]	29.2 ± 4.2 20 - 36 [29.4]	28.0 ± 4.4 20 - 35 [27.0]	27.8 ± 4.6 17 - 36 [27.7]
Alcohol Use (drinks per week)	1.8 ± 4.55 0 - 22 [0.0]	0.6 ± 1.43 0 - 6 [0.0]	0.6 ± 1.39 0 - 6 [0.0]	0.2 ± 0.72 0 - 3 [0.0]	0.8 ± 2.50 0 - 22 [0.0]

Other factors that may have biased the results are that virtually all subjects were smokers, (see Table 147), which induces asenapine's metabolism and would decrease exposure, and Subjects were to have had their meals before dosing and to be finished eating at least 15 minutes before each dose which would also decrease exposures, (see). Consequently, those who don't smoke, those with smaller body mass, and more typical administration not in combination with a meal would all result in higher exposures even

with the 5 mg dose and the 10 mg dose than seen in the present study. All of these factors point to a greater risk for cardiotoxicity in patients with bipolar illness, as they are likely to include more nonsmokers, and children.

The QT data in women as well as the higher exposures seen in mild hepatic impairment and the elderly indicate that these groups may be at increased risk as well.

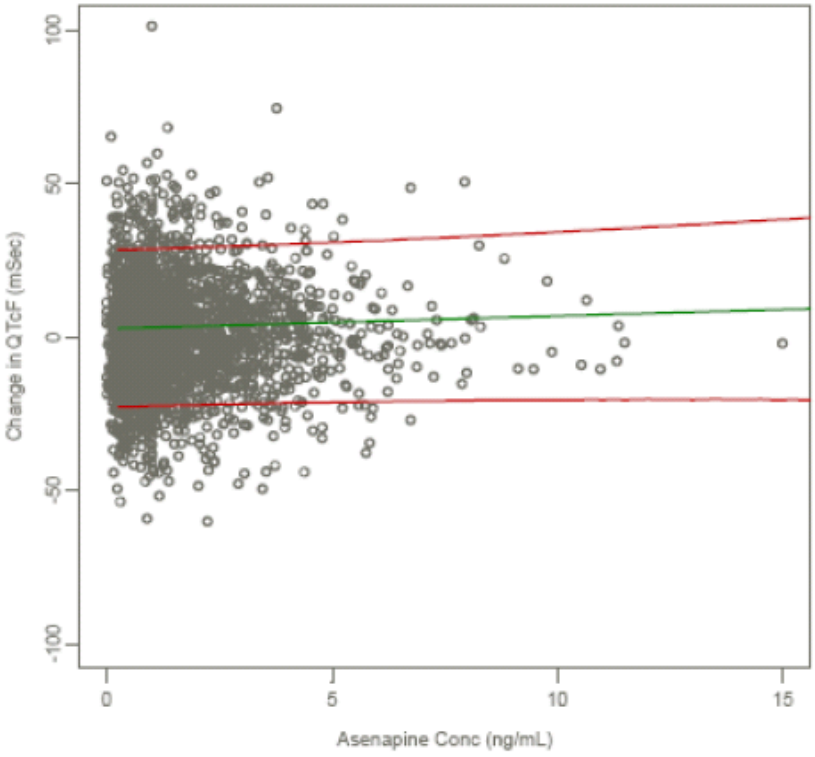
Figure 160 is claimed to be plot of observed ΔΔQTcF from the TQTc study vs. individual predicted concentrations based on a population pharmacokinetic model for a phase 3 schizophrenia trial of Asenapine 5 mg or 10 mg BID with sparse sampling.

Interpretation is difficult as it's not clear how you can even reasonably plot this information from two different studies with two different subject populations. Also the variability in ΔΔQTc is so wide even at zero concentration there is a positive QT effect with and upper limit of approximately 30 mSec.

However upon further review of the original study report it was realized that this is intended to not show the 90% CIs on the mean data, but rather the 90% CIs on all QTc changes in the population. Consequently we can see that we expect a significant amount of ΔΔQTcF of 30 – 60 mSec with clinical dosing and 4 values of greater than 60 mSec even with concentrations less than 5 ng/ml. Unfortunately the data files did not include ΔΔQTcF so the proportion of subjects at each dose that had significant changes could not be assessed. However examination of absolute QTcFs revealed that 1.1% of subjects had QTcF values of greater than 450 mSec.

Figure 160 Sponsor's Figure 4 from INT00036960 Plotting Observed ΔΔQTcF from Study A7501001 vs. Population PK individually Predicted Asenapine Concentrations from Phase III Efficacy Study 25517

Figure 4: Unconditional Prediction Interval Overlaid with Observed ΔΔQTcF vs. Individual Predicted Asenapine Concentrations from Study 25517, A Phase 3 Study



Sponsor's Figure 4, page 20 from Study INT00036960

5.6.2 Exposure Response

5.6.2.1 Schizophrenia

5.6.2.1.1 Acute Treatment of Psychosis

Table 170 and Table 171 show the sponsor's summary of the statistical analysis of 4 phase IIB and phase III active and placebo controlled trials of the efficacy of asenapine in the short term treatment of an acute psychotic episode in patients with schizophrenia as assessed by total PANSS score. These tables are from the sponsor's summary of clinical efficacy and only include those trials that utilized dosages that are proposed for marketing. Table 170 shows analysis by LOCF, where as Table 171 shows analyses using mixed models of repeated measures, (MMRM). No summary tables were provided for analyses by OC. As expected the mixed model of repeated measures shows a greater degree of statistical significance and this will be discussed later.

Even based on simple inspection of these data tables immediately reveal concerns with the studies, including:

- Of 4 studies only 2, the smaller initial phase IIb study 41004 and the last phase III study 41023, were positive. The other 2 phase III studies were negative.
- The active control risperidone failed to show efficacy in the positive phase IIb study 41004 in spite of adequate dosing and is therefore a 'failed' study.
- Only the lower dose of asenapine 5 mg BID and not the higher dose of 10 mg BID showed efficacy in the second positive study 41023.
- Although the most efficatious available antipsychotics were used at therapeutic doses, i.e. risperidone 3 mg BID, olanzapine 10 – 20 mg QD, and haloperidol 4 mg BID, the difference from placebo was minimal, i.e. ~5.6, -5.4 and -2.3, and -5.7 respectively. Whereas the difference from placebo expected with each of these compounds is on the order of at least -10 and closer to -15 units.

Due to the size and complexity of the submission, this reviewer's lack of skill in the new computer programs and CDISC data files and need for training, lack of assistance from the pharmacometrics group[12], lack of prior experience in analyzing antipsychotic ER data, and the insufficient time available for the present review, this reviewer in the time available simply undertook an exploratory evaluation of the exposure response relationships for efficacy for the two 'positive' studies 41004 and 41023.

[12] The pharmacometrics group was represented at the scoping meeting. The clinical division asked whether swallowing drug from the sublingual formulation would effect efficacy. This reviewer replied that on an individual basis this is possible however there would be variability from day to day and since the clinical studies were claimed to be positive this would have shown up as negative results or decreased efficacy in the clinical studies with the active comparator showing activity. No questions were asked by the clinical division regarding toxicity.

Table 170 Sponsor's Inferential Analysis of Change from Baseline in PANSS Total Score (LOCF, ITT group) for Short-Term Schizophrenia Trials 041004, 041021, 041022, and 041023

Study		041004			041021			
Treatments		Placebo	Asenapine 5 mg BID	Risperidone 3 mg BID	Placebo	Asenapine		Olanzapine 15 mg QD
						5 mg BID	10 mg BID	
Rx Arm (tcaf)		3	2	1	1			
N		60	58	56	93	102	96	95
Baseline		92.4 (1.9)	96.5 (2.2)	92.2 (2.1)	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
Δ to:	Day 4				-3.9 (.8)	-4.0 (0.8)	-5.5 (0.8)	-3.3 (0.8)
	Day 7	-3.9 (1.5)	-6.2 (1.7)	-5.6 (1.8)	-6.5 (1.0)	-7.8 (1.0)	-8.8 (1.0)	-7.1 (1.0)
	Day 14	-5.5 (1.6)	-11.3 (2.0)*	-8.3 (2.4)	-9.8 (1.3)	-13.1 (1.3)	-11.5 (1.3)	-11.6 (1.3)
	Day 21	-6.4 (2.1)	-16.9 (2.4)*	-10.8 (2.8)	-10.5 (1.4)	-12.9 (1.4)	-11.9 (1.4)	-12.8 (1.4)
	Day 28	-6.6 (2.3)	-16.9 (2.5)*	-10.3 (2.7)	-10.7 (1.5)	-14.0 (1.5)	-12.0 (1.5)	-14.6 (1.5)
	Day 35	-4.7 (2.2)	-16.0 (2.6)*	-10.5 (2.7)	-10.2 (1.6)	-14.5 (1.5)*	-13.1 (1.6)	-15.8 (1.6)*
	Day 42	-5.3 (2.3)	-15.9 (2.6)*	-10.9 (2.7)	-11.1 (1.6)	-14.4 (1.6)	-13.5 (1.6)	-16.5 (1.6)*
	Endpoint	—	—	—	-11.1 (1.6)	-14.5 (1.6)	-13.4 (1.6)	-16.5 (1.6)*

Study		041022			041023			
Treatments		Placebo	Asenapine	Olanzapine	Placebo	Asenapine		Haloperidol
			5/10 mg BID	10-20 mg QD		5 mg BID	10 mg BID	4 mg BID
Rx Arm (tcaf)								
N		89	85	85	122	109	105	112
Baseline		84.7 (1.1)	86.8 (1.1)	86.5 (1.1)	89.0(0.9)	88.9 (1.0)	89.4 (1.0)	88.5 (1.0)
Δ to:	Day 4	-2.9 (0.7)	-4.2 (0.7)	-3.7 (0.7)	-3.4 (0.7)	-2.9 (0.8)	-4.4 (0.8)	-3.4 (0.8)
	Day 7	-4.8 (1.2)	-4.9 (1.2)	-5.0 (1.1)	-5.9 (0.9)	-7.2 (1.0)	-7.7 (1.0)	-7.3 (1.0)
	Day 14	-7.1 (1.5)	-8.7 (1.5)	-9.2 (1.5)	-8.3 (1.1)	-10.5 (1.2)	-10.4 (1.2)	-11.0 (1.2)
	Day 21	-8.8 (1.6)	-9.5 (1.6)	-9.9 (1.6)	-9.1 (1.3)	-13.2 (1.4)*	-11.6 (1.4)	-13.8 (1.4)*
	Day 28	-8.9 (1.6)	-10.0 (1.6)	-10.7 (1.6)	-9.4 (1.4)	-14.2 (1.5)*	-11.7 (1.5)	-14.4 (1.5)*
	Day 35	-9.3 (1.7)	-10.1 (1.7)	-11.2 (1.7)	-10.2 (1.5)	-15.3 (1.6)*	-13.3 (1.6)	-14.7 (1.5)*
	Day 42	-10.1 (1.7)	-9.1 (1.7)	-11.4 (1.7)	-10.8 (1.6)	-16.2 (1.7)*	-14.7 (1.7)	-15.6 (1.6)*
	Endpoint	-9.9 (1.7)	-9.4 (1.7)	-11.5 (1.7)	-10.7 (1.6)	-16.2 (1.7)*†	-14.9 (1.7)	-15.4 (1.6)*

Source: Table 16 in CTR 041004, Table 15 in CTR 041021; Table 16 in CTR 041022; Table 16 in CTR 041023.
All values are mean (SE)
*indicates p≤0.05. In the Phase II trials, p-values were based on a two-sided t-test comparing each active treatment group with the placebo group; an ANOVA model with fixed effects for treatment and pooled investigative site was used. In the Phase III trials, an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate was used; p-values are based on the difference in the LS mean change for active treatment versus placebo.
† indicates adjusted p≤0.05. Adjusted p-values were determined in Trials 041021 and 041023 using Hochberg method for testing 2 asenapine groups versus the placebo group.

Table 171 Sponsor's Mixed Model for Repeated Measures (MMRM) Analysis of Change from Baseline in PANSS Total Score (ITT Group)

Study		041004			041021			
Treatments		Placebo	Asenapine 5 mg BID	Risperidone 3 mg BID	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Olanzapine 15 mg QD
Rx Arm (tcaf)		3	2	1	1			
N		60	58	56	93	102	96	95
Baseline		92.4 (1.9)	96.5 (2.2)	92.2 (2.1)	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
Δ to:	Day 4	NA	NA	NA	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
	Day 7	-4.8 (1.5)	-6.0 (1.6)	-6.3 (1.6)	-3.9 (0.8)	-4.0 (0.8)	-5.5 (0.8)	-3.3 (0.8)
	Day 14	-6.5 (2.0)	-12.3 (2.0)*	-9.6 (2.0)	-6.4 (1.0)	-7.6 (1.0)	-8.9 (1.0)	-7.2 (1.0)
	Day 21	-8.0 (2.4)	-20.1 (2.4)*	-13.7 (2.4)	-10.0 (1.4)	-13.1 (1.3)	-11.9 (1.4)	-11.8 (1.4)
	Day 28	-9.1 (2.9)	-20.8 (2.9)*	-12.4 (2.8)	-11.1 (1.6)	-13.3 (1.5)	-13.7 (1.6)	-14.0 (1.6)
	Day 35	-7.0 (3.3)	-20.1 (3.2)*	-15.5 (3.2)	-11.4 (1.7)	-15.2 (1.6)	-14.2 (1.7)	-16.7 (1.7)*
	Day 42	-8.5 (3.4)	-19.8 (3.3)*	-16.2 (3.3)	-11.6 (1.8)	-16.3 (1.7)	-16.3 (1.8)	-18.7 (1.8)*

Study		041022			041023			
Treatments		Placebo	Asenapine 5/10 mg BID	Olanzapine 10-20 mg QD	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Haloperidol 4 mg BID
Rx Arm (tcaf)								
N		89	85	85	122	109	105	112
Baseline		84.7 (1.1)	86.8 (1.1)	86.5 (1.1)	89.0 (0.9)	88.9 (1.0)	89.4 (1.0)	88.5 (1.0)
Δ to:	Day 4	-2.9 (0.7)	-4.1 (0.7)	-3.7 (0.7)	-3.4 (0.7)	-2.9 (0.8)	-4.4 (0.8)	-3.4 (0.8)
	Day 7	-5.5 (1.1)	-5.3 (1.2)	-5.8 (1.2)	-6.2 (0.9)	-7.3 (1.0)	-8.0 (1.0)	-7.7 (1.0)
	Day 14	-8.6 (1.5)	-10.4 (1.5)	-11.1 (1.5)	-9.4 (1.2)	-11.5 (1.3)	-12.0 (1.3)	-12.3 (1.2)
	Day 21	-12.2 (1.7)	-12.3 (1.7)	-12.6 (1.7)	-10.9 (1.3)	-15.7 (1.4)*	-13.9 (1.4)	-16.1 (1.4)*
	Day 28	-13.9 (1.7)	-13.9 (1.7)	-14.5 (1.7)	-12.0 (1.4)	-17.9 (1.5)*	-14.5 (1.5)	-17.2 (1.5)*
	Day 35	-14.2 (1.9)	-14.0 (2.0)	-15.2 (2.0)	-13.3 (1.5)	-19.7 (1.6)*	-17.4 (1.6)	-18.0 (1.6)*
	Day 42	-15.6 (2.0)	-11.6 (2.1)	-15.9 (2.1)	-14.6 (1.6)	-21.3 (1.7)*	-19.4 (1.7)*	-20.0 (1.7)*

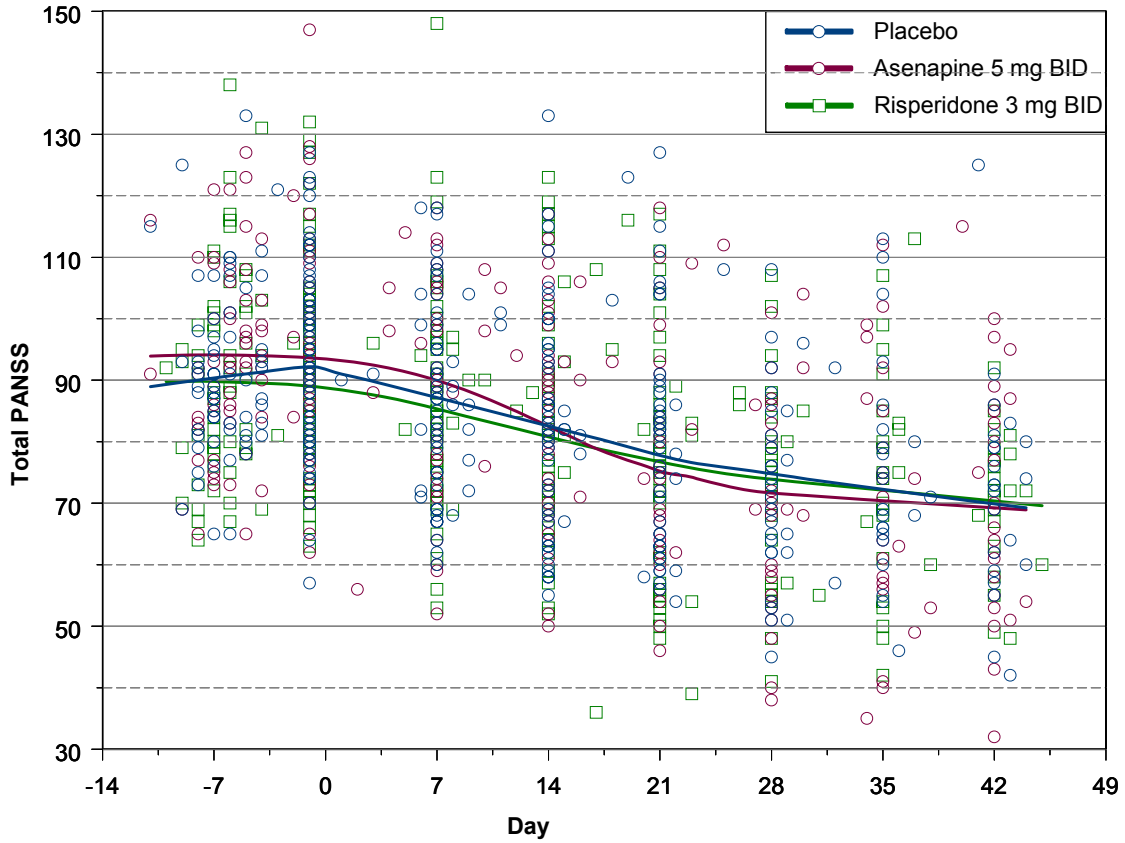
Source: Appendix A Table 41.1.S, Table 41.2.S, Table 41.3.S, and Table 41.4.S: referenced tables were (covariance structure = UN)
All values are mean (SE)
* indicates $p \leq 0.05$

5.6.2.1.1.1 Change in PANSS Score

5.6.2.1.1.1.1 Study 41004

Figure 161 plots Total PANSS score over time for the three treatment groups and is overlaid with LOESS curves. It's noteworthy that all treatments result in the same final value, thus the greater change from placebo with asenapine is due to a higher initial baseline score in the asenapine group.

Figure 161 Total PANSS Score vs. Time by Treatment – Study 41004



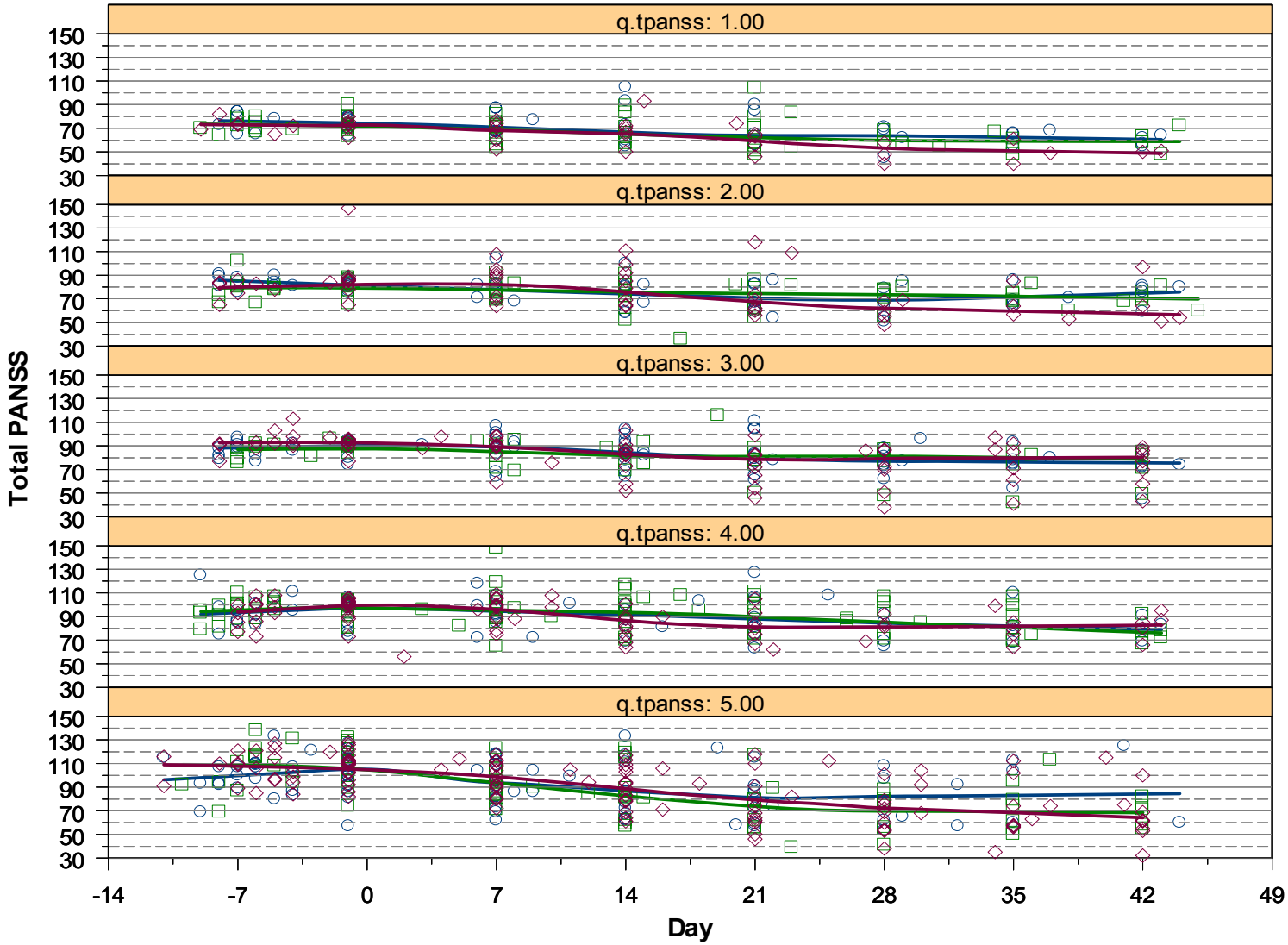
Next this reviewer examined the response while controlling for the initial severity of illness. To do this the highest PANSS score measured prior to treatment was determined for each subject. These scores were then divided into quintiles and the treatment responses for each quintile were compared. Table 172 shows the dividing points for each quintile for total PANSS score as well as for each of the subscores.

Table 172 Summary Statistics for Baseline Total PANSS Scores and Subscores – Study 41004

Metric	TPANSS	PPANSS	NPANSS	GPANSS
N	182	182	182	182
Mean ± SD (%CV) Range [Median] Quintiles 20, 40, 60, 80	98.8 ± 15.4 (15.6) 64 - 147 [98.5] 85, 95, 101, 111.4	26.5 ± 4.1 (15.3) 17 - 37 [26] 23, 25, 27.8, 30	25.1 ± 5.6 (22.5) 12 - 41 [25 20, 24, 26, 30	49.0 ± 8.6 (17.5) 26 - 80 [49] 42, 47, 51, 55

Figure 162 shows the overlaid LOESS curves for responses for each treatment by degree of initial severity assigned by quintile. No clear pattern can be discerned with regard to response by initial severity.

Figure 162 Total PANSS Score vs. Time by Quintile of Initial Severity by Treatment – Study 41004[a]



A Placebo - Blue; Asenapine – Red; Risperidone - Green

However when all three treatment groups are compared side by side it does appear that there may be a trend for greater response in the most severely ill patients, (see Figure 163 to Figure 165).

Figure 163 Total PANSS Score vs. Time (Days) for Placebo Treatment by Quintile of Severity - Study 41004

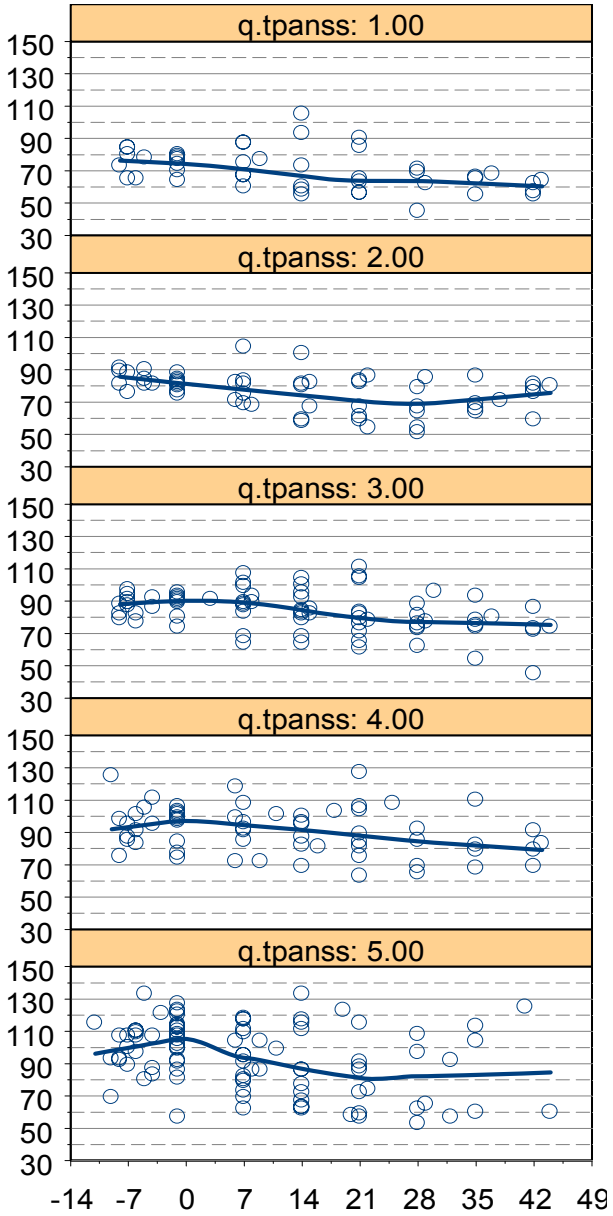


Figure 164 Total PANSS Score vs. Time (Days) for Asenapine 5 mg BID Treatment by Quintile of Severity - Study 41004

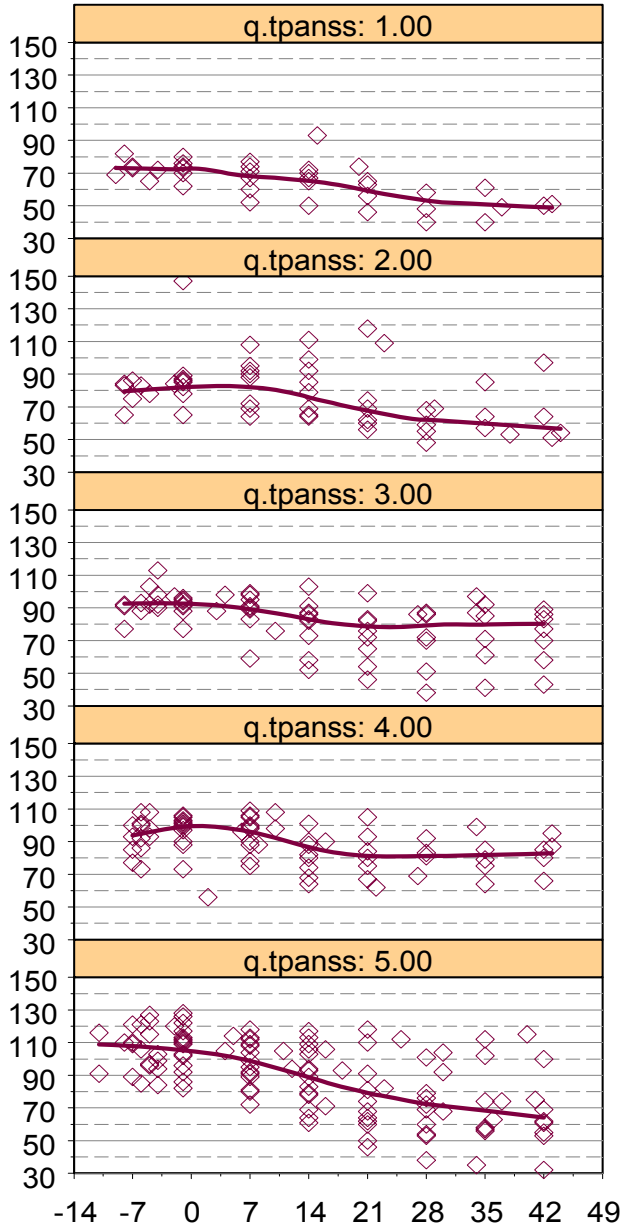
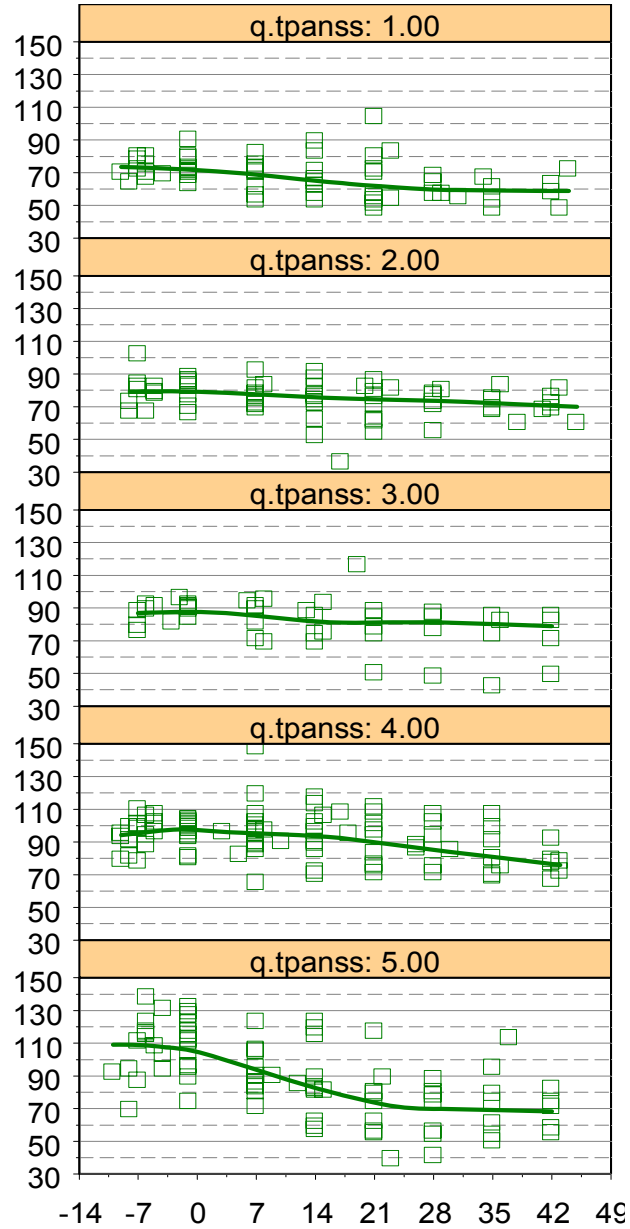


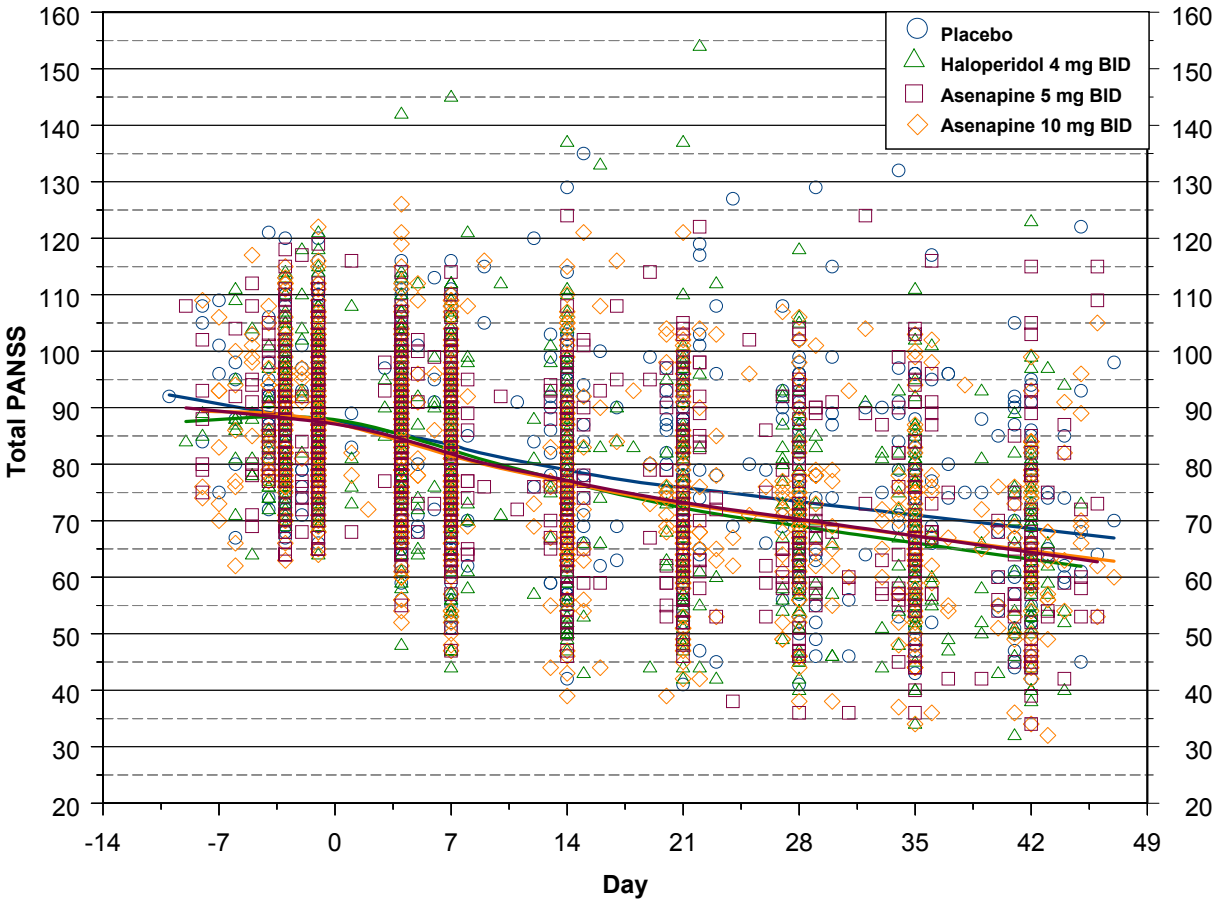
Figure 165 Total PANSS Score vs. Time (Days) for Risperidone 3 mg BID Treatment by Quintile of Severity - Study 41004



5.6.2.1.1.1.2 Study 41023

Figure 166 plots PANSS score over time for the four treatment groups in study 41023 and is overlaid with LOESS curves. In contrast to study 41004 the active treatments did result in final values different from placebo but the decrease in PANSS scores were only about 5 units greater than with placebo. Whereas the differences from placebo usually seen with active drugs in on the order of 12 – 15 units.

Figure 166 Total PANSS Score vs. Time by Treatment - Study 41023



In contrast to study 41004 the intial values were similar across treatments as shown by Table 173.

Table 173 Summary Statistics for Total PANSS Scores by Treatment – Study 41023

Treatment	Placebo	Asenapine 5mg BID	Asenapine 10mg BID	Haloperidol 4mg BID	All Treatments
N	123	111	106	115	456
Mean ± SD (CV) Min - Max [Median] Quntiles 20, 40, 60, 80	94.3 ± 10.7 (11.4) 74 - 121 [94] 83.8, 91.6, 97.4, 103	93.8 ± 10.7 (11.4) 72 - 122 [94] 84, 91, 96.2, 103.6	93.3 ± 12.4 (13.3) 63 - 121 [93] 82, 91, 95, 105.6	93.6 ± 12.4 (13.2) 65 - 118 [94] 82, 89.4, 98.6, 105	93.7 ± 11.5 (12.3) 63 - 122 [94] 83, 91, 97, 104

Figure 167 to Figure 170 shows total PANSS score vs. Time by quintile for each treatment. When examined there doesn't appear to be any clear pattern for efficacy by severity of illness. As with study 41004 quintles calculations were based on all treatments combined.

Figure 167 Total PANSS vs. Time by Quintile for Placebo – Study 41023

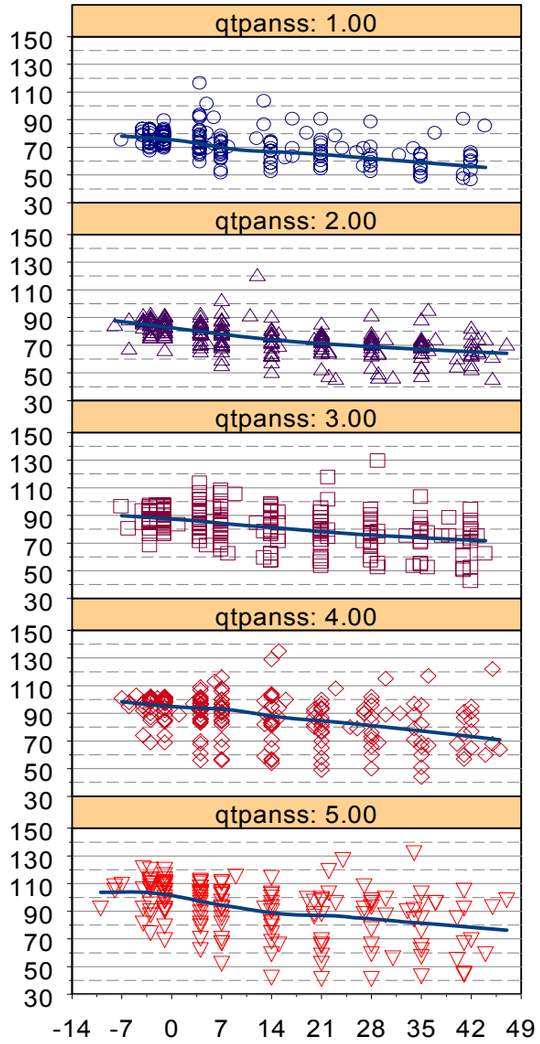


Figure 168 Total PANSS vs. Time by Quintile for Asenapine 5 mg BID – Study 41023

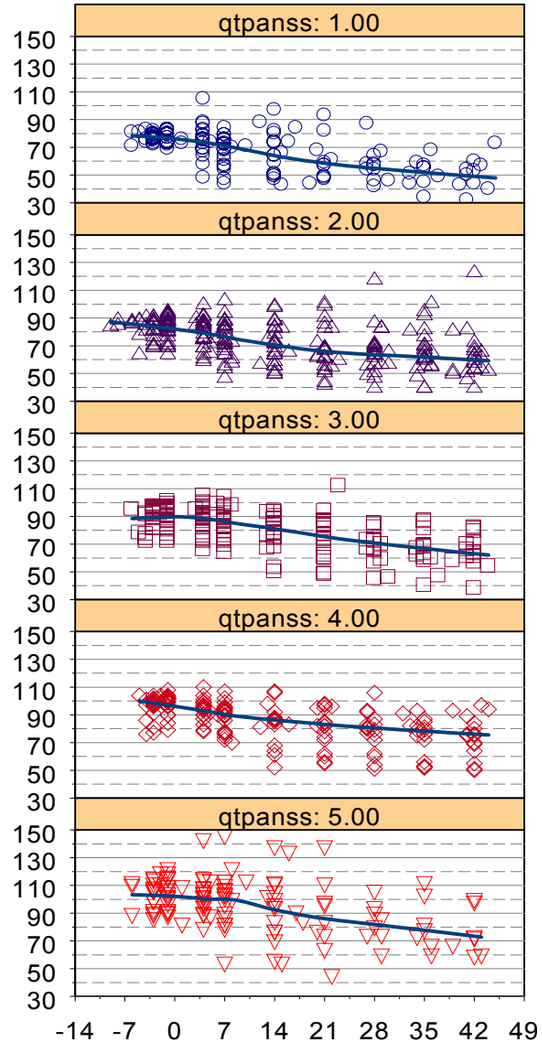


Figure 169 Total PANSS vs. Time by Quintile for Asenapine 10 mg BID – Study 41023

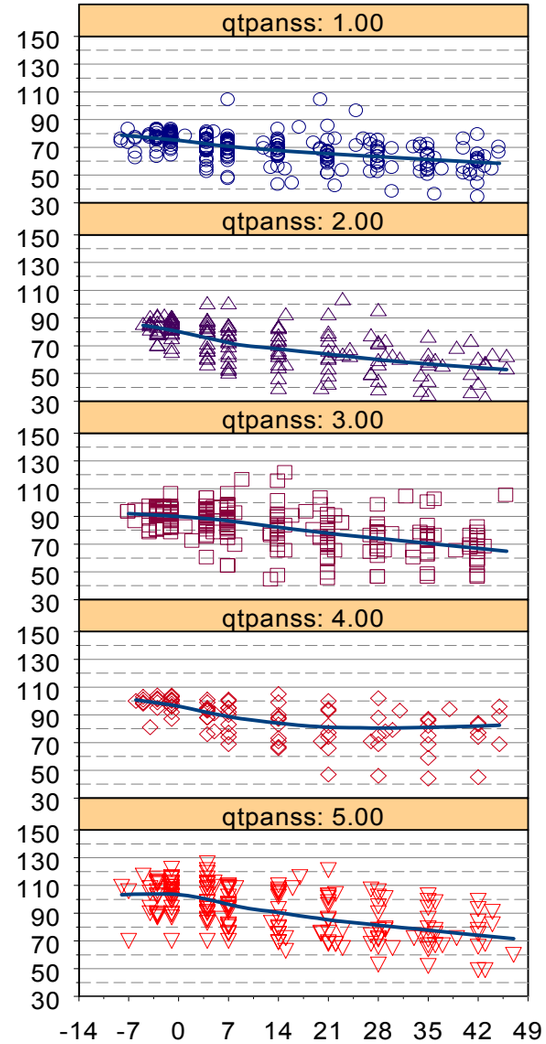


Figure 170 Total PANSS vs. Time by Quintile for Haloperidol 4 mg BID – Study 41023

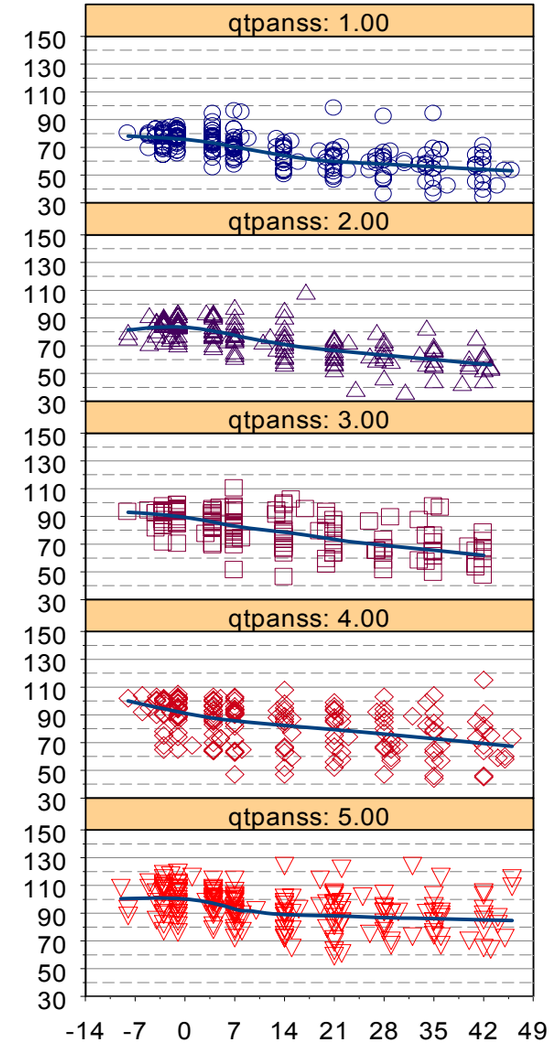


Figure 171 to Figure 174 shows similar plots but for positive PANSS score vs. Time by quintile for each treatment. Again there isn't any clear pattern for efficacy by severity of illness.

Figure 171 Positive PANSS vs. Time by Quintile for Placebo – Study 41023

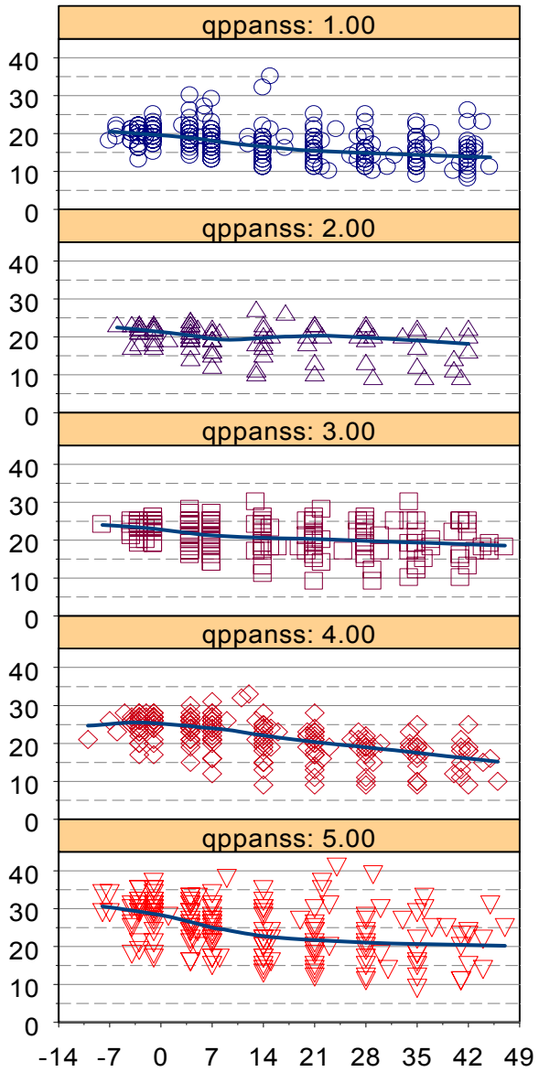


Figure 172 Positive PANSS vs. Time by Quintile for Asenapine 5 mg BID – Study 41023

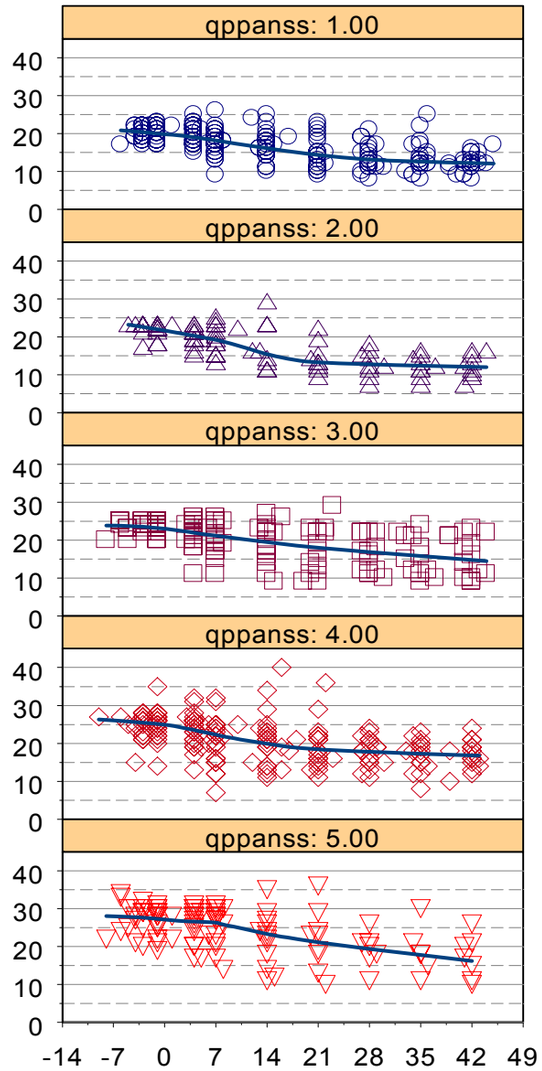


Figure 173 Positive PANSS vs. Time by Quintile for Asenapine 10 mg BID – Study 41023

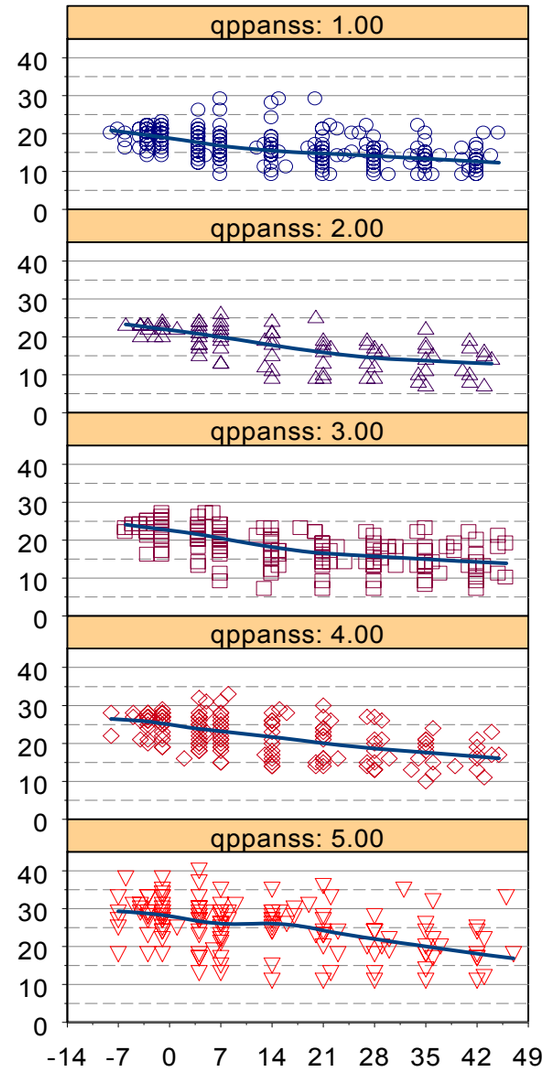
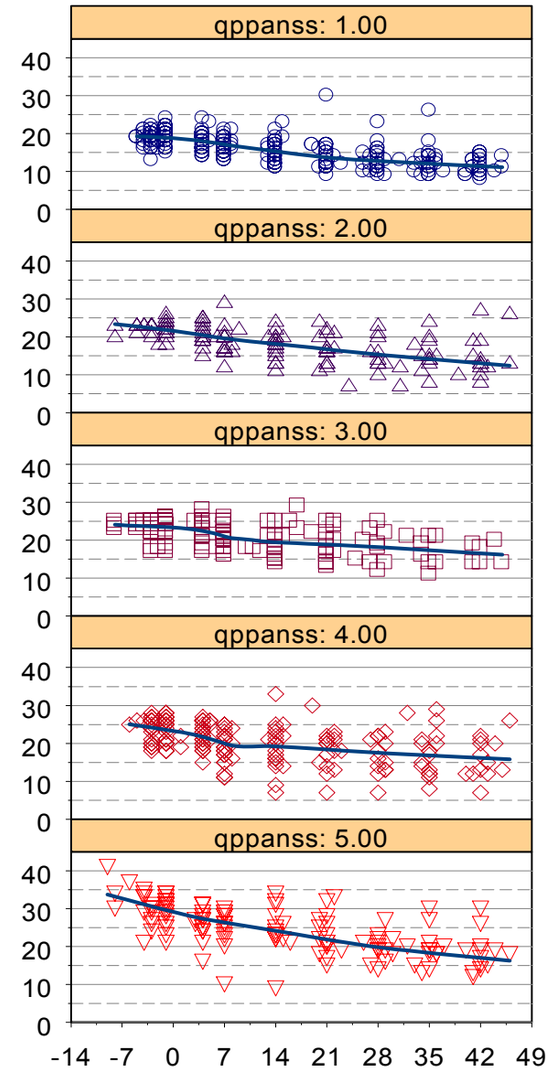


Figure 174 Positive PANSS vs. Time by Quintile for Haloperidone 4 mg BID – Study 41023



5.6.2.1.1.1.3 Sponsor's Combined ER Analysis of Phase IIb and III Acute Efficacy Studies

The sponsor performed an exposure response analysis of total PANSS score vs. asenapine exposure based on the following 3 Phase IIb and 3 Phase III 6-week efficacy studies for the efficacy in treating acute psychotic episodes associated with schizophreniae

The specifice studies included in the ER analysis follow:

Phase IIb studies
- 41002
- 41013
- 41004

Phase III studies
- 41021
- 41022
- 41023

Per the sponsor: *'The primary endpoint total PANSS was assessed at baseline and then weekly for 6 weeks with an extra assessment on Day 4 in the Phase 3 trials. Asenapine was administered sublingually and the doses ranged between 0.2 mg bid to 10 mg bid in the different treatment arms. Samples for the assessment of asenapine pharmacokinetics were obtained according to sparse sampling designs. The patients were hospitalized for 3 weeks in the Phase 2 trials and for at least 2 weeks in the Phase 3 trials.'*

'The dataset for analysis included all assessments on Total PANSS (except screening scores) and their time of observation, study number, study arm, treatment, dose, asenapine AUC, observed baseline PANSS, and the covariates weight, age, race, smoking status, ethanol intake, duration of present episode, patient studied in the United States or not and hospitalization status as well as information on dropout and reason for dropout. The placebo and asenapine treated patients were included in the exposure response analysis.' (See Table 174)

Table 174 Covariates Examined by the Sponsor in Exposure Response Modeling - Report INT00039918

Covariate	Abbreviation	Reason for Investigation
Age	AGE	Disease symptoms as well as placebo response could be different for different age classes, gender or race
Gender	SEX	
Race	RACE	
Smoking status	SMOK	Behavioral aspects may correlate with placebo response
Alcohol use	ETH	
Weight	WGT	
Duration of present episode	DDUR	More acute patients (shorter episode duration) could show a different placebo response
Inpatient/outpatient	HOSP	Hospitalized patients could show a different placebo response
US/non-US	US	US sites might have recruited different types of patients (not covered by above covariates)

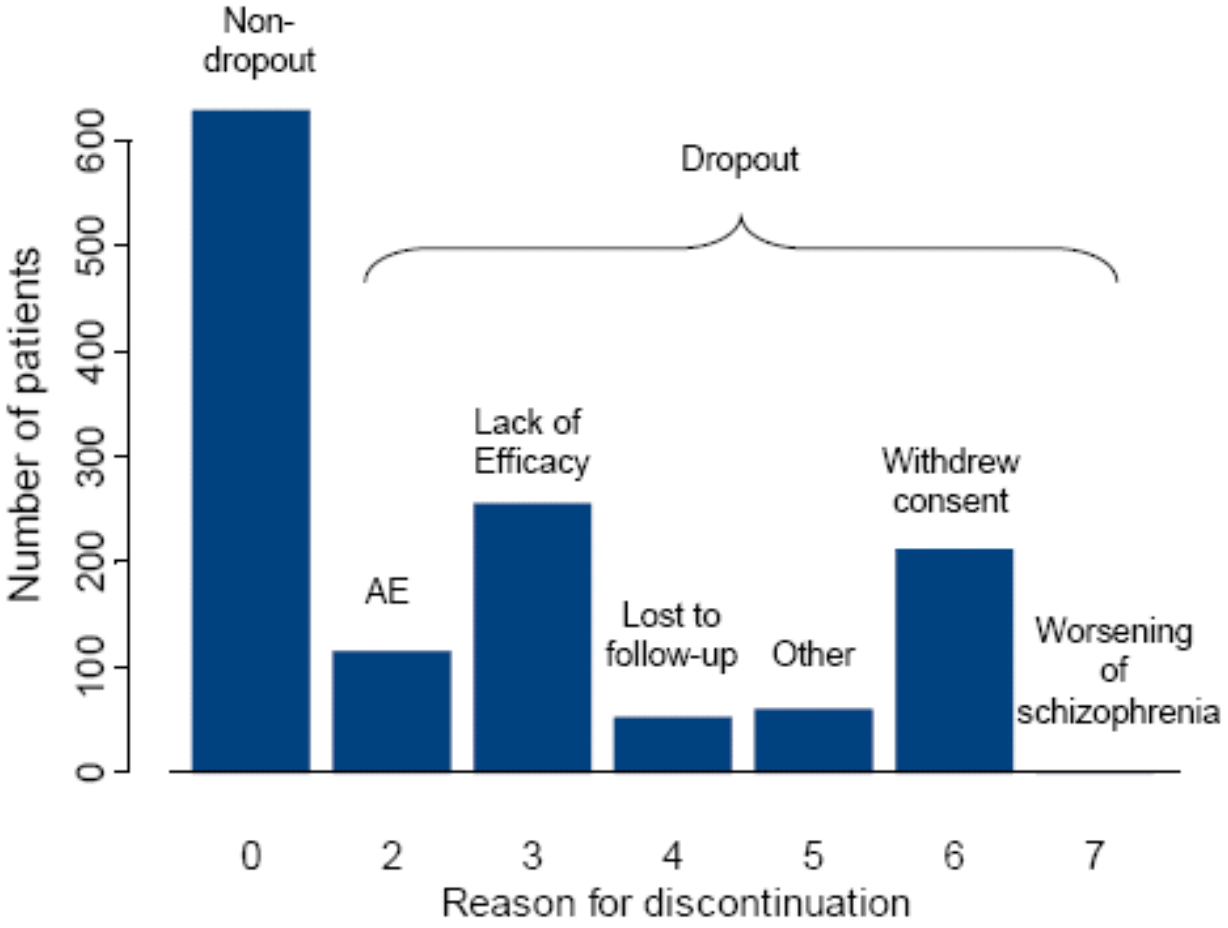
'A population pharmacokinetic-pharmacodynamic of Total PANSS time course was developed in NONMEM VI using AUC as a measure of asenapine exposure. In a first step a placebo model was

developed from the placebo data. In the next step the asenapine data were included and a drug effect model was added to describe the exposure response of asenapine. Covariate relationships were investigated for the covariates mentioned above. A logistic regression model to describe drop-out patterns was developed separately from the PANSS model. Simulations were performed from the combined model of Total PANSS and the model describing the time-course of dropout. The simulated LOCF responses were compared with observed trial results, and retrospective success rates for each of the asenapine treatment arms in comparison to placebo were calculated.'

Drop Out Model

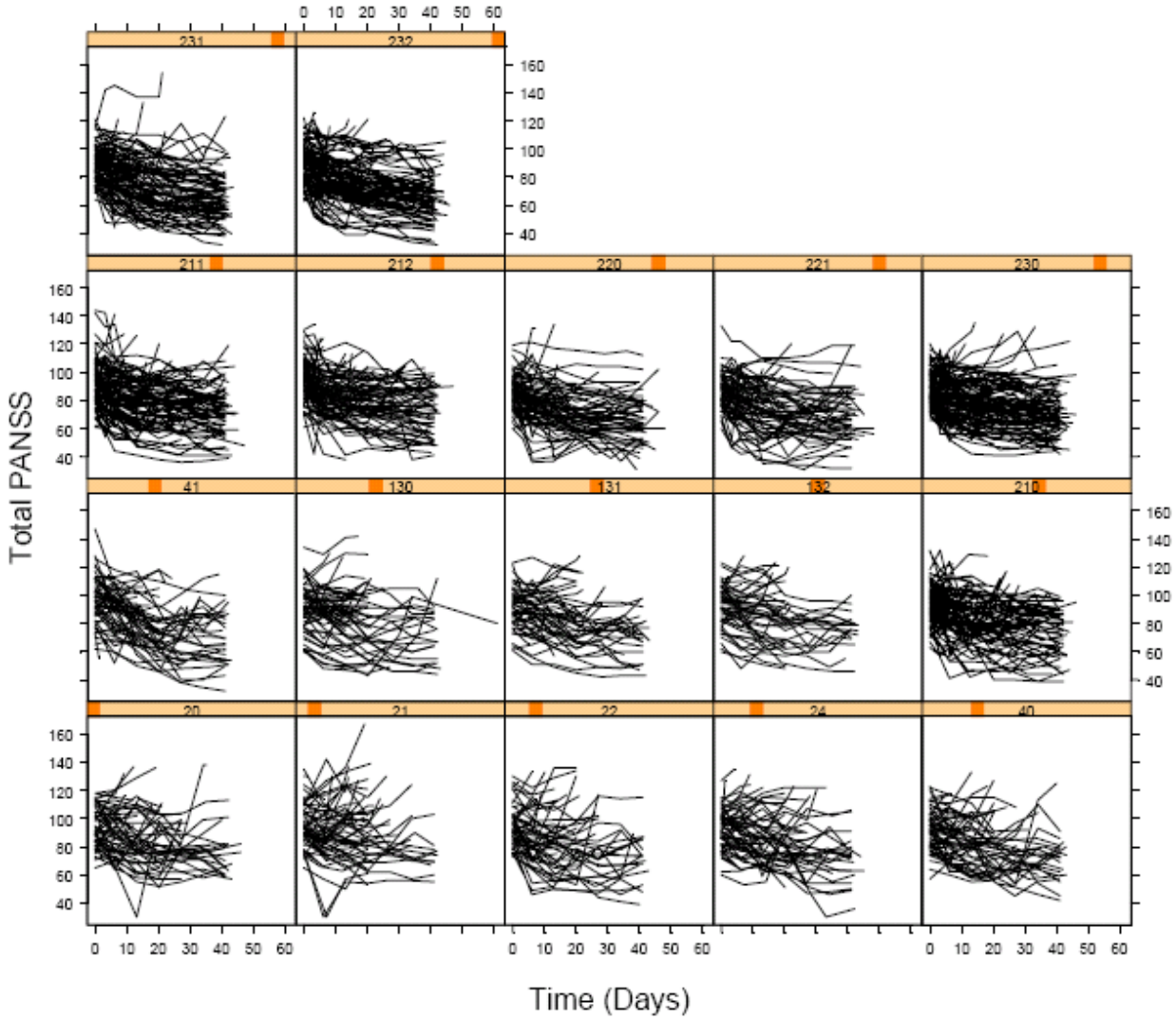
Figure 175 shows the categorization of reasons for drop-outs used by the sponsor. The large proportion of drop-outs categorized as lost to follow-up, other, and especially withdrew consent is troubling. In addition, that only one subject was assigned to worsening of schizophrenia is not believable as this appears to be inconsistent with spaghetti plots of response vs. time, (see Figure 176).

Figure 175 Reasons for Dropout and their Distribution - Report INT00039918



Other possibilities that need to be considered is whether subjects on drug may be more likely to remain in the study in spite of a lack of efficacy due to subconscious bias, or placebo subjects being more likely to remain on treatment if adverse effects are evident, as well as other possibilities. The only way to control for this may be to have a separate blinded individuals assess efficacy and tolerability and have no other communication with the subjects or each other so they can't influence drop out rate. Then have a third individual assessing the reason why a subject wants to drop out.

Figure 176 Spaghetti Plots of Individual Subject Total PANSS Scores vs. Treatment Duration by Study Treatment Arm[a]



a Numbers in shingles indicate treatment arms which are defined in Table 175.

Table 175 Sponsor's Treatment Arm Codes for Asenapine Exposure Response Analysis – Report INT00039918

Variable	Variable Label	Description including Categories and Units
STUDY Number	Study Number	ORG041002 = 2 ORG041004 = 14 ORG041013 = 13 ORG041021 = 21 ORG041022 = 22 ORG041023 = 23
STUDY ARM	**Study** Study Arm Number	**ORG041002** 20 : placebo 21 : 0.2 mg asenapine 22 : 0.4 mg asenapine 23 : 0.6 mg asenapine 24 : 0.8 mg asenapine 29 : risperidone 3 mg **ORG041004** 40 : placebo 41 : 5 mg asenapine 49 : risperidone 3 mg **ORG041013** 130 : placebo 131 : 1.6 mg asenapine 132 : 2.4 mg asenapine **ORG041021** 210 : placebo 211 : 5 mg asenapine 212 : 10 mg asenapine 219 : Olanzapine 15 mg **ORG041022** 220 : placebo 221 : 5-10 mg flex dose asenapine 229 : Olanzapine 10-20 mg **ORG041023** 230 : placebo 231 : 5 mg asenapine 232 : 10 mg asenapine 239 : haloperidol 4 mg
Treatment	Treatment Number	0=Placebo 1=Asenapine 2=Risperidone 3=Olanzapine

Figure 177 shows PANSS Score vs. Duration of Treatment divided into drop-out and non-drop groups for both asenapine and placebo. While the curves are similar for the subjects on placebo and asenapine who didn't drop out, which is noted elsewhere in this review by the super-imposition of the placebo and treatment groups, the dropout are different by treatment. The problem as noted in the discussion to Figure 175 is that the reason for dropping out especially by treatment and duration on treatment is poorly explained and therefore modeling dropouts while possible may not be especially accurate in the present ER analysis. This is demonstrated by the differing naïve drop-out models for placebo for the phase II and phase III trials as shown in Figure 178

Figure 177 PANSS Time Course by Treatment in Individuals who Dropped Out and Remained on Treatment – Report INT00039918

Figure 3. PANSS Time course in patients who dropped out and who did not drop out

Observed PANSS (o) and smooth through the observed data (—).

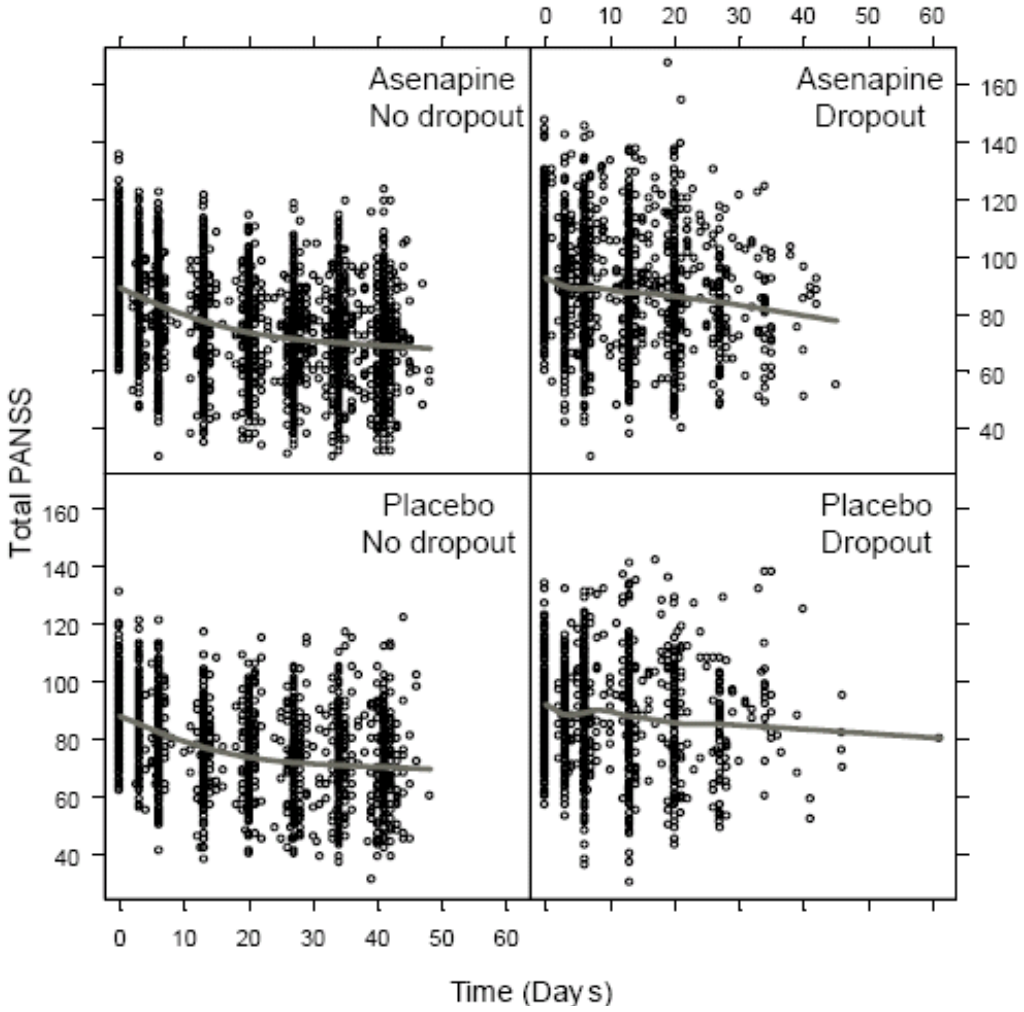
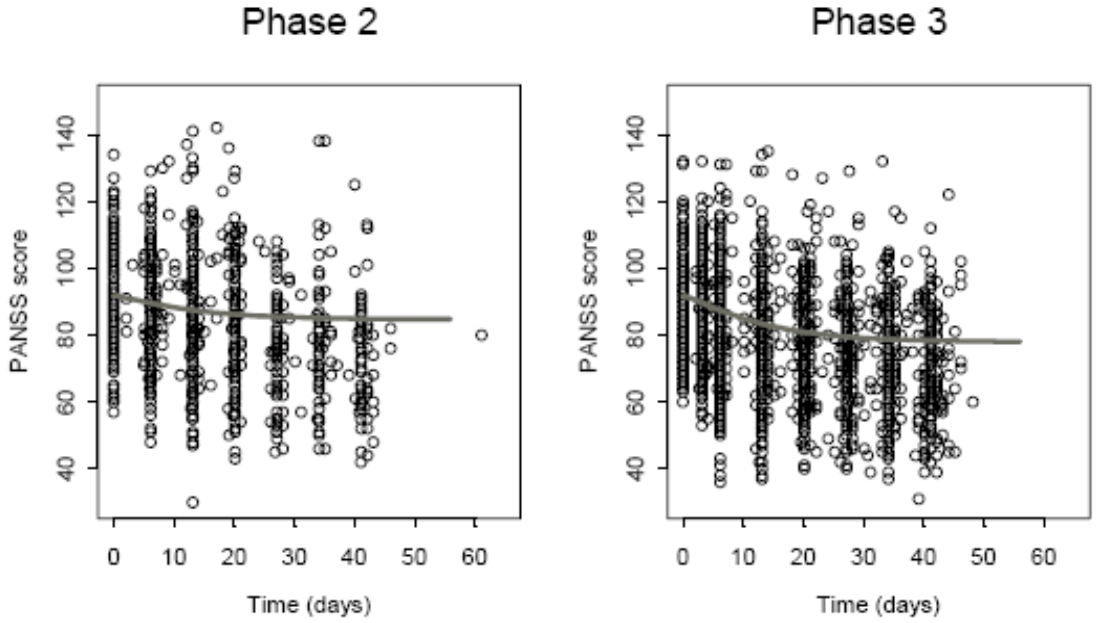


Figure 178 Typical PANSS Time Course as Predicted by the Final Placebo Model – Report INT00039918

Figure 4. Typical PANSS time course as predicted by the final placebo model.

Included are all observations (o) and model predictions for a typical individual without consideration of dropout (—).



Exposure Response Relationship for Asenapine

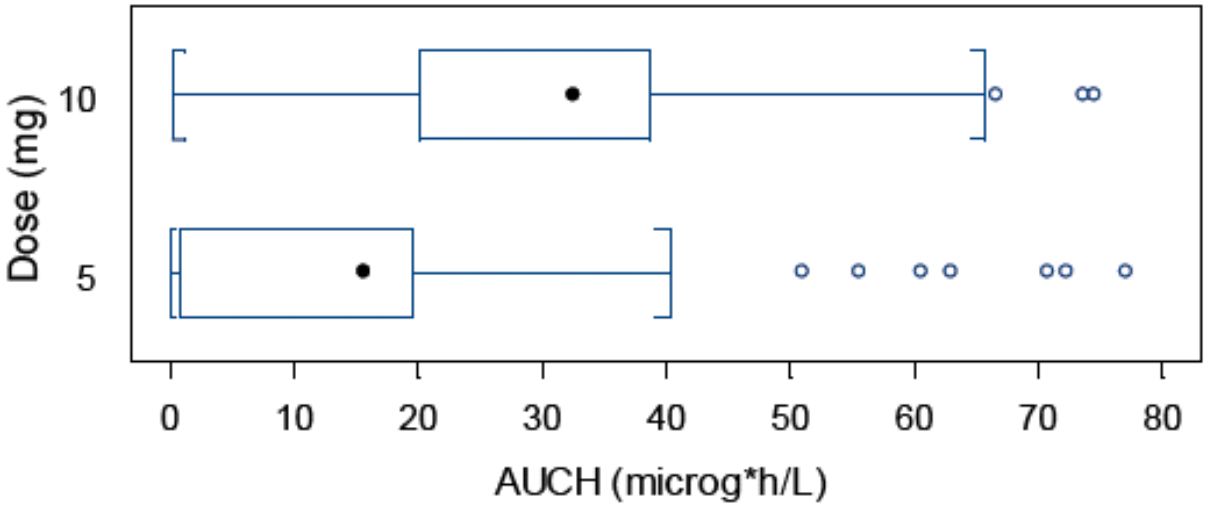
Exposure was assessed by AUCs assessed by sparse sampling and population pharmacokinetic modeling. The sponsor assessed various ways to model AUC, including the following:

- AUCH Individual AUC
- AUCI Individual AUCs differing for in- and outpatient periods due to differences in bioavailability
- IAUC Imputed AUCH after dropout
- AUCP Predicted Individual AUC

According to the sponsor AUCH was superior to dose as a measure of exposure (ΔOFV= -13.7) although there was not improvement in OFV <objective function value> when comparing the different exposure measurements of AUC, AUCI, AUCP, and AUCH. AUC was used in the initial modeling, however AUCH was later on in the modeling process chosen as it is less sensitive to differences due to deviations from the dosing protocol at the day of concentration determination but can account for the lower exposure in the outpatient period which was observed in some patients.

Figure 179 shows the sponsor's plots of the distribution of individual AUCs by dose for each asenapine dose used in the Phase IIb and III trials.

Figure 179 Asenapine AUC Distribution by Dose for 5 and 10 mg Doses in Phase IIb/III Efficacy Studies – Report INT00039918[a]



a Panel descr bes the observed individual AUC (AUCH) distribution in the phase IIb/III trials for 5 and 10 mg asenapine. AUCH values within the first and third quartiles are included in the boxes and dots indicate the medians. The whiskers represent 1.5 times the inter-quartile range or the range of the data, whichever is less. Circles are observations outside 1.5 times the inter-quartile range. In addition 3 AUCH values (range 104-1891 µg·h/L) were omitted from the plot.

Figure 180 shows the typical mean predicted decrease in PANSS score from baseline (solid lines) from Baseline and 90% PIs (dotted lines) vs, AUC grouped by study phase. The large discrepancy between the predictions for the two phases that includes the lack of overlap indicate that there are unknown cofactors influencing the relationship.

Figure 180 Predicted Mean Decrease from Baseline in PANSS at Day 42 and 90% vs. AUC by Study Phase IIb or III – Report INT00039918

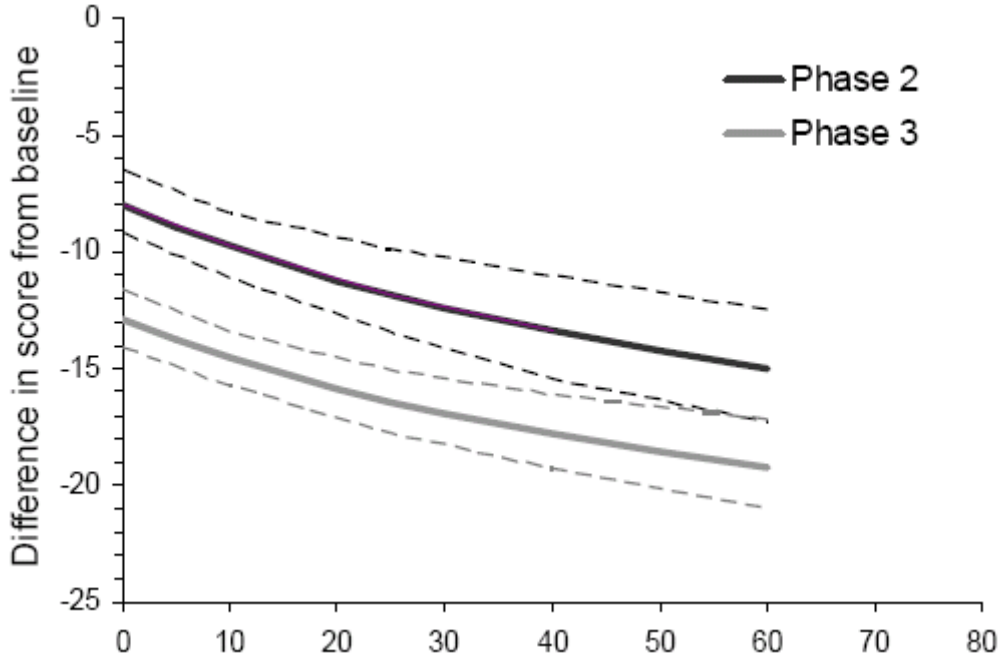
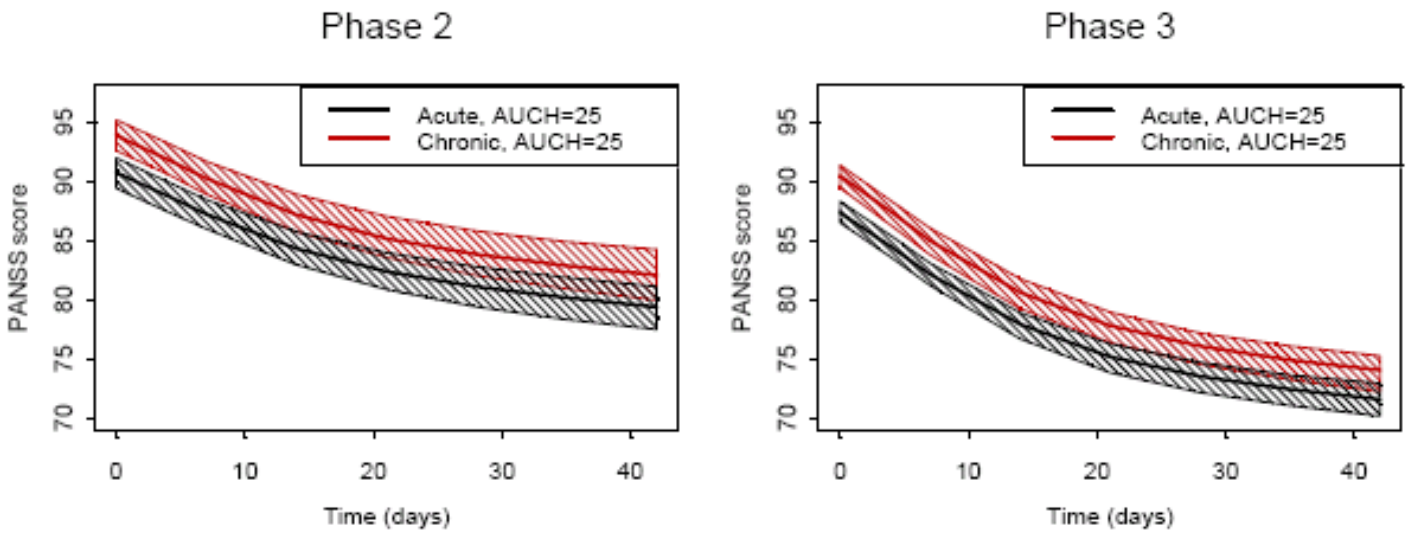


Figure 181 shows that when controlled for AUC this difference in response by study phase is partly due to the difference in baseline PANSS score as well as the duration of the current episode, however it's also clear that this cannot totally explain the difference as the 'chronic' subjects in the phase III studies had a greater response than the 'acute' subjects in the phase II studies in spite of similar baseline scores. This is opposite what is expected based on the sponsor's argument.

Figure 181 Fit of Individual AUCs versus Time with 90% CIs Asenapine Dose and Development Phase for Schizophrenic Patients with Current Acute Episodes of Less than 1 month Duration ('Acute') and Greater than 1 month Duration ('Chronic') – Report INT00039918



A N.B. Graphs only show the influence of duration of the psychotic episode patients for Phase 2 and Phase 3 for a mean AUC of 25 µg·h/L (5 mg) but not 40 25 µg·h/L (10 mg).

Figure 182 shows the sponsor's final predictions that appear to show a dose response relationship however, close examination of the plots indicate that the true values plateau and there is no increased response to a 10 mg dose over a 5 mg dose.

Figure 182 Observed and Simulated PANSS LOCF Time Course – Report INT00039918

Figure 9. Observed and from the final model simulated PANSS LOCF time course

Mean observed (---) and mean (90% PI) simulated (—) overall PANSS LOCF are visualized.

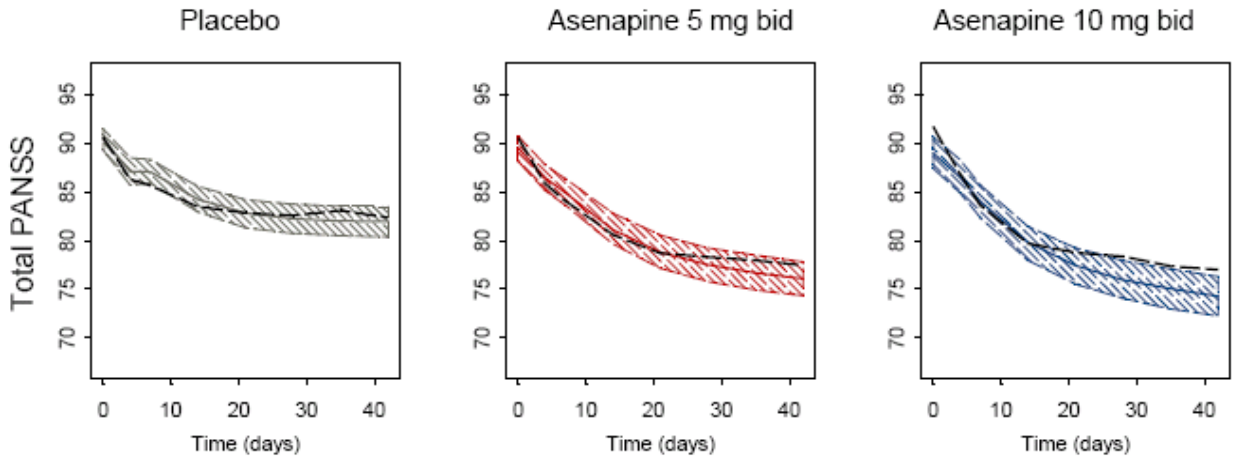
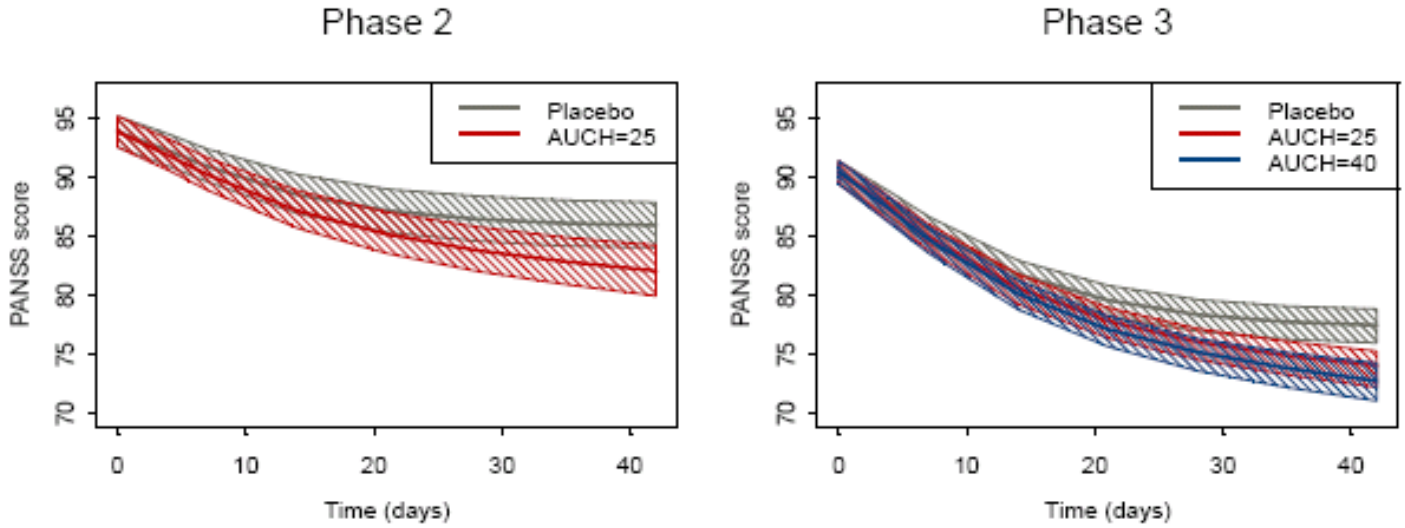


Figure 183 shows what the sponsor based this on. The sponsor assigned a typical AUC of 25 mcg/ml x hr^{-1} to a dose of 5 mg and 40 mcg/ml x hr^{-1} to a dose of 10 mg. Yet Figure 179 indicates that this is inappropriate as the true mean AUCs are respectively around 10 and 30 mcg/ml x hr^{-1}. This figure also indicates that even with a dose of 10 mg fewer than 25% of subjects with have an AUC of 40 mcg/ml x hr^{-1}.

Figure 183 Fit of Individual AUCs versus Time with 90% CIs by Asenapine Dose and Development Phase – Report INT00039918[a]



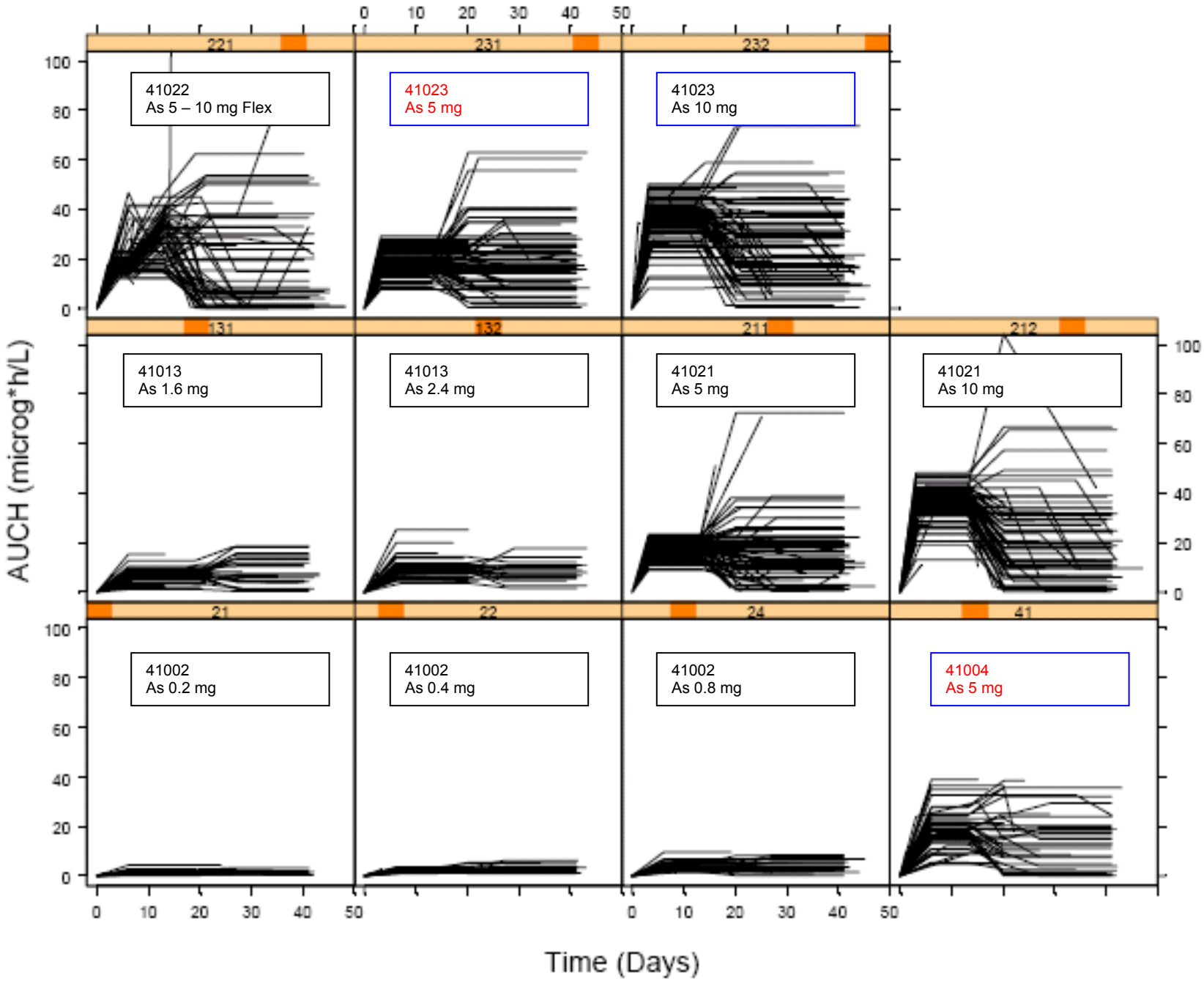
a Sponsor claims that graphs show the predicted mean and 90% CI for PANSS Score vs. time for placebo and for the typical individual AUC (AUCH) following 5 mg (AUCH=25 µg·h/L) and 10 mg (AUCH=40 µg·h/L).

In addition, the exposure response relationship shown in Figure 182 averages both the phase II and phase III studies when examining the effect if an AUCH of 25 mcg/ml x hr^{-1} on PANSS. Plus the correction for baseline severity is not clearly indicated. Even though the sponsor states: *'Thus the PANSS model predicts that a patient with a high baseline score will typically have a larger absolute decrease in PANSS from placebo than a patient with a low baseline score as the placebo response was slightly less than proportional to the baseline value. The placebo response was estimated to reach a plateau around 30 days after start of the study, while the maximum asenapine effect did not occur before the end of the study (Day 42). The model characterized the considerable difference in placebo effect between Phase 2 and Phase 3 well and all placebo arms were well predicted by the model (Figure X). The asenapine response was dependent on the underlying PANSS score so that patients with a high estimated baseline and a low estimated placebo response had typically a higher estimated absolute reduction in score than those with a low estimated baseline and high estimated placebo response. As the placebo response and asenapine effect response were predicted to have different time-courses subjects treated with asenapine can also contribute.'*

Lastly Figure 184 shows spaghetti plots of individual AUCs over time for each asenapine treatment arm in the phase IIb and phase III acute efficacy studies. This also shows that compliance is a major issue once subjects are discharged from the hospital. However the positive response in the phase II study vs. the phase III studies at 5 mg indicate that the baseline score and not the duration of treatment prior to discharge is a better predictor of response. In addition, the lower concentrations in addition to noncompliance may indicate change in diet and the elevated concentrations might indicate taking a additional doses immediately prior to a visit in contrast to being noncompliant the rest of the time.

In conclusion this analysis indicates that in spite of modeling in the 'real world' this drug may not be a useful addition to the antipsychotic armamentarium, although this could be shown to be untrue with additional studies.

Figure 184 Individual AUC (AUCH) versus Time by Asenapine Efficacy Study Treatment Arms[a,b]



a Numbers in shingles indicate treatment arms which are defined in Table 175.
b Blue boxes indicate studies with positive results for asenapine. Red text indicate treatment arms that were statistically significant different from placebo

5.6.2.1.1.2 Evaluation of Drop-Out Patterns

The sponsor evaluated modeling of drop-outs in two different sections of the NDA that were located under the following two pathways:

5. Clinical Study Reports
5.3.5 Reports of Efficacy and Safety Studies [Schizophrenia]
5.3.5.3 Reports of Analyses of Data from More than One Study
[INT00039918 – Exposure response of total PANSS based on Phase 2 and Phase 3 trials for Asenapine]
5.3.5.3.1 Legacy Study Report [INT00039918]
MODELING & SIMULATION ANALYSIS REPORT
Exposure response analysis of total PANSS based on Phase 2 and Phase 3 6-week trials for asenapine
May 2007

5. Clinical Study Reports
5.3.5 Reports of Efficacy and Safety Studies [Bipolar Disorder]
5.3.5.3 Reports of Analyses of Data fro More than One Study
[INT00039918 – Exposure response of total PANSS based on Phase 2 and Phase 3 trials for Asenapine]
5.3.5.3.1 Legacy Study Report [INT00043090]
Position Paper for Asenapine:
LOCF vs. MMRM in the Efficacy Analyses for Asenapine Trials
May, 2007

In section 2.5 of the NDA, in the clinical overview document under subsection 2.5.4., 'Overview of Efficacy' the sponsor reports the following *'During the February 22, 2007 Pre-NDA meeting, the sponsor was encouraged to further investigate the possibility of using a mixed model for repeated measures (MMRM) analysis as a primary method of analysis.'*

As reported in NDA 22-117 Amendment # 002 submitted Octocber 24th, 2007 in a response to an FDA request to provide the regulatory history the information in Table 176 was provided regarding this pre-NDA meeting.

Table 176 Regulatory History Regarding Pre-NDA Meeting Submitted in Amendment 002

Topic / Issue	Correspondence			Regulatory History
	Date	SN	Description	
Pre-NDA Meeting – February 22, 2007*	12/21/06	294	Letter to FDA	Type B (Pre-NDA) Meeting Request
	01/22/07	300	Letter to FDA	Type B (Pre-NDA) Meeting Information Package
	02/20/07		E-mail from FDA	Agency's preliminary responses to Pre-NDA Meeting Questions
	02/28/07	307	Letter to FDA	Sponsor's Minutes – Type B (Pre-NDA) Meeting
	03/06/07		Letter from FDA	Agency's Minutes – Type B (Pre-NDA) Meeting
	03/13/07	310	Letter to FDA	Organon provides comments on Agency's Minutes – Type B (Pre-NDA) Meeting
	03/21/07		E-mail from FDA	Agency states that Sponsor comments will be on permanent record as additions to the meeting minutes, correspondence related to the meeting minutes

* the serial numbers listed refer to those associated with IND No. 51,641. Certain information submitted to IND No. 51,641 may also have been applicable to IND No.70,329; this information was incorporated into IND No. 70,329 by cross-reference and has been denoted with an asterisk (*)

On March 26, 2008 upon attempting to check the FDA records regarding this meeting in DFS, no records or any type were returned upon a search of either IND 51.641 or IND 70,329.

As indicated in this review in §5.6.2.1.1 Acute Treatment of Psychosis the sponsor proposed using mixed models of repeated measures, (MMRM), and a critique of the sponsor's evaluation may be found there. Prior to reviewing this document this review had already performed an exploratory data analysis of drop-out patterns in the two pivotal acute schizophrenia trials, 41004 and 41023, and those analyses are presented here.

Figure 185 and Figure 186 show Kaplan-Meir survival curves of drop-outs over time by treatment for the two pivotal acute efficacy studies, 41004 and 41023. Ninty percent confidence intervals although not shown were approximately ± 0.1, and the curves are statistically indistinguishable.

Figure 185 shows a higher rate for dropouts in the Risperidone arm during the first week of treatment followed by greater dropouts in the placebo and asenapine arms until day 21 (1 week after discharge allowed) followed by greater dropouts in the placebo group compared to both active treatments.

Figure 186 shows similar dropouts in all groups in the first week followed by more dropouts in the haloperidol and asenapine 5 mg arms, which was eventually matched after 4 weeks by the dropout rate for placebo patients, with the dropout rate in the 10 mg arm being the lowest from week 1 onwards.

Subjects in this study had lower baseline PANSS scores and greater response than in study 41004. The increase in dropout rate for placebo in both studies after 3 and 4 weeks of therapy respectively during the outpatient phase might be due to unintentional bias from observers who might encourage subjects experiencing adverse effects to remain on drug. In addition the time to drop out may also have been influence both by initial severity and duration of inpatient treatment. However, more detailed analysis is needed than can be accomplished during the present review cycle.

Figure 185 Kaplan-Meir Plot of Dropout Rate over Time by Treatment Group - Study 41004

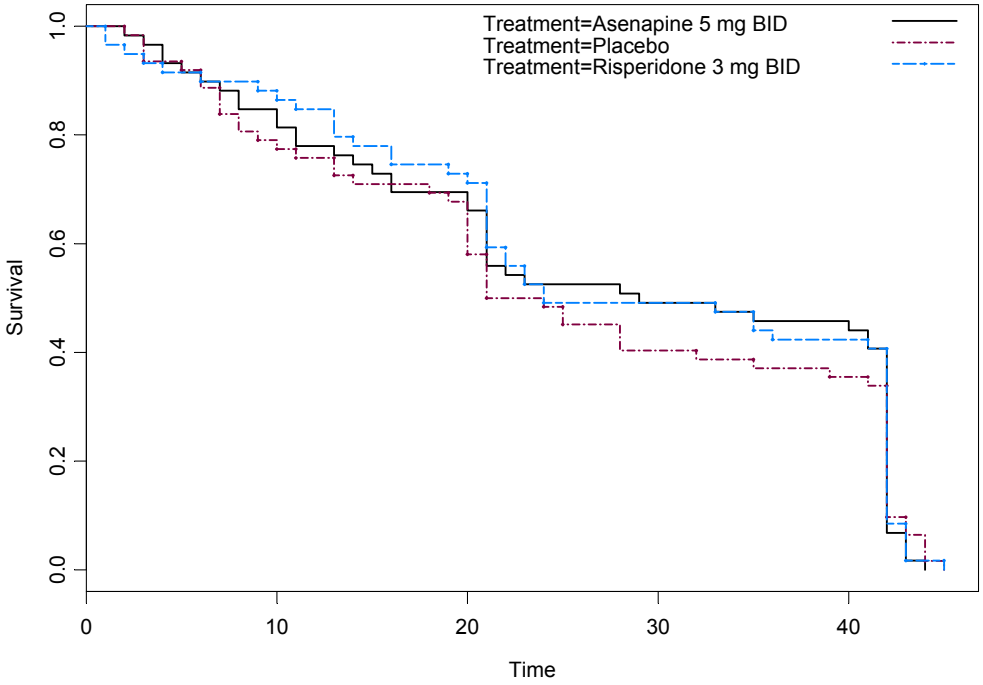


Figure 186 Kaplan-Meir Plot of Dropout Rate over Time by Treatment Group - Study 41023

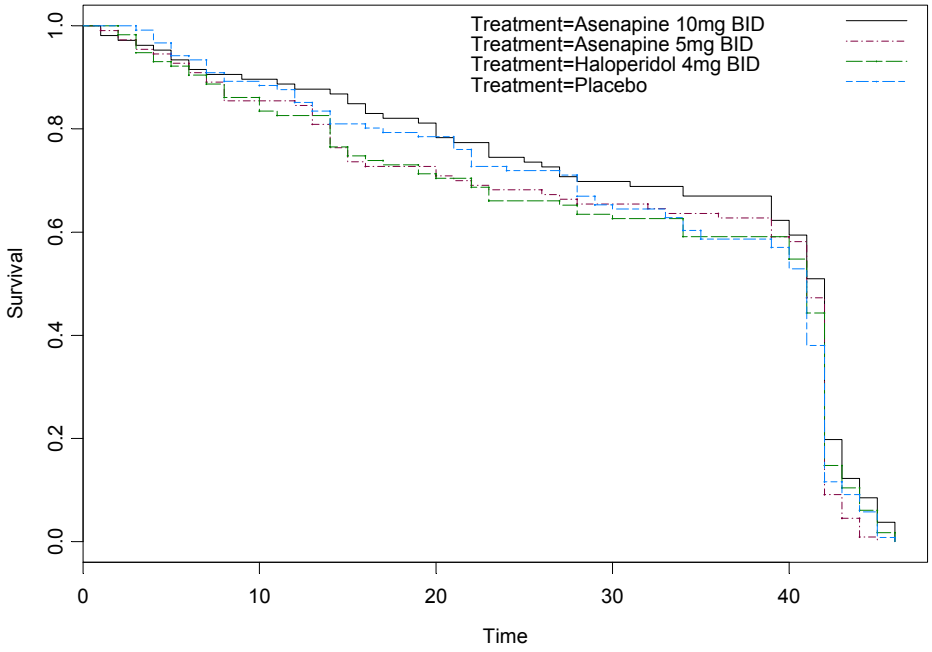


Figure 187 is an exploratory plot of dropout rates by intial disease severity in study 41004. It appears that for most subjects there is little difference in dropouts by treatment, whereas in the most severely ill patients after the first week of treatment drop outs increase for the placebo group and remain higher for the rest of the trial. There are two possible answers for this, a) there is poorer historicity and therefore greater dropouts in the placebo are for the most severely ill patients, b) the difference in drop outs is primarily due to an unconscious bias in the investigators on dropouts during the inpatient phase followed by little difference in the slope of the dropout rate thereafter.

Figure 187 - Dropout Rate (Precent) by Study Visit (week) by Initial Severity and Treatment - Study 41004

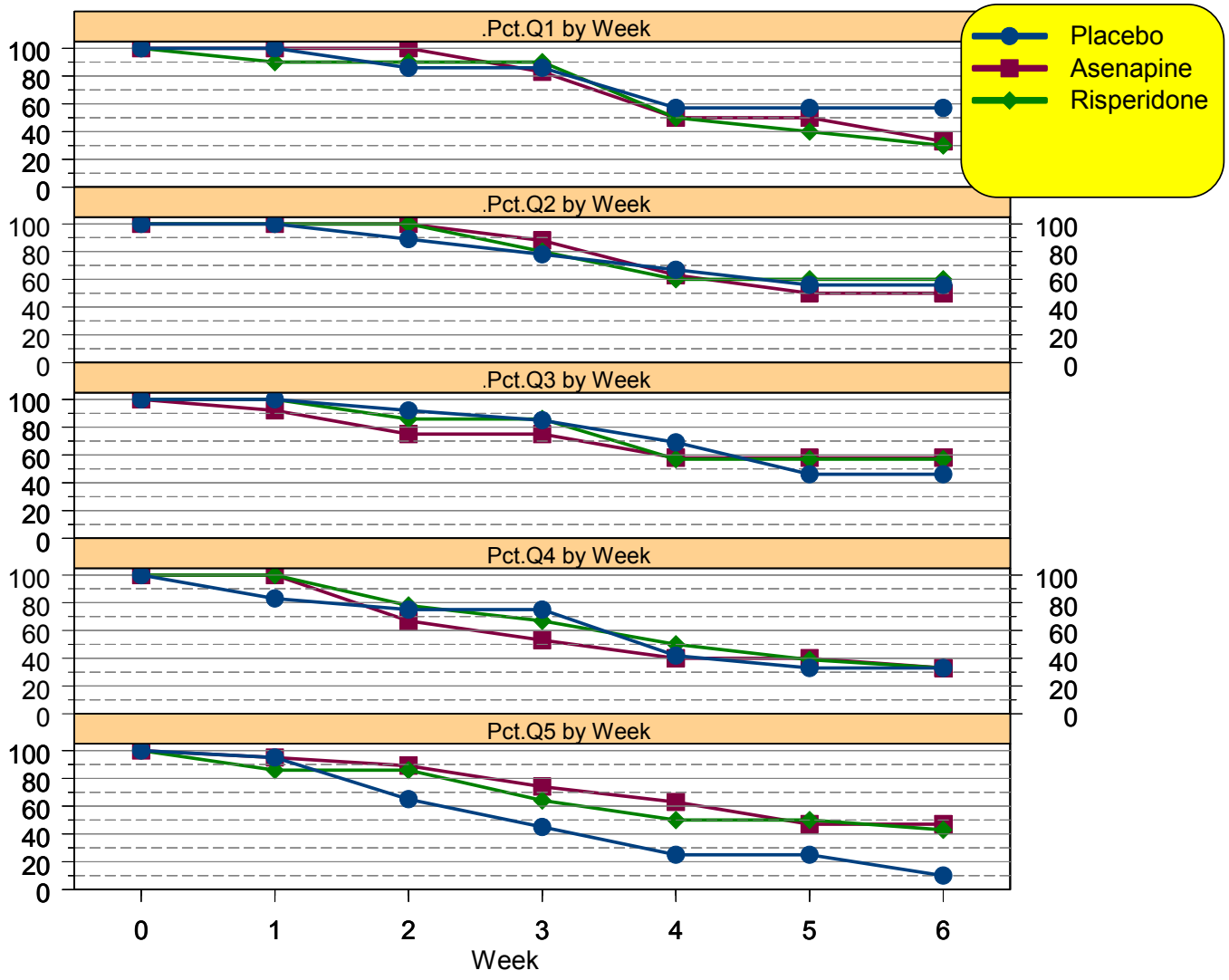


Table 177 and Table 178 show numerical calculations of drop out rates and odds ratios by treatment and initial disease severity for studies 41004 and 41023 respectively. Examination of Table 177 reveals an apparent pattern that in the phase II study 41004 with the more severely ill patients, the least severely ill were less likely to remain on drug compared to placebo but only toward the end of the study, whereas the most severely ill were much more likely to stay on drug.

Table 177 Numerical Calculations of Drop out Rates and Odds Ratio by Treatment and Initial Disease Severity – Study 41004

Treatment	Duration of Rx	Number of Subjects on Treatment						% Remaining on Treatment						Odds Ratio of Remaining on Active Drug Treatment Compared to Placebo					
		Q1	Q2	Q3	Q4	Q5	Total	Q1	Q2	Q3	Q4	Q5	Total	Q1	Q2	Q3	Q4	Q5	Total
Placebo	Baseline	7	9	13	12	20	61	100	100	100	100	100	100	–	–	–	–	–	–
	Screen	7	9	13	12	20	61	100	100	100	100	100	100	–	–	–	–	–	–
	Visit 1	7	9	13	10	19	58	100	100	100	83	95	95	–	–	–	–	–	–
	Visit 2	6	8	12	9	13	48	86	89	92	75	65	79	–	–	–	–	–	–
	Visit 3	6	7	11	9	9	42	86	78	85	75	45	69						
	Visit 4	4	6	9	5	5	29	57	67	69	42	25	48	–	–	–	–	–	–
	Visit 5	4	5	6	4	5	24	57	56	46	33	25	39	–	–	–	–	–	–
	Visit 6	4	5	6	4	2	21	57	56	46	33	10	34	–	–	–	–	–	–
Asenapine	Baseline	6	8	12	15	19	60	100	100	100	100	100	100	1.0	1.0	1.0	1.0	1.0	1.0
	Screen	6	8	12	15	19	60	100	100	100	100	100	100	1.0	1.0	1.0	1.0	1.0	1.0
	Visit 1	6	8	11	15	18	58	100	100	92	100	95	97	1.0	1.0	0.92	1.20	1.0	1.02
	Visit 2	6	8	9	10	17	50	100	100	75	67	89	83	1.17	1.13	0.81	0.89	1.38	1.06
	Visit 3	5	7	9	8	14	43	83	88	75	53	74	72	0.97	1.13	0.89	0.71	1.64	1.04
	Visit 4	3	5	7	6	12	33	50	63	58	40	63	55	0.88	0.94	0.84	0.96	2.53	1.16
	Visit 5	3	4	7	6	9	29	50	50	58	40	47	48	0.88	0.90	1.26	1.20	1.89	1.23
	Visit 6	2	4	7	5	9	27	33	50	58	33	47	45	0.58	0.90	1.26	1.00	4.74	1.31
Risperidone	Baseline	10	10	7	18	14	59	100	100	100	100	100	100	1.0	1.0	1.0	1.0	1.0	1.0
	Screen	10	10	7	18	14	59	100	100	100	100	100	100	1.0	1.0	1.0	1.0	1.0	1.0
	Visit 1	9	10	7	18	12	56	90	100	100	100	86	95	0.90	1.0	1.0	1.2	0.90	1.00
	Visit 2	9	10	6	14	12	51	90	100	86	78	86	86	1.05	1.13	0.93	1.04	1.32	1.10
	Visit 3	9	8	6	12	9	44	90	80	86	67	64	75	1.05	1.03	1.01	0.89	1.43	1.08
	Visit 4	5	6	4	9	7	31	50	60	57	50	50	53	0.88	0.90	0.83	1.20	2.00	1.11
	Visit 5	4	6	4	7	7	28	40	60	57	39	50	47	0.70	1.08	1.24	1.17	2.00	1.21
	Visit 6	3	6	4	6	6	25	30	60	57	33	43	42	0.53	1.08	1.24	1.00	4.29	1.23

In contrast, examination of Table 178 reveals an apparent pattern that in the phase III study 41023 with the less severely ill patients, the opposite pattern was seen with the highest asenapine dose with the least severely ill more likely to remain on drug compared to placebo.

Table 178 Numerical Calculations of Drop out Rates and Odds Ratio by Treatment and Initial Disease Severity – Study 41023

Treatment	Duration of Rx	Number of Subjects on Treatment						% Remaining on Treatment						Odds Ratio of Remaining on Active Drug Treatment Compared to Placebo					
		Q1	Q2	Q3	Q4	Q5	Total	Q1	Q2	Q3	Q4	Q5	Total	Q1	Q2	Q3	Q4	Q5	Total
Placebo	Baseline	24	25	25	25	21	120	100	100	100	100	100	100	–	–	–	–	–	–
	Visit 1	23	25	25	25	21	119	96	100	100	100	100	99	–	–	–	–	–	–
	Visit 2	18	23	23	23	18	105	75	92	92	92	86	88	–	–	–	–	–	–
	Visit 3	14	22	22	22	16	96	58	88	88	88	76	80						
	Visit 4	11	22	20	19	15	87	46	88	80	76	71	73	–	–	–	–	–	–
	Visit 5	11	20	19	14	14	78	46	80	76	56	67	65	–	–	–	–	–	–
	Visit 6	11	19	16	14	11	71	46	76	64	56	52	59	–	–	–	–	–	–
Asenapine 5 mg BID	Baseline	21	28	24	19	18	110	100	100	100	100	100	100	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	21	26	21	19	18	105	100	93	88	100	100	95	1.04	0.93	0.88	1.00	1.00	0.96
	Visit 2	17	26	19	17	15	94	81	93	79	89	83	85	1.08	1.01	0.86	0.97	0.97	0.98
	Visit 3	11	26	16	17	10	80	52	93	67	89	56	73	0.90	1.06	0.76	1.02	0.73	0.91
	Visit 4	10	24	14	17	9	74	48	86	58	89	50	67	1.04	0.97	0.73	1.18	0.70	0.93
	Visit 5	10	23	14	17	8	72	48	82	58	89	44	65	1.04	1.03	0.77	1.60	0.67	1.01
	Visit 6	10	22	14	16	7	69	48	79	58	84	39	63	1.04	1.03	0.91	1.50	0.74	1.06
Asenapine 10 mg BID	Baseline	27	16	28	11	23	105	100	100	100	100	100	100	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	27	16	27	10	22	102	100	100	96	91	96	97	1.04	1.00	0.96	0.91	0.96	0.98
	Visit 2	25	16	25	10	19	95	93	100	89	91	83	90	1.23	1.09	0.97	0.99	0.96	1.03
	Visit 3	23	15	22	9	18	87	85	94	79	82	78	83	1.46	1.07	0.89	0.93	1.03	1.04
	Visit 4	22	14	18	8	17	79	81	88	64	73	74	75	1.78	0.99	0.80	0.96	1.03	1.04
	Visit 5	21	11	18	8	15	73	78	69	64	73	65	70	1.70	0.86	0.85	1.30	0.98	1.07
	Visit 6	21	11	18	8	13	71	78	69	64	73	57	68	1.70	0.90	1.00	1.30	1.08	1.14
Haloperidol 4 mg BID	Baseline	29	21	17	22	26	115	100	100	100	100	100	100	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	28	17	17	21	26	109	97	81	100	95	100	95	1.01	0.81	1.00	0.95	1.00	0.96
	Visit 2	24	15	16	19	22	96	83	71	94	86	85	83	1.10	0.78	1.02	0.94	0.99	0.95
	Visit 3	20	14	13	17	20	84	69	67	76	77	77	73	1.18	0.76	0.87	0.88	1.01	0.91
	Visit 4	19	13	11	17	16	76	66	62	65	77	62	66	1.43	0.70	0.81	1.02	0.86	0.91
	Visit 5	18	12	11	17	14	72	62	57	65	77	54	63	1.35	0.71	0.85	1.38	0.81	0.96
	Visit 6	17	11	11	15	14	68	59	52	65	68	54	59	1.28	0.69	1.01	1.22	1.03	1.00

5.6.2.2 Bipolar Disorder

5.6.2.2.1 Acute Efficacy

5.6.2.2.1.1 Sponsor's Exposure Response Modeling of Effect of Asenapine on Young Mania Rating Scale (YMRS)

The sponsor developed an exposure response model relating asenapine exposure to YRMS score for bipolar disorder, by combining the data from both acute treatment studies A7501004 and A7501005. This model was development and results were reported in report INT00039919.

The sponsor used the population two compartment PK model with an absorption lag phase and nonlinear bioavailability previously developed using phase 1/2 pharmacokinetic data, (see §5.5.8.1 for PK model development and critique).

A number of empiric (non mechanism based) pharmacodynamic models were fit to the data. Due to the low number of subjects receiving a dose of 5 mg, a dose reponse model was not examined. However the pharmacokinetic data was incorporated into an exposure response model with all other data.

Table 179 shows the study designs of the two acute mania studies used for the exposure reponse modeling.

Table 179 Acute Mania Study Designs Used for Exposure Response Modeling – Report INT00039919

Study	Phase	Design	Inclusion Criteria	Dose/Regimen[a]	Asenapine (PK) Assessment Schedule	YMRS (PD) Assessment Schedule
A7501004	3	Randomized, DB, PBO and Active Controlled Parallel Design in subjects with Acute Manic Attack	YMRS ≥20 at Baseline	Placebo Aasenapine 10 mg SL BID × 1 day then 5 or 10 mg SL BID for 3 weeks	**Days 1, 14, and 21:** Predose **Day 7:** Predose and 1-3, 4-6, and 8-12 hours postdose	Screening and Days 1,2,4,7,14, and 21 / Study Endpoint
A7501005	3	Randomized, DB, PBO and Active Controlled Parallel Design in subjects with Acute Manic Attack	YMRS ≥20 at Baseline	Placebo Asenapine 10 mg SL BID × 1 day, then 5 or10 mg SL BID for 3 weeks	**Days 1, 14, and 21:** Predose **Day 7:** Predose and 1-3, 4-6, and 8-12 hours postdose	Screening and Days 1,2,4,7,14, and 21 / Study Endpoint

a excluding active control olanzapine

Table 180 shows the summary of subject demographics in the two acute mania studies. It's especially noteworthy that over 1/3 of subjects are nonsmokers and thus may have higher exposures than seen with similar doses in the schizophrenia studies.

Table 180 Demographic Summary by Acute Mania Study Patient – Report INT00039919

Patient Attribute	Study		Total (%)
	A7501004	A7501005	
	N (%)	N (%)	
Race			
Caucasian	155 (56.0)	177 (60.4)	332 (58.3)
Black	52 (18.8)	49 (16.7)	101 (17.7)
Hispanic	8 (2.9)	6 (2.1)	14 (2.5)
Asian	62 (22.4)	54 (18.4)	116 (20.4)
Other	0 (0)	7 (2.4)	7 (1.2)
Sex			
Female	138 (49.8)	130 (44.4)	268 (47.0)
Male	139 (50.2)	163 (55.6)	302 (53.0)
Smoking Status			
None	117 (42.2)	99 (33.8)	216 (37.9)
<1 pack/day	97 (35.0)	132 (45.1)	229 (40.2)
1-2 packs/day	60 (21.7)	59 (20.1)	119 (20.9)
>2 packs/day	3 (1.1)	3 (1.0)	6 (1.1)
Hormonal Statusa			
Pre-menopausal	93 (33.7)	96 (32.8)	189 (33.2)
Post-menopausal	44 (15.9)	34 (11.6)	78 (13.7)
Male	139 (50.4)	163 (55.6)	302 (53.1)
Ethanol Consumption (Past 1 Month)			
None	0 (0)	0 (0)	0 (0)
<1 drink/week	234 (84.5)	246 (84.0)	480 (84.2)
1-6 drinks/week	37 (13.4)	36 (12.3)	73 (12.8)
7-12 drinks/week	5 (1.8)	7 (2.4)	12 (2.1)
13-18 drinks/week	1 (0.4)	3 (1.0)	4 (0.7)
19-24 drinks/week	0 (0)	0 (0)	0 (0)
25-35 drinks/week	0 (0)	0 (0)	0 (0)
36+ drinks/week	0 (0)	1 (0.3)	1 (0.2)

N = number
a1 missing value

The final structural model as defined by the sponsor is shown below:

$$Y = \exp\left[\left(base + \eta_{base}\right) + \left(slp + \eta_{base}\right)t^{\gamma} - \left(dslp + \eta_{dslp}\right) \bullet C_e(t)\right] + \varepsilon$$

Figure 188 and Figure 189 show model fits overlaid on observed data for asenapine and placebo respectively.

It's clear even with the modeling there's minimal difference between drug and placebo indicating a statistical difference but possibly not a clinical difference.

Figure 188 Observed YMRS Measurements and the Average IPRED and Population Mean Response for Asenapine (Mean for the Final Model (OM1-DM1+keo)§ – Report INT00039919

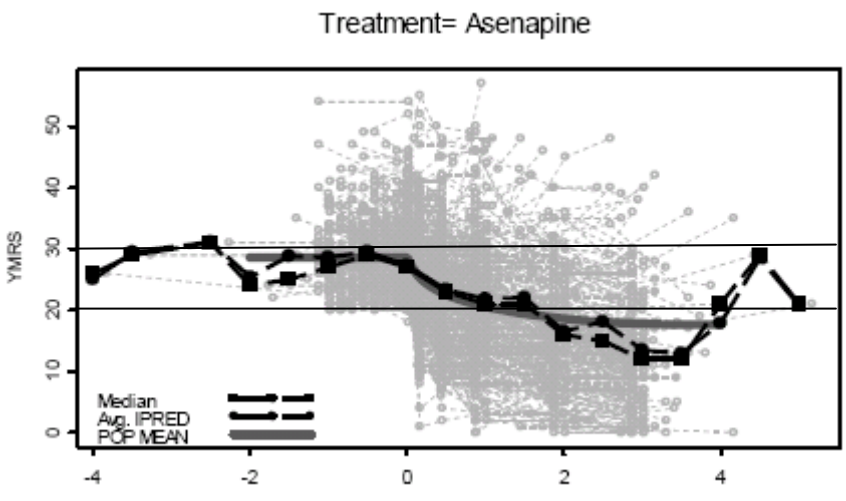


Figure 189 Observed YMRS Measurements and the Average IPRED and Population Mean Response for Placebo – Report INT00039919

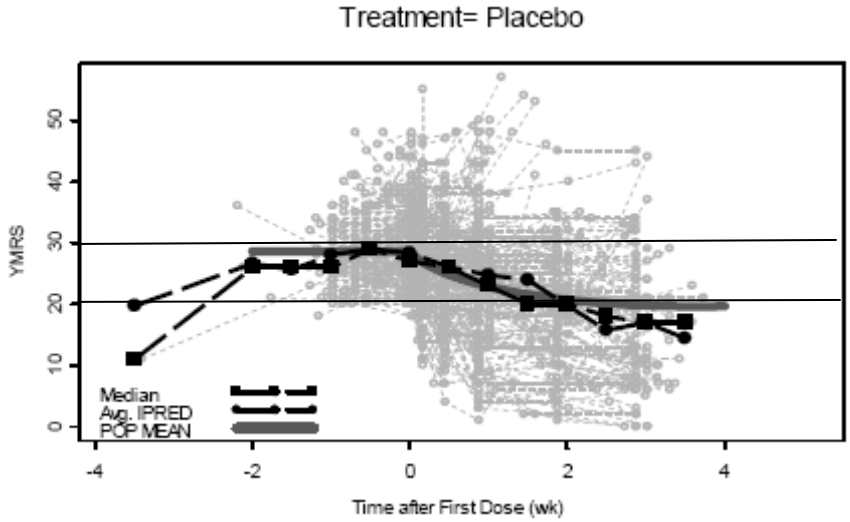


Table 181 of the Sponsor's analysis confirms that the differences although statistically significant may have minimal clinical significance.

Table 181 Medians of the Typical Individual Model Predictions of the YMRS Response, Median Differences in the Typical Individual YMRS Response (ΔYMRS), and 90% Confidence Intervals

	Week	Placebo		5 mg BID		10 mg BID	
		Median	90%CI	Median	90%CI	Median	90%CI
YMRS[a]	0	28.5	(28.1, 28.9)	28.5	(28.1, 28.9)	28.5	(28.1, 28.9)
	0.5	24.4	(23.8, 26.1)	22.9	(22.5, 24.4)	22.0	(21.5, 23.5)
	1	21.8	(21.2, 24.3)	20.3	(19.8, 22.3)	19.5	(18.9, 21.3)
	1.5	19.8	(19.0, 22.8)	18.4	(17.8, 20.9)	17.6	(17.0, 19.8)
	2	18.1	(17.2, 21.4)	16.8	(16.1, 19.6)	16.1	(15.4, 18.7)
	2.5	16.6	(15.7, 20.2)	15.4	(14.7, 18.4)	14.8	(14.0, 17.6)
	3	15.3	(14.4, 19.0)	14.2	(13.4, 17.4)	13.6	(12.8, 16.6)
	Week	**10 mg BID−5 mg BID**		**5 mg BID−Placebo**		**10 mg BID−Placebo**	
		Medianb	**90%CI**	**Medianb**	**90%CI**	**Medianb**	**90%CI**
ΔYMRS[b,c]	0	0 [0]	--	0 [0]	--	0 [0]	--
	0.5	-0.8 [-3.7]	(-1.1,-0.4)	-1.5 [-6.3]	(-2.1, -0.7)	-2.4 [-9.7]	(-3.2, -1.2)
	1	-0.8 [-4.1]	(-1.2,-0.4)	-1.5 [-7.0]	(-2.3, -0.7)	-2.4 [-10.8]	(-3.5, -1.1)
	1.5	-0.8 [-4.2]	(-1.2,-0.4)	-1.4 [-7.0]	(-2.2, -0.7)	-2.2 [-10.9]	(-3.4, -1.0)
	2	-0.7 [-4.2]	(-1.1,-0.3)	-1.3 [-7.0]	(-2.1, -0.6)	-2.0 [-10.9]	(-3.2, -1.0)
	2.5	-0.6 [-4.2]	(-1.1,-0.3)	-1.2 [-7.0]	(-2.0, -0.6)	-1.8 [-10.9]	(-3.1, -0.9)
	3	-0.6 [-4.2]	(-1.0,-0.3)	-1.1 [-7.0]	(-1.9, -0.5)	-1.7 [-10.9]	(-2.9, -0.8)

a Medians of the typical individual predictions with parameter uncertainty on the YMRS scale
b Median of the differences between the typical individual predictions for treatments.
c The numbers in brackets, [ ], represent median percent changes (i.e., median of 100×ΔYMRS/YMRS).

5.6.2.2.1.2 Reviewer's Exploratory Assesments of Exposure Response of Asenapine on Young Mania Rating Scale (YMRS)

This reviewer performed an exploratory assessment of response by baseline disease severity. Rather than define baseline severity as the sponsor did, i.e. YMRS on immediately before the first dose of drug or placebo, this reviewer used the highest YMRS score at anytime prior to beginning treatment, i.e. screening, 'baseline', or other evaluations. Baseline values from all subjects regardless of treatment were then divided into quintiles based on the combined values for subjects from both studies A7501004 and A7501005. The data from the two efficacy studies were then combined to compensate for the smaller numbers of subjects per quintile as the studies were powered without the regard to any plan for division into quintiles, and the cutoffs were then used for all treatments.

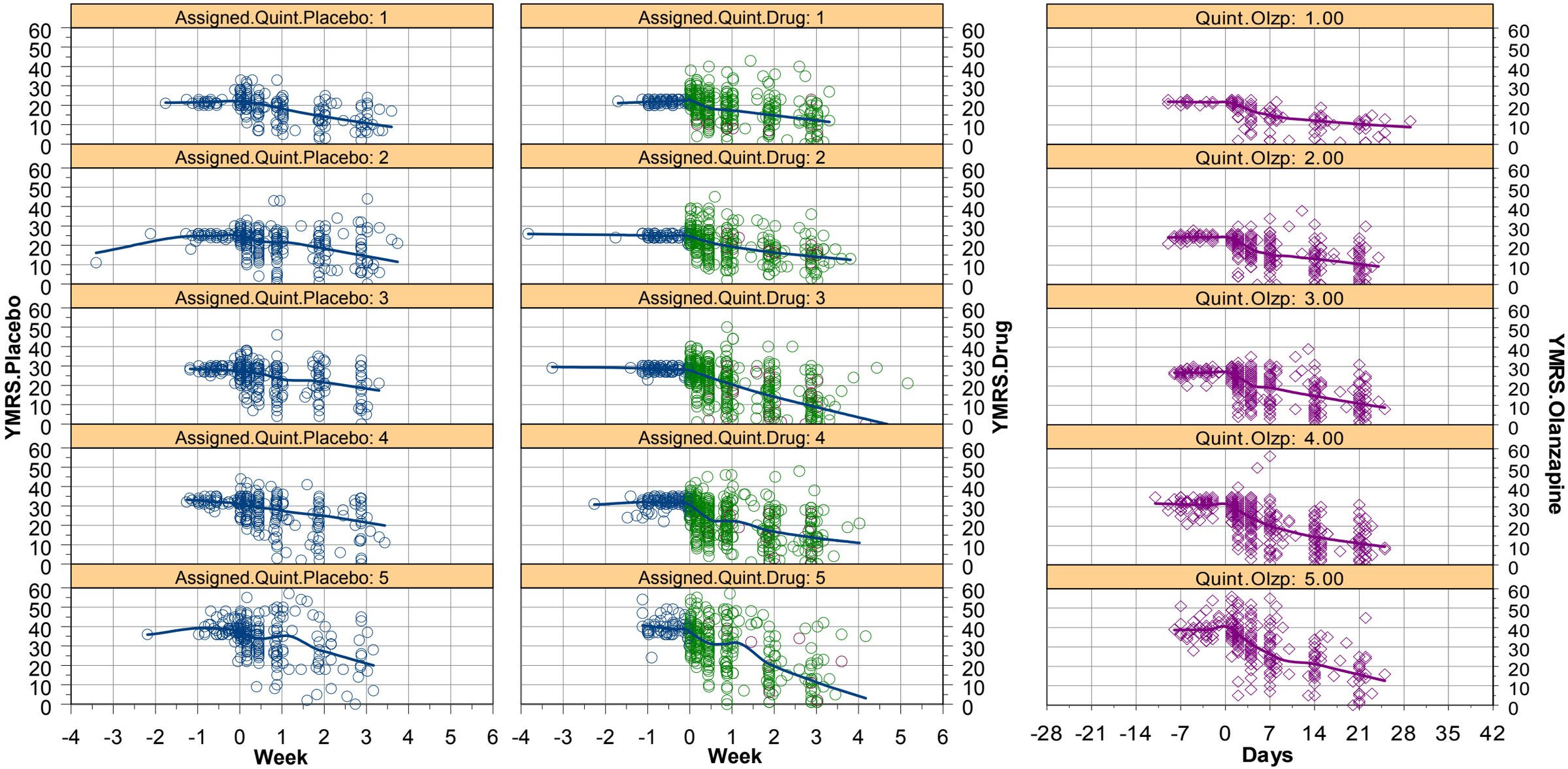
YMRS was then plotted over time using the actual day the evaluations were performed rather than the nominal day (visit) employed by the sponsor. It was noted that each of these steps resulting in the patterns becoming more readily visible, (data not shown), and emphasizes the importantance of using the best data available rather than rounding the data in some way.

Figure 190 shows the YMRS over time by quintile for each of the three treatment arms overlaid with LOESS curves. In addition, for asenapine pretreatment YMRS scores are shown by blue circles, the 10 mg dose by green circles and decreases to the 5 mg dose by purple circles. The sparcity of doses administered and their distribution indicate that they should not influence the interpretation. For olanzapine almost all subjects received 15 – 20 mg so the dose was not differentiated as that level of granularity was not included in the data files, and to pursue this would have been onerous.

Examination of the YMRS score over time by quintile in Figure 190 reveals that for placebo the final score at 3 weeks is correlated with the initial baseline score indicating that initial disease severity is a good predictor of placebo response. When the plots for asenapine and for the active control olanapine are examined regardless of the initial baseline score the mean final score at the end of 3 weeks of treatment is approximately 10 – 13 which is consistent with hypomania. Comparison of the responses with active treatments to placebo by quintile of severity reveals that the responses to the first two quintiles are virtually identical between active treatment and placebo and only differentiate with the 3 more severe quintiles. In addition, there appears to be a greater difference from placebo as severity increases.

Although this suggests that the drug might be approved in more severe cases, since these results are only achieved by combining the data from two studies we do not have the robustness of repeated study results and we may even have an underpowered study. Consequently this may be insufficient for approval and a second study may be needed.

Figure 190 Change in Young Mania Rating Score over Time by Baseline Severity for Asenapine 10 mg SL BID and the Active Control Olanzapine 5 - 20 mg QD Compared to Placebo from Studies 1004 and 1005


Assigned.Quint.Placebo: 1
Assigned.Quint.Placebo: 2
Assigned.Quint.Placebo: 3
Assigned.Quint.Placebo: 4
Assigned.Quint.Placebo: 5
Assigned.Quint.Drug: 1
Assigned.Quint.Drug: 2
Assigned.Quint.Drug: 3
Assigned.Quint.Drug: 4
Assigned.Quint.Drug: 5
Quint.Olzp: 1.00
Quint.Olzp: 2.00
Quint.Olzp: 3.00
Quint.Olzp: 4.00
Quint.Olzp: 5.00
YMRS.Placebo
YMRS.Drug
YMRS.Olanzapine
Week
Week
Days

This raises two important points. First until about 2000 practice treatment guidelines for the use of antipsychotics in mania were limited to subjects essentially who were hypermanic, and by inclusion of all subjects with full blown mania in drug trials we may have driven the mean results by these morely severely ill subjects. Second, it indicates that promotion of off-label use and current 'expert opinion' practice treatment guidelines for the off-label use of antipsychotics in hypomania and especially in bipolar spectrum disorder in children such as promoted by NIMH in a May 5th, 2007 press release are likely inappropriate. Since, the YMRS scores in children with BSD are on the order of 4 for a few hours at a time whereas in this study efficacy only appears to be with scores equal to or greater than 27, (see) and the drugs barely bring the YMRS scores to 5 after 3 months, (see Figure 223). The patterns seen in this study was also confirmed by analysis of data from studies with other antipsychotics from other NDAs and there are even hints in some of the statistics reviews for other NDAs. (As data or information from one NDA or IND is not generally included in the review of another submission these analyses are not shown here.)

Table 182 shows the YMRS scores associated with each quintile and the overall distribution. This table indicates that asenapine should only be employed with in a patient who has a YMRS at any time prior to treatment of 27 or greater. However, further analyses with more subjects and other drugs are needed to refine the cutoff.

Table 182 Quintile Calculations Associated with Acute Mania Studies A7501004 and A7501005

Quintile	Ideal YMRS Percentiles Included in quintile	Ideal Number of Subjects in Quintile	Ideal Subject Number Cutoff (Inclusive)	Actual Subject Number Cutoff (Inclusive)	Actual Number of Subjects in Quintile	Cumulative % of Subjects in Quintile	YMRS Scores Associated with Quintile
1	0% - 20%	97	97	93	93	19.2	≤23
2	>20% - 40%	97	194	206	113	42.5	24 - 26
3	>40% - 60%	97	291	302	96	62.5	27 - 30
4	>60 % - 80%	97	388	405	103	83.5	31 - 35
5	>80% - 100%	97	—	—	80	83.5	≥36
Total	—	485	—	—	—	—	Range 11 - 56

A preliminary examination of subscale data by combined symptoms indicative of psychotic features was performed but was insufficient to even result in clear differentiation by psychotic features or not. Thus without much larger studies with sufficient power we cannot presently determine whether asenapine or other drugs work on the psychotic features of mania, and whether this is driving the efficacy in more severely ill subjects or not, or if the efficacy is independent of psychotic features but only a function of severity alone.[13] If the latter is true and the drug does not work well in schizophrenia but does work in mania due to a differential response by indication. Then there may be a different mechanistic reason for differential responses by indication and even by the antipsychotic employed unrelated to D2 receptor blockade.

Discussion of the differential response by severity with the statistician revealed that the statistician had found differing degrees of efficacy by race, with Asians driving the statistical significance of the study. As this reviewer had previously found an increased pharmacodynamic sensitivity to olanzapine in healthy Chinese to psychometric testing that was not explainable by pharmacokinetic differences this reviewer decided to examine whether the distribution of subjects by race was similar across quintiles.

[13] Even with schizophrenia examination of the PPANSS subscale in schizophrenia which did not improve the evaluation over total PANSS score even though total PANSS score is thought to be primarily driven by PPANSS. This indicates that there may be additional minor non-specfic or secondary effects on NPANSS or GPANSS simply due to improvement in PPANSS.

This exploratory analysis by study is shown in Table 183 and Table 184. There were clearly a greater percentage of subjects in quintiles 4 and 5 in study A7501004 and Study A7501005 but the ratio was not higher in quintile 3, where there was also a difference in efficacy. In addition the percentage of Asians was equal or greater in the placebo arms indicating that disease severity and not race is the important predictive factor.

Table 183 Racial and Ethnic Characteristics in Acute Mania by Treatment and Disease Severity - Study A7501004

Treatment	Group	Number of Subjects							% of Subjects					
	Quintile	Total	Asian	Black	Caucasian	Ethiopian	Hispanic	Puerto Rican	Asian	Black	Caucasian	Ethiopian	Hispanic	Puerto Rican
Placebo	1	32	4	1	25	0	2	0	12.5	3.1	78.1	0.0	6.3	0.0
	2	16	3	3	8	0	2	0	18.8	18.8	50.0	0.0	12.5	0.0
	3	19	3	5	11	0	0	0	15.8	26.3	57.9	0.0	0.0	0.0
	4	13	5	1	6	0	1	0	38.5	7.7	46.2	0.0	7.7	0.0
	5	16	7	5	4	0	0	0	43.8	31.3	25.0	0.0	0.0	0.0
	Total	96	22	15	54	0	5	0	22.9	15.6	56.3	0.0	5.2	0.0
Asenapine	1	46	7	5	34	0	0	0	15.2	10.9	73.9	0.0	0.0	0.0
	2	32	5	5	21	0	1	0	15.6	15.6	65.6	0.0	3.1	0.0
	3	44	7	11	25	0	1	0	15.9	25.0	56.8	0.0	2.3	0.0
	4	28	8	8	11	0	1	0	28.6	28.6	39.3	0.0	3.6	0.0
	5	34	13	9	12	0	0	0	38.2	26.5	35.3	0.0	0.0	0.0
	Total	184	40	38	103	0	3	0	21.7	20.7	56.0	0.0	1.6	0.0
Olanzapine	1	44	7	8	26	0	3	0	15.9	18.2	59.1	0.0	6.8	0.0
	2	33	2	1	27	0	3	0	6.1	3.0	81.8	0.0	9.1	0.0
	3	50	9	12	28	0	0	1	18.0	24.0	56.0	0.0	0.0	2.0
	4	38	13	8	16	0	1	0	34.2	21.1	42.1	0.0	2.6	0.0
	5	37	13	9	13	1	1	0	35.1	24.3	35.1	2.7	2.7	0.0
	Total	202	44	38	110	1	8	1	21.8	18.8	54.5	0.5	4.0	0.5

Table 184 Racial and Ethnic Characteristics in Acute Mania Efficacy Study A7501005 by Treatment and Disease Severity

Treatment	Group	Number of Subjects								% of Subjects						
	Quintile	Total	Asian & Oriental	Asian Indian	Black	Caucasian	Hispanic	Latino	Native American & American Indian	Asian & Oriental	Asian Indian	Black	Caucasian	Hispanic	Latino	Native American & American Indian
Placebo	1	20	0	0	3	14	3	0	0	0.0	0.0	15.0	70.0	15.0	0.0	0.0
	2	18	0	0	6	10	0	1	1	0.0	0.0	33.3	55.6	0.0	5.6	5.6
	3	20	1	0	4	15	0	0	0	5.0	0.0	20.0	75.0	0.0	0.0	0.0
	4	20	5	0	4	11	0	0	0	25.0	0.0	20.0	55.0	0.0	0.0	0.0
	5	26	13	1	2	10	0	0	0	50.0	3.8	7.7	38.5	0.0	0.0	0.0
	Total	104	19	1	19	60	3	1	1	18.3	1.0	18.3	57.7	2.9	1.0	1.0
Asenapine	1	47	4	0	9	32	2	0	0	8.5	0.0	19.1	68.1	4.3	0.0	0.0
	2	35	4	0	6	25	0	0	0	11.4	0.0	17.1	71.4	0.0	0.0	0.0
	3	43	5	0	7	28	1	1	1	11.6	0.0	16.3	65.1	2.3	2.3	2.3
	4	40	7	0	5	28	0	0	0	17.5	0.0	12.5	70.0	0.0	0.0	0.0
	5	27	14	1	4	8	0	0	0	51.9	3.7	14.8	29.6	0.0	0.0	0.0
	Total	192	34	1	31	121	3	1	1	17.7	0.5	16.1	63.0	1.6	0.5	0.5
Olanzapine	1	51	6	0	8	33	3	1	0	11.8	0.0	15.7	64.7	5.9	2.0	0.0
	2	39	6	1	8	21	2	0	1	15.4	2.6	20.5	53.8	5.1	0.0	2.6
	3	40	5	0	7	27	1	0	0	12.5	0.0	17.5	67.5	2.5	0.0	0.0
	4	25	7	0	4	14	0	0	0	28.0	0.0	16.0	56.0	0.0	0.0	0.0
	5	33	10	1	4	17	1	0	0	30.3	3.0	12.1	51.5	3.0	0.0	0.0
	Total	188	34	2	31	112	7	1	1	18.1	1.1	16.5	59.6	3.7	0.5	0.5

An additional concern is whether a 5 mg dose may be sufficient in this population, not only because it was not studied, but also as it appeared effective in the schizophrenia studies and as the bipolar subjects are not as likely to be smokers and therefore are expected to have higher exposures than the subjects with schizophrenia and thereby have a different risk benefit ratio.

5.6.2.2.1.3 Evaluation of Drop out Patterns

Drop out patterns were not assessed by this reviewer. The sponsor indicated that they applied their assessment of drop out patterns from the schizophrenia studies to bipolar disorder, however this reviewer believes this may not be a valid approach as the the level of historicity and insight between the two diseases are different as was the dose and the use of tobacco that may result in higher exposures in bipolar patients.

5.6.2.2.2 Maintenance Effect

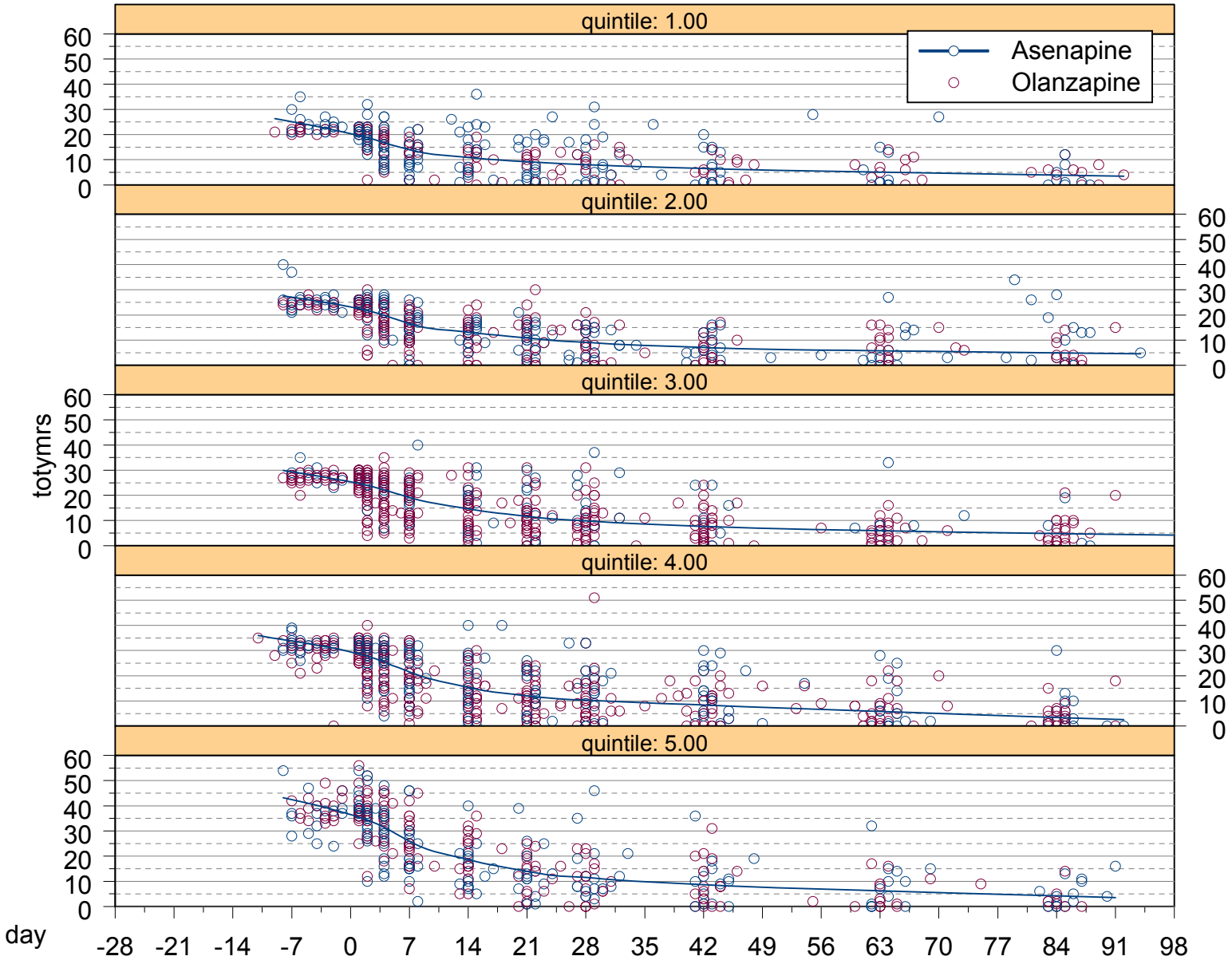
Study A7501007 was a double-blind, 40-week continuation study evaluating the safety of asenapine and olanzapine in the treatment of subjects with acute mania. The primary objective of this study is to characterize the longterm safety of asenapine and olanzapine in the treatment of acute mania in subjects with manic or mixed episode associated with Bipolar-1 Disorder for up to 52 weeks. Patients on placebo were not included as a comparator group.

Figure 191 shows plots of YMRS over time for all subjects on asenapine and olanzapine from screening until just over 90 days of dosing. Between 3 and 4 weeks of treatment Mean YMRS falls to 10 regardless of intial severity in contrast to placebo treated subjects who have similar patterns in the lowest two quinitles but not in the more severely ill subjects.

Regardless of severity (i.e. quintile) the mean YMRS in Figure 191 continues to decrease slowly so that shows by 2.5 – 3 months of treatment the mean score is below 5 which is on the order of severity with 'bipolar spectrum disorder' which these drugs are being recommended for by NIMH. However, it's clear that even by 3 months most subjects have dropped out with only 85 of 213 subjects (40%) still enrolled. This raises the question whether long term maintanence treatment is truly appropriate or if it's simply a function of who had a response at 3 or 4 weeks regardless of any continuing effect. This is especially concerning as there is no placebo control and other approved treatments have shown minimal advantages over placebo, and as this is only a single study and not two separate studies.

A better design would be a controlled withdrawal trial that was preferably placebo controlled. Consequently, there is insufficient information for a maintenance effect claim.

Figure 191 YMRS over Time for Subjects on Asenapine or Olanzapine from Studies A7501004 or A7501005 – 'Maintenance Effect' Study A7501007



5.6.2.3 Extrapyramidal Symptoms

In Amendment 010, the 4 month Safety Update, submitted Dec 27, 2007 the sponsor included study report INT00065682, Exploratory exposure response analyses of extrapyramidal symptoms (EPS) based on Phase 2 and Phase 3 trials for asenapine.

According to the sponsor, *'The dataset for analysis included all assessments on SARS (except screening scores) and their time of observation, study number, study arm, treatment, dose, asenapine AUC, information on dropout and reason for dropout as well as recorded adverse events. Only EPS-related adverse events were used in the analysis. The placebo and asenapine treated patients were included in the time-to EPSrelated adverse event analysis.*

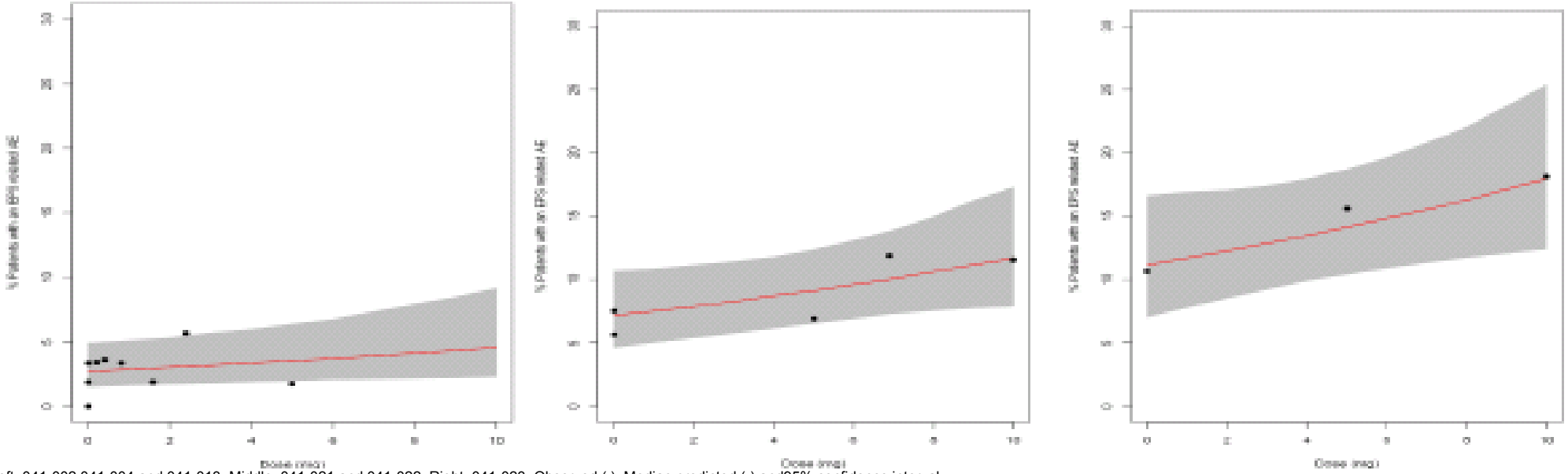
Possible dose- or exposure-response for asenapine using SARS scores and the incidence of EPS related adverse events were explored graphically. Model development was undertaken if a relationship was indicated. A time-to-event model was developed to describe the time to first EPS related AE. Bootstrapping was applied to evaluate the robustness of the final model. The final model was used to simulate proportions of patients with an EPS-related AE versus dose, which were compared with the observed proportions of patients with an EPS-related AE in the different trials.'

There was insufficient time for the reviewer to perform a detailed critique of the study report and data submitted however even examination of the sponsor's graphical analysis indicates a dose response relationship with symptoms of EPS over a period of six weeks, (see Figure 192 to Figure 196). Although the SARS scores decrease over 6 weeks (see Figure 193 to Figure 196), over a longer period of time we might see a dose response with tardive dyskinesia. Although haloperidol had higher SARs scores, observations consistent with this have been seen with other atypicals and may also be due to the saturable bioavailability with asenapine. Thus comparative risks of EPS cannot be determined for these analyses with respect to tardive or with respect to other atypical antipsychotics.

It should be noted that SARS scores only reflect pseudoparkinsonism. Thus effects on other types of EPS were not addressed. Due to high incidence of restless legs syndrome akathisia is also expected to be a problem.

Figure 192 appears to show an incidence of EPS of around 10% at a dose of 5 mg BID, which is in the range of what this reviewer expects based on his limited experience with reviewing antipsychotics.

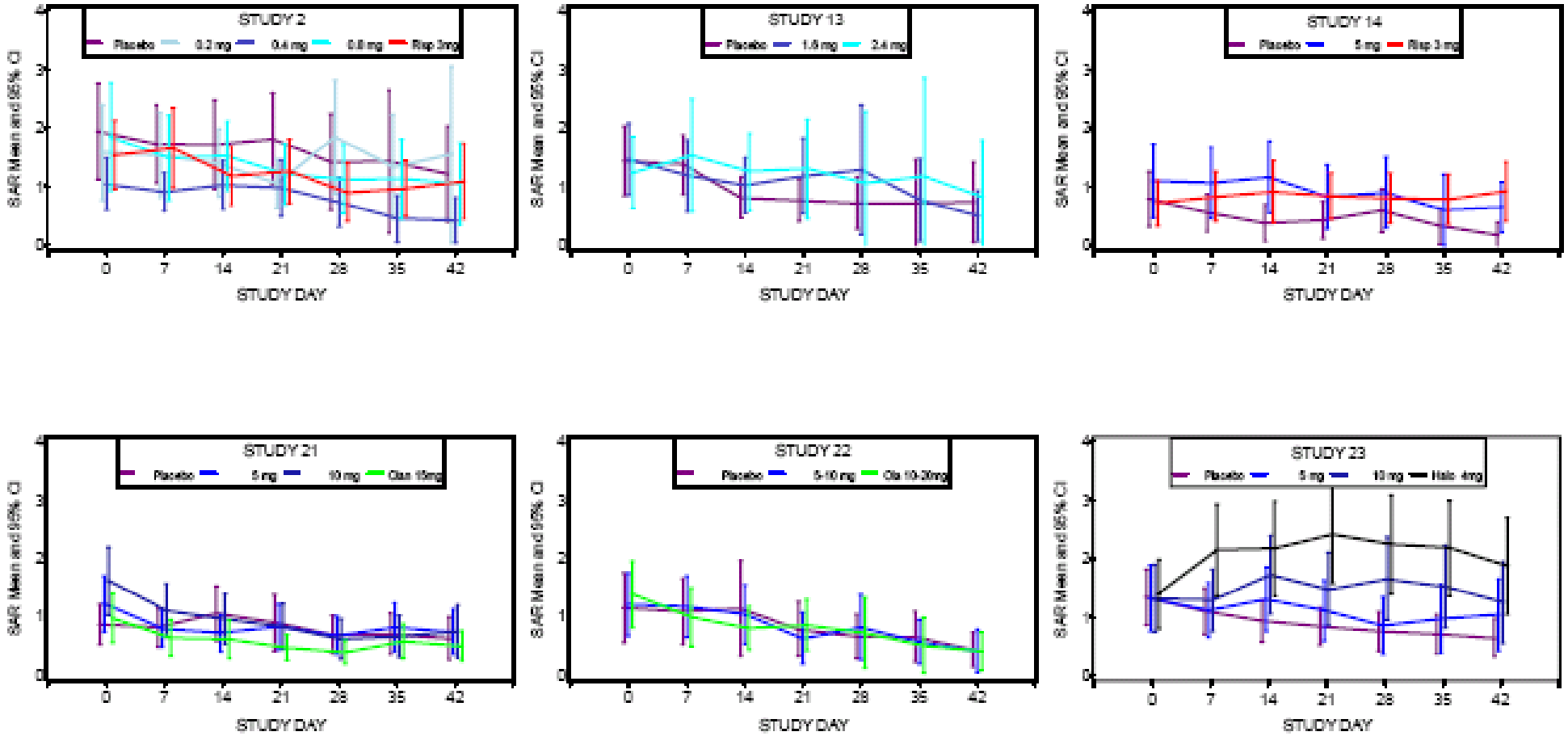
Figure 192 Proportion of Subjects with an EPS-Related Adverse Event in the Different Acute Schizophrenia Trials vs. Dose in Milligrams – Report INT00065682



Left: 041-002,041-004 and 041-013. Middle: 041-021 and 041-022. Right: 041-023. Observed (.), Median predicted (-) and95% confidence interval.

Figure 193 shows a decrease in the SARS score over time, possibly due to drop outs, with mixed results otherwise.

Figure 193 Mean SARS (95% confidence interval) versus Time per Treatment Arm by Trial – Report INT00065682



Note: Numbers in legends refer to studies as follows: 2: 041002; 13: 041013; 14: 041004; 21: 041021; 22: 041022 and 23: 041023. Source: Appendix A, Figures 1-3 to 1-8.

Figure 194 and Figure 195 show two other analyses of EPS rate vs. asenapine dose and AUC also indicating a dose response relationship.

Figure 194 Histogram of EPS Rate vs. Asenapine Dose – Report INT00065682

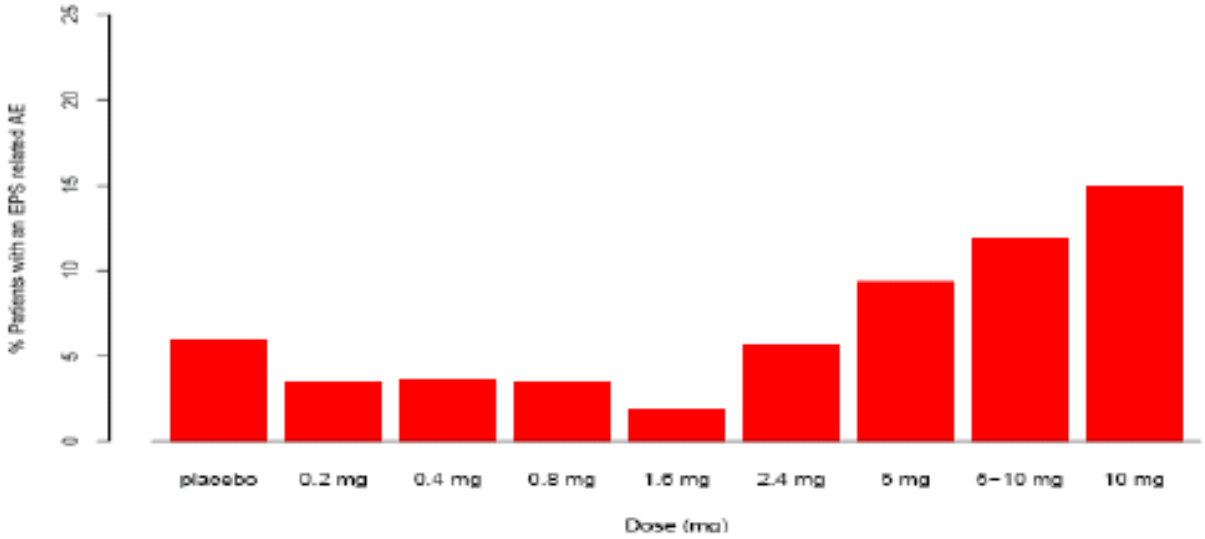


Figure 195 Histogram of EPS Rate vs. Asenapine AUC – Report INT00065682

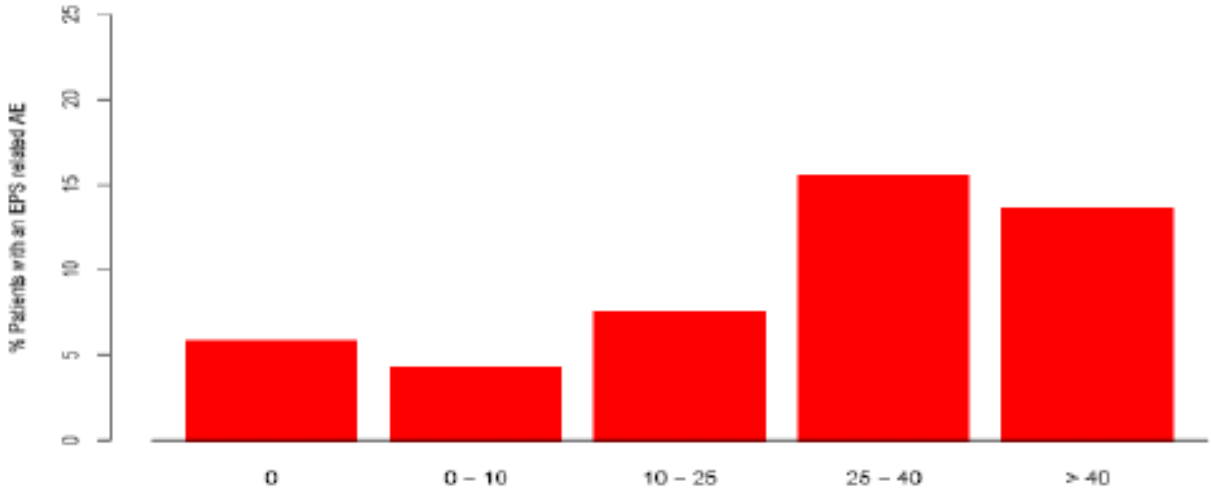
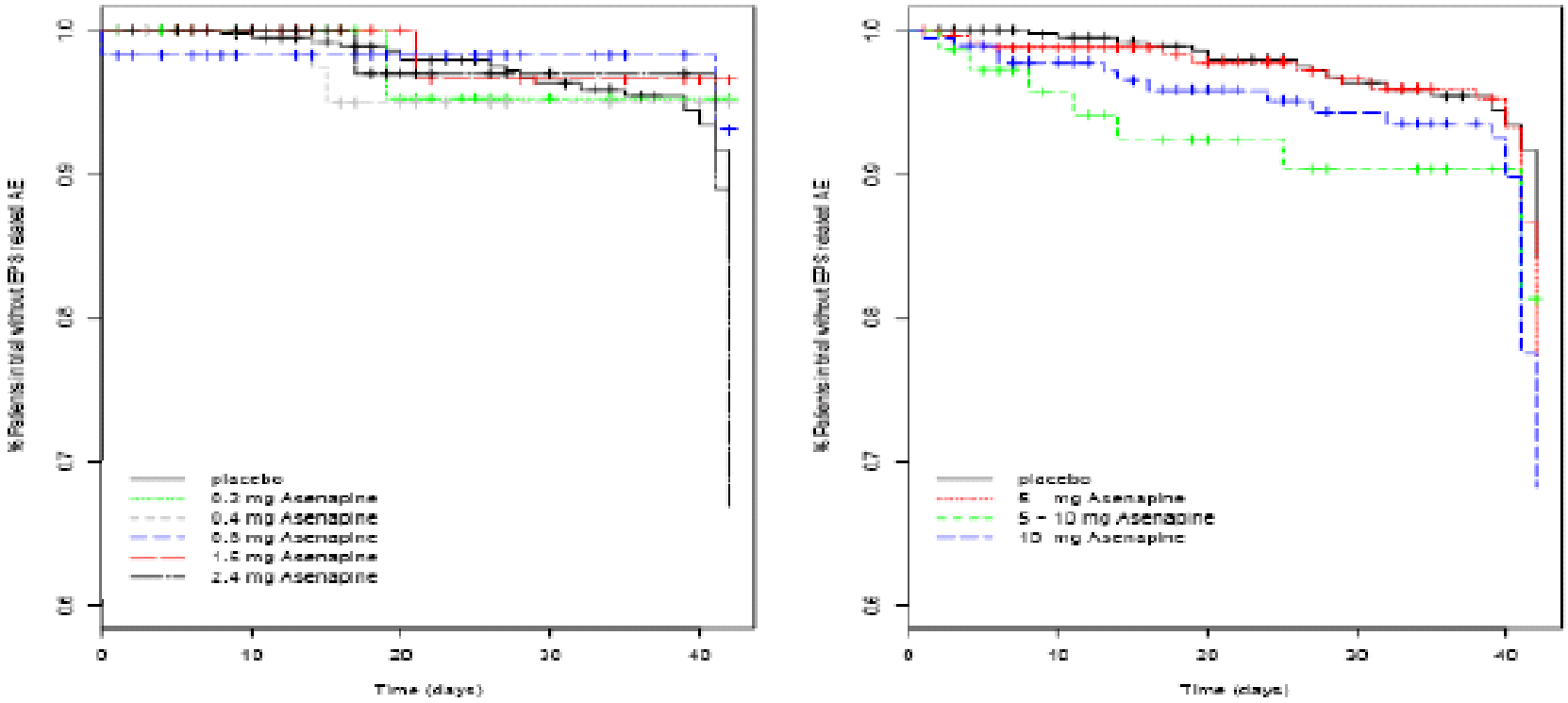


Figure 196 also indicates an increased incidence of EPS over time with asenapine doses of 5 - 10 mg as compared to placebo.

Figure 196 Proportion of Patients without an EPS-Related Adverse Event versus Time by Asenapine Dose. – Report INT00065682



Source: Appendix A Figure 2-3.

5.6.2.4 Suicidality

During one of the early meetings with the clinical meeting, (probably the scoping meeting) the issue of suicidality was raised by the clinical reviewer. It was stated that the number of cases of suicidality was high compared to placebo, but that it was lower than placebo when corrected for duration than exposure. Since no placebo was employed in the maintenance trials this reviewer performed a preliminary evaluation of exposure response for suicidality and found that when suicidality was appropriately compared for treatments of similar duration that there were similar rates between the drug treatments and placebo. In addition, suicidality was highest in the 1 – 2 weeks after discharge for acute treatment of schizophrenia, with a delay for the drug groups (presumably due to allowing any effect to wear off due to noncompliance). This is noteworthy for two additional reasons. The timing is similar to what is generally considered the period of highest risk and occurred in spite of subjects being evaluated prior to discharge as to risk of suicide. Consequently, the ability to assess risk of suicide is questionable and studies should be performed to determine if a longer duration of inpatient or another supervised living situation will decrease the risk of suicidality.

The following tables are slight modifications of tables taken from the Integrated summary of safety in section 2 of the NDA or from Appendix 1 of the Summary of Clinical Safety from NDA section 5.3.5.3.25.8

Table 185 and Table 186 show general information on adverse events. Table 185 indicates that there is a higher prevalence of severe AEs with the atypical antipsychotics compared to haloperidol.

Table 185 Overview of Adverse Events from All Phase 2/3 Studies Combined, (Cohort E)

Adverse Event	Placebo	Asenapine			Risperidone 3 mg BID	Haloperidol 4 mg BID	Olanzapine 5 – 20 mg QD
		<5 mg BID	5 - 10 mg[a] BID	All			
n (%)	(N=706)	(N=298)	(N=1953)	(N=2251)	(N=120)	(N=115)	(N=899)
Any Adverse Event	483 (68.4)	246 (82.6)	1523 (78.0)	1769 (78.6)	105 (87.5)	87 (75.7)	682 (75.9)
Related AEs	290 (39.7)	134 (45.0)	1099 (56.3)	1233 (54.8)	64 (53.3)	65 (56.5)	494 (54.9)
Severe AEs	52 (7.4)	59 (19.8)	260 (13.3)	319 (14.2)	21 (17.5)	7 (6.1)	105 (11.7)
Serious Adverse Events	61 (8.6)	50 (16.8)	275 (14.1)	325 (14.4)	21 (17.5)	8 (7.0)	87 (9.7)
Deaths	1 (0.1)	2 (0.7)	9 (0.5)	11 (0.5)	0	0	3 (0.3)
Discontinuations from any AE/SAE[b]	69 (9.8)	57 (19.1)	285 (14.6)	342 (15.2)	28 (23.3)	12 (10.4)	103 (11.5)
D/C'd 2^0 SAEs	36 (5.1)	16 (5.4)	125 (6.4)	141 (6.3)	12 (10.0)	5 (4.3)	40 (4.4)

a fixed and flexible doses
b data obtained from action taken on adverse event case report form
Risp=risperidone, Halo=haloperidol, Olan=Olanzapine
Source: 2.7.4 Appendix Table 2.0.E

Whereas Table 186 shows the prevalence of certain common AEs for asenapine as compared with the atypical antipsychotics risperidone and olanzapine, as well as with the classic antipsychotic haloperidol. Asenapine has a higher incidence of worsening schizophrenia whereas other AEs are closer to olanzapine. With the exception of weight gain which is intermediate. In contrast Risperidone has a high incidence of insomnia, agitation, anxiety and headache. Haloperidol in contrast has similar or lower incidences of common side effects.

Table 186 Adverse events by Preferred Term with an Incidence Greater Than or Equal to 2.0% for all Phase 2/3 Studies Combined, (Cohort E)

Adverse Event (Preferred Term)	Placebo	Asenapine			Risperidone 3 mg BID	Haloperidol 4 mg BID	Olanzapine 5 – 20 mg QD
		<5 mg BID	5 - 10 mg[a] BID	All			
n (%)	(N=706)	(N=298)	(N=1953)	(N=2251)	(N=120)	(N=115)	(N=899)
Any Adverse Event	483 (68.4)	246 (82.6)	1523 (78.0)	1769 (78.6)	105 (87.5)	87 (75.7)	682 (75.9)
Insomnia	80 (11.3)	52 (17.4)	293 (15.0)	345 (15.3)	28 (23.3)	16 (13.9)	98 (10.9)
Headache	114 (16.1)	79 (26.5)	207 (10.6)	286 (12.7)	28 (23.3)	5 (4.3)	105 (11.7)
Schizophrenia	30 (4.2)	39 (13.1)	177 (9.1)	216 (9.6)	7 (5.8)	8 (7.0)	47 (5.2)
Agitation	66 (9.3)	46 (15.4)	118 (6.0)	164 (7.3)	16 (13.3)	9 (7.8)	42 (4.7)
Anxiety	53 (7.5)	36 (12.1)	186 (9.5)	222 (9.9)	19 (15.8)	7 (6.1)	41 (4.6)
Somnolence	16 (2.3)	16 (5.4)	181 (9.3)	197 (8.8)	5 (4.2)	2 (1.7)	84 (9.3)
Sedation	31 (4.4)	6 (2.0)	179 (9.2)	185 (8.2)	8 (6.7)	4 (3.5)	129 (14.3)
Weight increased	3 (0.4)	1 (0.3)	167 (8.6)	168 (7.5)	6 (5.0)	1 (0.9)	150 (16.7)

Table 187 to Table 190 shows the information on suicidality.

Table 187 is the summary data the sponsor uses to claim that despite a higher prevalence of suicidality with active treatment as compare to placebo that the incidence when normalized to 100 patient years is lower with asenapine than with placebo and is comparable to Olanzapine.

Table 187 Psychiatric Adverse events Related to Suicidality for all Phase 2 and 3 Studies Combined, (Cohort E)

Adverse Event SOC/ Preferred Term			Placebo	Asenapine <5 mg BID	Asenapine 5-10 mg[a] BID	Asenapine All	Risp BID	Halo BID	Olan QD
Number of Subjects			**(N=706)**	**(N=298)**	**(N=1953)**	**(N=2251)**	**(N=120)**	**(N=115)**	**(N=899)**
N (%)	Psychiatric SAEs		2 (0.3)	3 (1.0)	33 (1.7)	36 (1.6)	2 (1.7)	–	17 (1.9)
	Discontinuations due to Psychiatric AEs		4 (0.6)	2 (0.7)	15 (0.8)	17 (0.8)	2 (1.7)	–	7 (0.8)
	Suicidal and self-injurious behaviours		7 (1.0)	9 (3.0)	37 (1.9)	46 (2.0)	3 (2.5)	–	18 (2.0)
	Self injurious ideation		–	–	1 (0.1)	1 (0.04)	–	–	–
	Intentional self injury		1 (0.1)	1 (0.3)	2 (0.1)	3 (0.1)	–	–	2 (0.2)
	Suicidal ideation		5 (0.7)	8 (2.7)	22 (1.1)	30 (1.3)	2 (1.7)	–	6 (0.7)
	Suicidal behaviour		1 (0.1)	1 (0.3)	–	1 (0.04)	–	–	1 (0.1)
	Suicide attempt		1 (0.1)	–	9 (0.4)	9 (0.4)	1 (0.8)	–	7 (0.8)
	Completed suicide		–	–	6 (0.3)	6 (0.3)	–	–	2 (0.2)
	Total		15 (2.1)	19 (6.4)	77 (3.9)	96 (4.3)	6 (5.0)	0.0	36 (4.0)
Patient exposure years			52	34	611	645	21	10	285
Number of Cases and Incidence Per 100 Patient years	Suicidal and Self-Injurious Behaviors	Cases	7	9	37	46	3	–	17
		Incidence[b]	13.49	26.24	6.06	7.13	14.29	–	5.97
	Self Injurious Ideation	Cases	–	–	1	1	–	–	–
		Incidence[b]	–	–	0.16	0.16	–	–	–
	Intentional Self Injury	Cases	1	1	2	3	–	–	2
		Incidence[b]	1.9	2.9	0.3	0.5	–	–	0.7
	Suicidal Ideation	Cases	5	8	22	30	2	–	6
		Incidence[b]	9.63	23.32	3.60	4.65	9.52	–	2.11
	Suicidal behaviour	Cases	1	1	–	1	–	–	1
		Incidence[b]	1.9	2.9	–	0.3	–	–	0.4
	Suicidal Attempt	Cases	1	–	9	9	1	–	7
		Incidence[b]	1.93	–	1.47	1.40	4.76	–	2.46
	Completed Suicide	Cases	–	–	6	6	–	–	2
		Incidence[b]	–	–	0.98	0.93	–	–	0.70
	Total	Cases	15	19	77	96	6	–	35
		Incidence[b]	28.8	55.9	12.6	14.9	28.6	0.0	12.3

a fixed and flexible doses
b incidence /100 exposure years
Risp=risperidone, Halo=haloperidol, Olan=olanzapine
Source: 2.7.4 Appendix Tables 2.2.E, 2.18.E, 2.26.2.E, and 2.30.E

Consequently this reviewer compared only the data from studies that had similar durations of exposure to active drug and placebo.

Table 188 shows this data by week of treatment for the combined data for the phase II/III 6 week studies for the treatment of acutely ill schizophrenics, and Table 189 shows similar data for acutely ill patients with bipolar I disease.

Table 188 shows that the incidence of suicidal and self-injurious behaviours, as reported by the sponsor, were similar regardless of treatment an incidence of around 1%, (range 0.8% - 1.2%). As stated previously peak occurence is around week 4 or 5 just after discharge. Not all other categories were reported by the sponsor so each category was included in Table 188 by the reviewer.

Table 188 Prevalence of AEs Indicative of Suicidality over Time by Treatment in Acute Schizophrenia Trials, (Cohort A)

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Total Weeks 1 - 6
Placebo	N=503	N=439	N=372	N=301	N=263	N=233	N=503
Suicidal and self−injurious behaviours NEC	1 (0.2)	–	1 (0.3)	2 (0.7)	–	1 (0.4)	5 (1.0)
Self−injurious ideation	–	–	–	–	–	–	–
Intentional self−injury	–	–	–	–	–	–	–
Suicidal ideation	1 (0.2)	–	1 (0.3)	2 (0.7)	–	–	4 (0.8)
Suicide attempt	–	–	–	–	–	2 (0.9)	2 (0.4)
Completed Suicide	–	–	–	–	–	–	–
Total	**2 (0.4)**		**2 (0.5)**	**4 (1.3)**		**3 (1.3)**	**11 (2.2)**
Asenapine 5 mg BID (fixed)	N=274	N=247	N=215	N=186	N=167	N=159	N=274
Suicidal and self−injurious behaviours NEC	–	–	–	–	2 (1.2)	–	2 (1.2)
Self−injurious ideation	–	–	–	–	–	–	–
Intentional self−injury	–	–	–	–	–	–	–
Suicidal Ideation	–	–	–	–	1 (0.6)	–	1 (0.36)
Suicide attempt	–	–	–	–	1 (0.6)	1 (0.6)	2 (1.2)
Completed Suicide	–	–	–	–	–	–	–
Total					**4 (2.4)**	**1 (0.6)**	**3 (1.1)**
Asenapine 10 mg BID (fixed)	N=274	N=208	N=183	N=147	N=132	N=126	N=274
Suicidal and self−injurious behaviours NEC	–	–	–	–	1 (0.8)	–	1 (0.8)
Self−injurious ideation	–	–	–	–	1 (0.8)	–	1 (0.8)
Intentional self−injury	–	–	–	–	–	–	–
Suicidal ideation	–	–	–	–	–	–	–
Suicide attempt	–	–	–	–	–	–	–
Completed Suicide	–	–	–	–	–	–	–
Total					**2 (1.5)**		**2 (0.73)**
Asenapine 5 -10 mg BID (fixed & Flexible)	N=870	N=758	N=663	N=529	N=455	N=424	N=870
Suicidal and self−injurious behaviours NEC	1 (0.1)	–	1 (0.2)	2 (0.4)	3 (0.7)	1 (0.2)	8/870 (0.92%)
Self−injurious ideation	–	–	–	–	1 (0.2)	–	1 (0.1)
Intentional self−injury	–	–	1 (0.2)	–	–	–	1 (0.1)
Suicidal ideation	1 (0.1)	–	–	2 (0.4)	1 (0.2)	1 (0.2)	5 (0.6)
Suicide attempt	–	–	–	–	1 (0.2)	1 (0.2)	2 (0.2)
Completed Suicide	–	–	–	–	–	–	–
Total	**2 (0.2)**		**2 (0.3)**	**4 (0.8)**	**6 (1.32)**	**3 (0.7)**	**17 (2.0%)**
Olanzapine 10−20 mg QD	N=194	N=161	N=146	N=124	N=110	N=102	N=194
Suicidal and self−injurious behaviours NEC	–	–	–	1 (0.8)	–	–	1 (0.8)
Self−injurious ideation	–	–	–	–	1 (0.8)	–	1 (0.8)
Intentional self−injury	–	–	–	–	–	–	–
Suicidal ideation	–	–	–	1 (0.8)	–	–	1 (0.8)
Suicide attempt	–	–	–	–	–	–	–
Completed Suicide	–	–	–	–	–	–	–
Total				**2 (1.6)**	**1 (0.9)**		**3 (1.5)**

Adverse events coded using MedDRA (version 9.0). N is the number of subjects at risk from the beginning of that week.

Table 189 shows similar data for bipolar I disorder but due to the small sample size no firm conclusions can be drawn although suicides only occurred in the drug treatment groups.

Table 189 Prevalence of AEs Indicative of Suicidality over Time by Treatment in Acute Bipolar I Trials, (Cohort C)

	Week 1	Week 2	Week 3	Total Weeks 1 - 3
Placebo	N=203	N=166	N=131	203
Suicidal and self−injurious behaviours NEC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Self−injurious ideation				
Intentional self−injury				
Suicidal ideation				
Suicide attempt				
Completed Suicide				
Total				0 (0.0)
All Asenapine 5−10 mg BID (fixed and flexiible)	N=379	N=317	N=260	379
Suicidal and self−injurious behaviours NEC				
Self−injurious ideation				
Intentional self−injury	0 (0.0)	1 (0.3)	1 (0.4)	2 (0.53%)
Suicidal Ideation	0 (0.0)	0 (0.0)	1 (0.4)	
Suicide attempt				
Completed Suicide	0 (0.0)	1 (0.3)	0 (0.0)	
Total		2	2	4 (1.06%)
Olanzapine 5−20 mg QD	N=394	N=358	N=323	394
Suicidal and self−injurious behaviours NEC	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.51%)
Self−injurious ideation				
Intentional self−injury				
Suicidal ideation				
Suicide attempt	0 (0.0)	1 (0.3)	0 (0.0)	
Completed Suicide	0 (0.0)	1 (0.3)	0 (0.0)	
Total		4		4 (1.02%)

Table 190 is mainly useful as by combining data is appears to indicate that the incidence of self-injurious behaviour may be lower with Olanzapine.

Table 190 Sponsor's Table of Suicidal and Self−injurious Behaviors by Treatment for both Acute Schizophrenia and Acute Bipolar Studies Combined, (Cohorts A and C)

Placebo	5/503 (1.0%)
Asenapine	10/1249 (0.8%)
Olanzapine	3/588 (0.51%)

5.6.3 Other Safety Issues

Significant insights into exposure response and PK/PD relating to safety were gleaned from several phase I trials. Originally the reviewer was told not to review these studies (i.e. early phase I studies, studies of development formulations, and the QT study) and the reviewer had to agree in writing, however the reviewer included the provision that if any information pointed to the need to examine these studies in more detail then this reviewer would do so.

Review of the PET studies indicated dose and time dependent hepatotoxicity had been seen with high oral doses. However review of the original data was not pursued by this reviewer, rather the medical officer was informed. Then on April 10, 2008 while checking the history of the formulation for the executive summary of the review (i.e. §2.2.3 Pertinent Clinical Pharmacology and Biopharmaceutic Questions) this reviewer sereptitiously came across descriptions of serious cardiotoxicity in the early phase I studies. Since a potential myocardial infarction was identified in the paroxetine drug-drug interaction study (25525) that was dismissed as musculoskeletal in origin, this reviewer examined these cases more closely prior to communication with the medical officer. It was then noted that some of these serious cardiac toxicities were noted in the QT study but that they hadn't been highlighted and had been explained largely as vasovagal in origin. While looking into the cardiotoxicity issue additional pertinent information on hepatotoxicity came to light.

Upon further examination of the various study designs it was noted that virtually all studies used low doses of short duration and tended to avoid subjects who might be at increased risk of hepatotoxicity. In addition in those studies where the risk might be apparent, i.e. the QT study and the adolescent study laboratory and other data were not reported so that a safety assessment could not be performed. In addition, the medical team leader requested a review of the adolescent study on Friday April 11, 2008 immediately prior to the DFS due date (April 14, 2008) when a quick review was likely to overlook this important safety information, (see §6.6 April 11, 2008 Consult Request from Medical Team Leader).

With regards to cardiotoxicity there appears to be a high incidence of AV block with junctional rhythms. Thus the vaso-vagal explanation for the large number of subjects fainting is suspect. Generally this is not a great concern clinically however, in the elderly and in the presence of certain other drugs this could be quite important. This asw well as the risk of agranulocytosis may explain why the sponsor did not include data in elderly subjects in this submission.

A synopsis of a PK study in the elderly was accidentally found in the 120 day safety report several levels down under a folder for an efficacy study. This study synopsis was only identifiable by a study report code without a title and was only looked at because the study code did not match the study code for higher level folder. As with the adolescent study only mean PK data was provided without any safety information or laboratory values.

Abbreviated information on these serious AEs follow:

5.6.3.1 Hepatotoxicity

5.6.3.1.1 Single Rising Dose Oral Study 85029

The clinical study report for study 85029 was dated November 1989. However based on the study title, (A Phase I, double-blind, placebo controlled, single rising oral dose study with Org 5222 in healthy male volunteers to assess tolerance and safety), it appears to be the first in human study. In the background information for this study, dose and time dependent hepatotoxicity in dogs were noted as shown in Figure 197.

Figure 197 Background Information on Preclinical Safety for First in Man Study - Study 85029

A 13 week oral toxicological study in dogs has been completed. Doses used were 1.25, 7.5 and 20 mg/kg/day. Interim analysis was performed after one month because in previous studies the lowest dose (20 mg/kg/day) still caused hepatotoxicity. The interim analysis did not show any abnormality of some biochemical (in particular plasma liver enzyme concentrations) and haematological parameters in the 1.25 and 7.5 mg/kg/day groups. In the 20 mg/kg/day group a slight increase in plasma liver enzyme concentrations was elicited, although the values observed were still within normal limits. The final analysis of this study indicated signs of hepatotoxicity in some (but not all) dogs treated with 7.5 and 20 mg/kg/day. No indications of hepatotoxicity were apparent in the 1.25 mg/kg/day dose group of dogs. Neither reproductive toxicological nor mutagenicity studies revealed any effects which preclude evaluation in man.

No significant adverse events were reported for this trial.

5.6.3.1.2 PO MRD PK S/T Study 85136

Although this clinical study report, (Feb 3, 1988), predates the previous study report. The title, (A Phase I, double-blind, placebo controlled, sub-chronic study with increasing doses of Org 5222 up to 30 mg daily in healthy male volunteers) and other indicators suggest that study 85136 was the second study in man.

The sponsor's conclusions that are shown in the following figures clearly indicate a dose and time dependent direct hepatocellular hepatotoxicity (see Figure 198 to Figure **200**), and that occurs sooner with higher doses and later with lower doses, (i.e. as soon as Day 2 with 20 mg PO BID and no sooner than day 10 with 10 mg PO BID and below), (see Figure 201). Although transaminases declined with drug discontinuation in two of the nine subjects LFT increases were greater than 3 fold, (see Figure 202 and Figure 203).

Figure 198 Sponsor's Safety Conclusions Regarding Hepatotoxicity – Study 85136

V. Conclusion

1. ORG 5222 caused mild to moderate liver enzyme increases probably due to direct hepatocellular toxicity.

Figure 199 Sponsor's Safety Conclusions Regarding Hepatotoxicity (Continued A) – Study 85136

In summary, 9 out of 20 subjects given active medication developed changes in plasma liver enzymes during the study. Three of six subjects who received the highest dosage of ORG 5222 experienced elevation of AST and/or ALT to greater than twice the upper limit of normal. One of 8 placebo subjects had an elevated alkaline phosphatase throughout the study and had a single mildly elevated ALT level recorded.

Figure 200 Sponsor's Safety Conclusions Regarding Hepatotoxicity (Continued B) – Study 85136

The pattern of enzyme changes - elevation of transaminases with normal alkaline phosphatase and no accompanying rise in total bilirubin - suggests direct hepatocellular toxicity rather than cholestasis as the underlying mechanism. Enzyme induction alone is unlikely to have caused such changes in the plasma liver enzymes.

Figure 201 Sponsor's Table of Subject Characteristics for Cases of Hepatotoxicity – Study 85136

Group No.	Subject No & Initials	Dose	Abnormal Tests	Day of Onset of rise	Time of Peak of rise	Day of Ist subsequent normal value	Severity
II	14. (b) (6)	3 mg bd	ALT	10	10	14	++
III	18.	10 mg bd	ALT	10	11	21	++
			AST	10	11	13	+
IIIA	101	20 mg bd	T.bili	2 & 10	2 & 10	5 & 14	+ & +
	102	Placebo	Alk Phos	Raised at screening and throughout			+
			ALT	14	14	21	+
	104	20 mg bd	ALT	10	15	-	++
			AST	0	2 & 14	5 & 21	+
IV	28.	30 mg bd	ALT	9	9	-	+++
			AST	9	9	-	+++
	29.	30 mg bd	ALT	0	12	15	+++
			AST	10	12	14	+
			GGT	0	6	15	+
	30.	30 mg bd	ALT	6	11	-	+++
			AST	6	9	27	+++

+ = 0-49%
++ = 50-99%
+++ = 100%+

Figure 202 Plot of Significantly Elevated Liver Function Tests (> 3X ULN) vs. Time - Case 1 – Study 85136

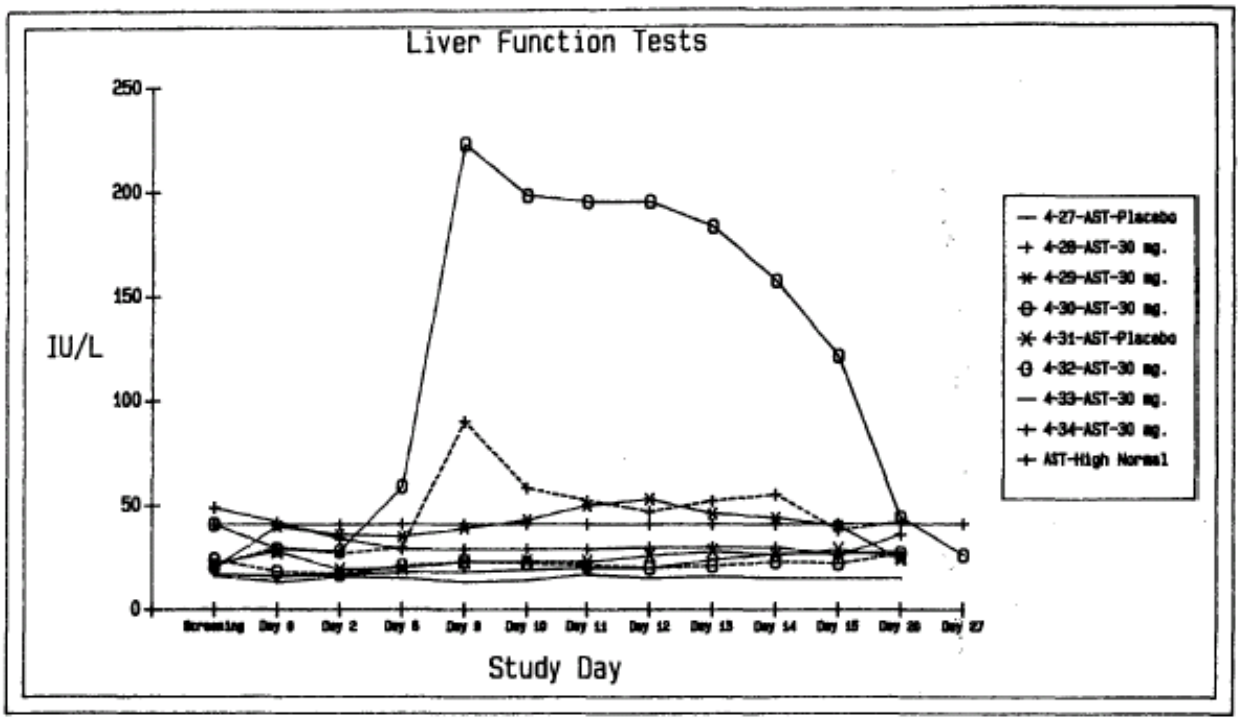
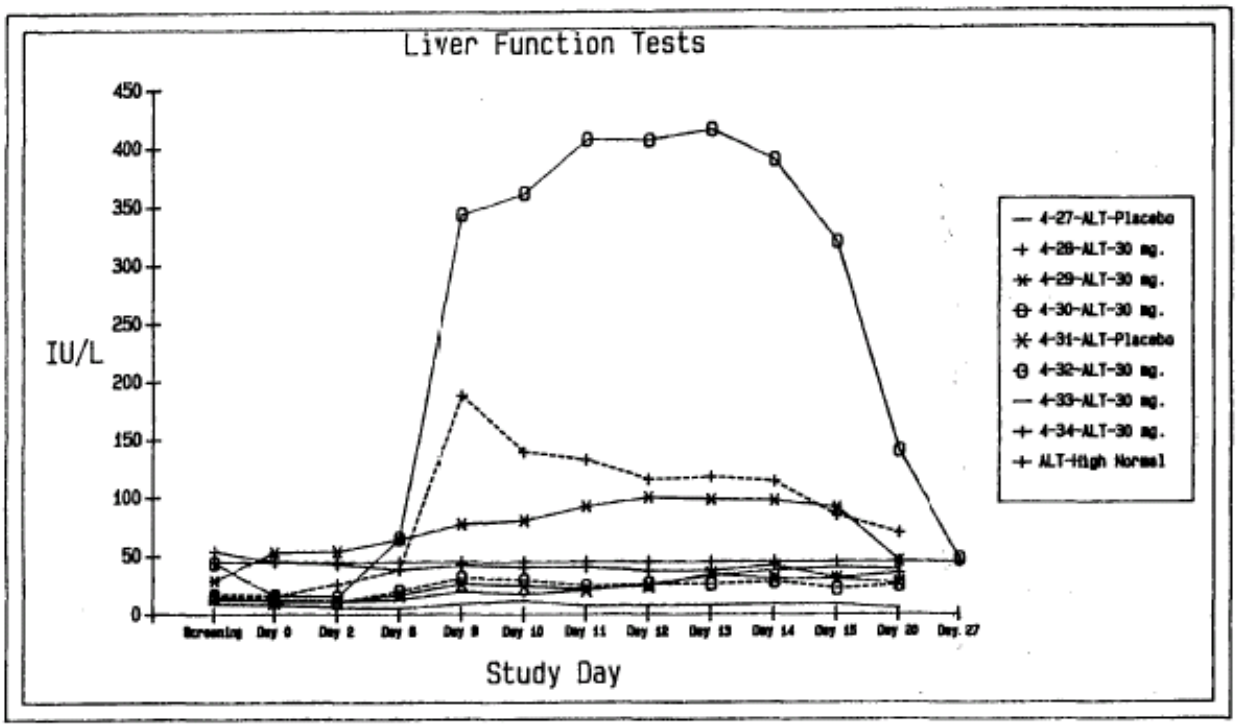


Figure 203 Plot of Significantly Elevated Liver Function Tests (> 3X ULN) vs. Time - Case 2 – Study 85136



5.6.3.1.3 Pivotal BE Study – (b) (4) vs. (b) (4) Tablet - Study 41026

Study 41026 was a pivotal bioequivalence study of a sublingual tablet manufactured by (b) (4) to the (b) (4) clinical trial formulation. The reason given for this proposed change in formulation was that asenapine maleate is bitter and this may improve the organoleptic characteristics. This is reasonable as a slower dissolving tablet would minimize the bitterness. However, the (b) (4) tablet was bio-inequivalent, presumably due to the slower disintegration and dissolution resulting in more drug being swallowed.

Subject 19 had elevated ALAT levels from Day 2 after treatment with the (b) (4) tablet, which resolved 14 days later. Since the pharmacokinetic characteristics are so close to the tablets with (b) (4) and since the margin of safety is so small this raises the concern whether the safety profile with (b) (4) tablets may be different than seen with the clinical trial formulation.

5.6.3.1.4 Paroxetine Drug Interaction Study - Study 25525

In study 25525 subject 15 in sequence A dropped out due to elevated ALAT (main reason) and elevated ASAT at Day 15. The ALAT concentration increased to a maximal value of 474 U/L at Day 16 (Upper Normal Limit (ULN): 50 U/L). ALAT increased the day after paroxetine administration and 4 days after administration with dextromethorphan raising the concern that there may be increased risk of toxicity when administered with other drugs, whether this is due to interactions via CYP2D6 and shunting or pharmacodynamic interactions cannot be discerned from this study.

Several other subjects had lessor degrees of increases in ALAT and ASAT, (see Figure 204 and Figure 205).

Figure 204 Text from Paroxetine DDI Study 25525

Seven clinically relevant abnormalities were observed in Sequence A.

Subject 02 had elevated ALAT (73 U/L) and ASAT (108 U/L) starting at Day 17, one day after administration of the last trial medication in Sequence A. Both elevations were judged probable related to the trial medication and of mild intensity. Ten days later ALAT and ASAT concentrations were decreased within normal ranges to 21 and 46 U/L, respectively (ULNs for ALAT and ASAT are 50 U/L and 40 U/L, respectively).

Subject 05 had elevated ALAT (99 U/L) starting at Day 17, one day after administration of the last trial medication in Sequence A (judged possibly related to the trial medication and of mild intensity). Six days later the ALAT was 86 U/L declining to 60 U/L after 14 days (judged to be abnormal but not clinically relevant).

Subject 12 had an elevated cholesterol level (8.4 mmol/L) starting at Day 17, one day after administration of the last trial medication in Sequence A (judged unlikely related to the trial medication and of mild intensity). Six days later the cholesterol level was decreased to 6.9 mmol/L (judged to be abnormal but not clinically relevant).

Subject 15 had an elevated ALAT concentration (58 U/L) starting at Day 7, after 3 days of administration of 1, 3 and 5 mg asenapine b.i.d., respectively (judged probably related to the trial medication and of moderate intensity). The ALAT concentration increased to a maximal value of 474 U/L at Day 16. Subsequently, the ALAT concentration declined to 78 U/L in 14 days (judged to be abnormal but not clinically relevant). Administration of trial medication was ended after dosing of 5 mg

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Figure 205 Text from Paroxetine DDI Study 25525 (continued)

asenapine in the morning of Day 15. Subject 15 had an elevated ASAT concentration (63 U/L) starting at Day 13, after 6 days of administration of asenapine b.i.d. (judged probably related to the trial medication and of mild intensity). Two days later the ASAT was 179 U/L declining to 44 U/L in 8 days (judged to be abnormal but not clinically relevant).

Subject 114 had elevated ALAT (119 U/L) starting at Day 7, after 3 days of administration of 1, 3 and 5 mg asenapine b.i.d., respectively, (judged probably related to the trial medication and of moderate intensity). From Day 26 the ALAT declined to 59 U/L 7 days later (judged to be abnormal but not clinically relevant).

No clinically relevant abnormalities were observed in Sequence B.

5.6.3.1.5 Thorough QT Study - Study A7501001

When examining the population pharmacokinetic report this reviewer observed that there a number of subjects with elevated bilirubins. The majority of these elevated bilirubins were in the thorough QT study. The medical reviewer was notified and lab values were requested from the sponsor, (see section 6.4 Identification of Elevated Bilirubins and Medical Reviewer Notification and the Pop PK Thorough QT study A7501001 in section 5.6.1.3 because it was reported over 4 different study reports.

There is some confusion regarding the units reported for some of these studies and whether conversion was done appropriately. However, what's disconcerting is that the sponsor only reported laboratory values from before and after treatment and not during treatment.

5.6.3.1.6 Relative BE Study New Formulation - Study 41009

This was a comparison of different polymorphic forms. One subject (0002) had ALT elevations of 5 fold ULN and a second subject (008) had ALT elevations of 3 fold ULN.

5.6.3.2 Cardiotoxicity

A number of cases of serious cardiotoxicity have been found in young healthy volunteers. These include myocardial infarction, AV block with junctional rhythms, and Afib. In addition a there have been a number of reported cases of tachycardia as well as bradycardia and syncope.

Some of these are reported in the QT study report but were not highlighted by the QT team.

It appears that there may be a concentration dependent effect on AV conduction that occurs at higher doses than QT prolongation, thus explaining the QT effect at the lower dose but not at the higher dose. Whether this is due to differing effects at different concentrations and/or due to a metabolite formed via first pass from swallowed drug is presently unknown. If there is AV block we might expect to see a shortened QT at higher exposures.

There is also some indication that the cardiac toxicity may be worse in individuals taking other drugs that might effect cardiac conduction or CYP2D6, e.g. paroxetine, etc.. Thus the risk with concomitant drugs such as lithium, paroxetine, carbamazepine, dextromethorphan, OTC sympathomimetics etc. needs to be investigated and assessed

In study 25509 the sponsor indicates that the asenapine is unsafe at drug exposures obtained with clinical dosages and due to cardiotoxicity and direct hepatotoxicity.

The fact that little information is included in this NDA regarding expected combination use with other drugs or use in women or the elderly and the increased risk the elderly have with this type of arrhythmia indicates further safety assessment is needed if development of the compound is pursued.

Additional information on events indicative of cardiotoxicity follow:

A summary of the selected cardiac AEs that were found in the limited time available (2 days) are shown in Table 192.

5.6.3.2.1 IV Study - Study 25506 - Nov 1992

Study 25506 was a pharmacokinetic study of intravenous administration of asenapine at four different doses, with each dose to be administered to two healthy male volunteers which was then to be followed by a pilot bioavailability study of 30 mg orally in the two volunteers who received the highest tolerated intravenous dose.

The study was stopped after the first two subjects due to asystole requiring external cardiac massage and atropine. Although attributed by the sponsor to a vasovagal effect, an external cardiologist deemed it a serious AE of asenapine affecting the conducting system of the heart, (see Figure 206 to Figure 211).

What is particularly worrisome is that this occurred at a dose of 0.7 mg shortly after a 30 minute infusion in a young healthy individual with no evidence of any cardiac disease. With an average absolute bioavailability of 33% (and up to 50%) this translates into a sublingual dose of 1.4 mg - 2.1 mg and is unlikely due to metabolites. Thus arrhythmias are a concern with clinical doses.

Figure 206 Text from IV Study 25506

This study was stopped after one of the two subjects collapsed in asystole. Prompt resuscitation resulted in the patient being asymptomatic 24 minutes after the initial collapse. Anxiety about the other subject's adverse event may have contributed to subject's 1/2(0.7mg) dizziness.

Figure 207 Text from IV Study 25506 (Continued)

Cardiac investigations - including a 24 hour Holter ECG, echocardiogram, exercise ECG and carotid sinus massage - revealed no cardiac pathology that may have predisposed to the event.

Org 5222 has alpha-blocking activity. It is possible that the drug aggravated hypotension (during sitting) and this precipitated an inappropriate vagal response in a vagotonic (athletic) subject. However, this does not adequately explain the persistence of the sinus arrest and the lack of response to lying supine.

Figure 208 Text from IV Study 25506 (Continued)

This study was stopped because subject 1/1(0.7mg) collapsed 45 minutes after the start of the 30-minute infusion, while having his sitting blood pressure measured. Before he collapsed he stated that he felt dizzy and unwell, then immediately fell back onto the bed. The ECG monitor showed asystole. The subject was shaken and made a transient verbal

Figure 209 Text from IV Study 25506 (Continued)

response. He had no pulse and was very pale. The foot of the bed was elevated. Cardiac massage commenced and after approximately five thrusts to the sternum, he made a transient verbal response: he asked what was happening. The cardiac massage, which lasted about 5 seconds, appeared to stimulate a nodal bradycardia before reverting to asystole. The subject again lost consciousness. The cardiac massage was repeated for another 5 seconds, with improvement in consciousness. The subject was continuously unconscious for not more than 30 seconds. However, severe bradycardia with intermittent nodal complexes and AV dissociation persisted until two doses of atropine (0.6mg i.v.) had been administered at 01 00 49 and 01 00 54. Haemaccel (one unit i.v.) was administered at 01 00 59. Oxygen was removed at 01 01 10. Sinus tachycardia resulted within seconds, the subject became normotensive and fully regained consciousness. Twenty-four minutes after the initial collapse, the subject was asymptomatic. Plasma electrolytes (Na, K, Ca and Mg) in the additional blood samples taken (see section 6.2) were normal. Subsequent cardiac investigations and cardiological opinion (see letter of 23 december 1991 in appendix 14) revealed no predisposing or post-event cardiac pathology. The cardiological investigations - a physical examination, 24-hour tape-recorded ECG, two-dimensional echocardiogram, treadmill exercise ECG, and carotid sinus massage - could not identify any cardiac abnormality.

Subject 1/2(0.7mg) had been dosed and began to feel dizzy before subject 1/1(0.7mg) collapsed. This adverse event was initially considered mild, but when he felt dizzy on standing - 30 minutes after dosing - it was considered to be of moderate severity. By that time subject 1/1(0.7mg) had collapsed.

Figure 210 Cardiologist's Report from IV Study 25506

(b) (4)

Re: (b) (4) 001 026 5222 I.V. STUDY

Thank you for asking me to assess this 27 year old chap who had an unfortunate event as a result of participating in a normal volunteer study. I've looked at the sequence of ECGs and there's no doubt that he became asystolic and as you pointed out you had to perform cardiac massage to sustain an output. It is interesting looking at the sequence of events because in the first instance there's obviously sinus arrest but then as he recovers there's evidence of AV conduction abnormalities also with a gradual return back to normal sinus rhythm.

With regard to him, he's always been fit, well and very active and though he currently works as a casino manager, in the past he's had a healthy lifestyle being an ex-marathon runner and still keeping reasonably fit. He's single, a non smoker, only drinks alcohol at the weekends. He's never been ill apart from a road traffic accident five years ago when he had some cervical spine damage.

EXAMINATION

He looks fit and well. JVP not raised, sinus rhythm, blood pressure 110/80. There were no murmurs, there were two heart sounds, there was no suggestion of heart failure and the lungs were normal and clear.

INVESTIGATIONS

24 Hour Tape Recorded ECG: Normal sinus rhythm with respiratory variation.

2D Echocardiogram: Normal.

Treadmill Exercise ECG: He managed an above average 15 minutes going to his maximal heart rate of 194 beats per minute. There were no arrhythmias and no ischaemic changes.

Carotid Sinus Massage: Massage of both the right and left carotids did not induce any significant bradycardia.

OPINION

First of all I cannot identify any cardiac problem in (b) (4) and I've reassured him that there's no evidence of any cardiovascular disease.

Figure 211 Cardiologist's Report from IV Study 25506 (Continued)

Secondly, this almost certainly has to be classed as a drug induced effect with a serious adverse effect on the conducting system of the heart.

If you require any further report or details from me please let me know.

Kind regards,

Yours sincerely,

(b) (4)

CONSULTANT CARDIOLOGIST

5.6.3.2.2 Multiple Rising Oral Dose Study - Study 25501 – June 1993

Study 25501 was a multiple rising dose study to examine the pharmacokinetics in 12 young, healthy, male volunteers using Org 5222 both after a single oral dose (30 mg) and at steady state (5 days, 15 mg twice daily orally).

One subject had asystole for 8.7 seconds with a junctional escape rhythm. Even though this was a single oral dose of 30 mg and the asenapine exposures was low compared to what is typically seen with sublingual dosing, the N-desmethylasenapine exposures were similar to those seen in multiple dose studies with sublingual dosing, (see Table 191). It's noteworthy that the sponsor did not include the data range for the most important study in any of the summary tables for the pharmacokinetics. In addition, the study durations were short, (5 and 6 days), and with a half-life in some cases of a couple of days and likely time dependent kinetics for desmethyl-asenapine the true exposures at steady-state are likely underestimated.

Figure 212 Text from PO MRD Study 25501

A previous study showed that multiple dosing with Org 5222 15mg twice daily for six or more days increased serum alanine aminotransferase and aspartate aminotransferase in three out of six healthy, male subjects.

Figure 213 Text from PO MRD Study 25501 (Continued)

In a previous study at GDRU, intravenous Org 5222 was associated with a cardiac arrest.

After oral administration the bioavailability of Org 5222 is minimal in most subjects.

Figure 214 Conclusions from PO MRD Study 25501

SUMMARY - CONCLUSIONS

After the single, oral dose of Org 5222 to the six subjects of the first group, the study was terminated due to a serious adverse event in one subject.

Two hours, 25 minutes post dosing the subject suffered an 8.7 second asystolic episode followed by junctional escape rhythm until sinus rhythm was restored. A subsequent 24-hour ECG was normal and no abnormalities were detected on echo cardiography. There were no other serious events. In general, subject's supine blood pressure and pulse rate showed only the random fluctuations expected. Apart from the subject who suffered the asystolic episode, there were no clinically significant changes in the 12-lead-ECG recordings following Org 5222 in the 5 other subjects. There were no clinically significant abnormalities on either physical examination, Multistix® urinalysis, clinical chemistry or haematology.

Figure 215 PK from PO MRD Study 25501

Pharmacokinetics

Blood samples were taken at pre-dose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 24, 36 and 48 hours after drug administration. Mean values (n=6) for the pharmacokinetic parameters are summarized in the table below.

Summary of the pharmacokinetic data

Parameter	Org 5222				Org 30526			
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.
C_{max} (pg.ml^{-1})	390	186	144	682	3813	617	3330	4930
t_{max} (h)	1.50	0.89	0.50	3.00	2.86	1.13	1.50	4.00
$AUC_{0-\infty}$ (pg.ml^{-1}.h)	3701	1146	1937	4988	44119	10804	29824	58452
$t_{1/2}$ (h)	7.87	1.96	6.27	11.13	10.54	1.50	8.54	12.11

SD = Standard Deviation; Min. = Minimal value; Max. = Maximal value

Conclusions

The Org 30526 plasma levels were considerably higher than those of Org 5222. The elimination half-life of Org 30526 was slightly, but significantly longer than the half-life of Org 5222. A single oral dose of 30 mg Org 5222 in healthy male subjects was not well tolerated as it produced a serious adverse event in one of the six subjects treated.

Table 191 Comparison of Selected Pharmacokinetic Metrics for Study 22501 and Multiple Dose PK Studies.

Metric	Cmax (ng/mL)			AUCτ[b] (ng/ml x hr^{-1})		
Study	Study 22501	25542	41012	Study 22501	25542	41012
Dosage Regimen	30 mg PO x 1	10 mg SL BID x 6 days	10 mg SL BID x 5 days	30 mg PO x 1	10 mg SL BID x 6 days	10 mg SL BID x 5 days
Asenapine	0.39 ± 0.18 0.14 – 0.68	5.57±2.36 0.94 – 8.81	8.84 2.17 - 15.5	3.7±1.2 1.9 - 5.0	28.2±16.0 6.0 – 53.5	37.3 16.5 - 58.1
Desmethyl-Asenapine	3.8 ± 0.62 3.33 - 4.93	3.14±1.2 0.48 – **5.16**	1.33 1.23 - 1.42	44.1±10.8 29.8 – 58.4	31.8±14.3 4.7 – **53.8**	12.7 11.0 - 14.4

a Text in red was not reported in clinical study report or in any summary tables, had to be extracted from raw data
b For single dose study AUC = AUCinf

5.6.3.2.3 Initial SL Single Rising Dose Study - Study 25509

The following is the background safety information from the initial sublingual dose study with a dose range of 10 - 100 mcg, (see Figure 216 and Figure 217).

What noteworthy about this summary is that it is precludes chronic oral dosing of greater than 4 mg / day due to safety reasons, which is equivalent to 8 – 12 mg /day administered sublingually. In addition it indicates that subjects with high Cmax's have serious AEs, and that interindividual variability results in greater risk in some individuals. Although it's reported that high Cmax's are potentially related to serious AEs individual Cmax's from these studies are not reported and it's unclear if this is related to asenapine or desmethyl-asenapine concentrations.

This was another study that this reviewer was told not to review as it did not include the proposed clinical dose range.

Figure 216 Text from SL SRD Study 25509

1.2 Summary of relevant safety data

Org SL94 appears to be safe in endocrinological, biochemical and haematological terms, however single high doses of Org SL94 may induce cardiovascular adverse experiences in animals and humans.

Single dose i.v. administration of Org SL94 to rats at dose levels up to 21 mg/kg caused no mortalities but was associated with neurological symptoms. The i.v. toxicity studies in rats and dogs with daily administration for 2 weeks at dose levels up to 3 mg/kg caused no overt signs of toxicity. Results from cardiotoxicity studies suggested that Org SL94 may cause postural hypotension at high doses.

In the initial Phase I studies in healthy male volunteers, single oral doses up to 30 mg Org SL94 did not cause any safety problems. In a two week multiple dose study oral doses up to 15 mg twice daily were administered. Time and dose dependent increases in ALT and AST serum levels were observed.

In two subsequent studies with healthy male volunteers, two serious adverse experiences (SAEs) were observed. The first SAE (cardiac arrhythmia - asystole) occurred 15 min after the i.v. infusion of 0.7 mg Org SL94 (given over 30 min), when the subject was asked to sit up. He required brief external cardiac massage and atropine and made a full

Figure 217 Text from SL SRD Study 25509 (Continued)

recovery. He was never unconscious for more than 30 seconds. The second SAE occurred 2 h 35 min after a single oral dose of 30 mg Org SL94 without an obvious precipitating factor. This subject collapsed whilst already sitting and recovered spontaneously. His ECG at the time of the collapse showed a prolonged sinus pause. The pharmacokinetic results revealed large inter-individual variation in oral Org SL94 plasma levels and relatively high C_{max} values were observed in the individuals exhibiting serious adverse events. However, in view of the limited data it is not possible to draw definite conclusions as to the quantitative relationship between C_{max} and the SAE. The oral bioavailability of Org SL94 was calculated to be approximately 1%.

Three Phase II studies have been conducted with orally administered Org SL94 in the treatment of schizophrenic patients. The results indicate that the highest dose applied (4 mg/day) may be considered the minimal effective dose. No safety problems were encountered.

From a safety point of view, chronic administration of doses higher than 4 mg/day is precluded for two reasons: 1) the risk of hepatotoxicity 2) due to the fact that low oral bioavailability predisposes to highly variable plasma levels, patients may be put at increased risk for cardiovascular adverse experiences.

5.6.3.2.4 Pivotal BE Study (b) (4) - Study A7501015

The sponsor states that there were 12 serious AEs however other than indicating the number of AEs they are not identified in any way. In addition two subjects withdrew due to "hypotension" 2 withdrew consent and 2 for other reasons however they were not identified so even the hypotension cannot be verified.

In the background information the co-sponsor (Pfizer) identified the above cardiac arrhythmias as Neurally Mediated Reflex Bradycardia, (see Figure 218). It is inconceivable to this reviewer how the sponsor can make this statement.

Figure 218 Pfizer's Discussion of Previously Observed Cardiotoxicity – Study A7501015

In early trials, a total of 4 young healthy male volunteers experienced an untoward adverse experience identified as Neurally Mediated Reflex Bradycardia (NMRB) with sinuspause; ie, 1 subject after receiving 0.15 mg asenapine by the sublingual route, 1 after receiving placebo via the sublingual route, 1 after receiving 30 mg via the oral route, and one 45 minutes after receiving 0.7 mg/30 min asenapine intravenous. All occurred after the first dose and after postural challenge. This reflex is seen in 5%-10% of the general population and is benign and self-limiting. It occurs typically secondary to postural changes, younger age, and high vagal tone (low resting heart rate).

5.6.3.2.5 Pivotal BE Study (TBM vs. CTF) - Study A7501016

Study A7501016 was a pivotal bioequivalence study of a To-Be-Marketed formulation using (b) (4) asenapine to the Clinical-Trial-Formulation that used (b) (4) asenapine. The D95 for the (b) (4)

The following is from the clinical study report:

"During telemetry monitoring, 10 subjects experienced bradycardia; eight subjects experienced tachycardia; seven subjects experienced sinus pause, 3 subjects experienced junctional rhythm; and 1 Subject experienced bradycardia with junctional rhythm (Appendix B9.3)."

This was a single dose study with a 5 mg dose that included both healthy men and women. Due to the lack of time further evaluation was not feasible but needs to be done, including evaluation of exposure response.

5.6.3.2.6 Pivotal BE Study – (b) (4) vs. (b) (4) Tablet - Study 41026

For study 41026 with single 5 mg doses and low bioavailability in young healthy volunteers the sponsor reported a variety of AEs that may be indicative of cardiotoxicity. The sponsor's descriptions follow: It's unclear if these are the same or different subjects and if they refer to the same AEs or not. A minimum of 4 subjects were effected, 3 with the formulation with the lower bioavailability. Additional review would be needed to clarify this.

'Vital signs: several adverse events regarding vital signs were reported. Three subjects had a vasovagal reflex after treatment with the (b) (4) tablet and one subject after treatment with the (b) (4) tablet.

One subject showed hypotension after treatment with the (b) (4) tablet. Two subjects showed orthostatic hypotension after treatment with the (b) (4) tablet.

One subject (Subject 20) had a neurally mediated reflex bradycardia (without loss of consciousness) in supine position after treatment with the (b) (4) tablet.

Another subject (Subject 23) had a neurally mediated reflex bradycardia (without loss of consciousness) after standing up after treatment with the (b) (4) tablet.'

However, the description of subject 20 is not consistent with othrostatic hypotension.

5.6.3.2.7 Paroxetine Interaction Study - Study 25525

Study 25525 was a multiple dose interaction study of asenapine 5 mg SL BID with paroxetine 20 mg x and dextromethorphan 30 mg. See section 5.5.7.5.2 CYP2D6 Interactions - Study 25525 for a description of the study design.

The following AEs were described:

Besides Afib requiring cardioversion, a myocardial infarction (possibly two), and hepatotoxicity were the most serious AEs observed.

8.7.1.3 Discontinuation Due to Adverse Events

Eight subjects discontinued the trial. Six subjects discontinued due to adverse events.

Sequence B

The main observation is the drop out of subject 29 (101029) a black male due to an SAE (atrial fibrillation), which was considered related to the treatment with asenapine in combination with (steady state concentrations of) paroxetine at Day 13.

Subject 29. At Day 13 (07 November 2005) during Sequence A (Day 8 asenapine day after DM) atrial fibrillation was reported. The subject was dosed at 08:38 hr with 20 mg paroxetine and at 09:08 hr with 5 mg asenapine. Atrial fibrillation started 1 hr and 22 minutes after administration of 5 mg asenapine and was ended after chemical cardioversion with sotalol at 09:27 the next day. The investigator judged the SAE of mild intensity and probable related to either asenapine or paroxetine or the combination of both trial medications. After the trial, the subject visited the cardiologist of the CWZ for several assessments.

The cardiologist concluded that the subject had no structural heart disease (see for more details Appendix A, narratives). In this period (lasting until March 2006) the subject was diagnosed with presumably diabetic ketoacidosis due to new-onset of diabetes mellitus at 02 March 2006. The outcome of the SAE was recovered with sequelae (diabetes). The investigator judged this SAE of severe intensity and unlikely related to asenapine, unlikely related to paroxetine and not related to dextromethorphan administered at Day 11.

*Subject 37 (treatment **sequence B**) showed a vasovagal syncope when he went to the toilet a few minutes prior to placebo dosing. The investigator judged the subject not eligible for participation without knowing he had been given placebo. Therefore, this subject was actually discontinued due to a pre-dose adverse event.* (reviewer's note – this subject had received paroxetine for 1 week and this was two days after dextromethorphan so it was only pre-dose with respect to asenapine).

Sequence A

During **Sequence A**, 4 subjects discontinued the trial due to the occurrence of AEs.

Subject 09 dropped out due to ECG changes (negative T in II, III and AVF, main reason), non-cardiac chest pain, pain between scapulae and shortness of breath at Day 7. (Day 2 of asenapine)

Subject 14 dropped out due to hypertension (154/88 mmHg with a PR of 93 bpm, main reason), mental restlessness, insomnia, intermittent night sweating, emotional lability, fatigue, nightmares, myalgia shoulders and neck and headache at Day 9. (Day 4 of Asenapine)

Subject 08 dropped out at Day 15 due to persistent moderate headache (main reason), drowsiness and intermittent nightmares. (Day 10 of asenapine 1 day after paroxetine day 4 after DM)

Subject 15 dropped out due to elevated ALAT (main reason) and elevated ASAT at Day 15. The ALAT concentration increased to a maximal value of 474 U/L at Day 16 (Upper Normal Limit (ULN): 50 U/L) (day after paroxe Day 4 DM)

Subjects 08 and 15 discontinued dosing with asenapine but completed all other assessments and were not replaced.

Although samples were taken for genotyping, genotyping was not performed.

In addition to these AEs other AEs seen included restless legs syndrome in 54% in the paroxetine arm and in the asenapine Arm diarrhea 71% and agitation 18%

For paroxetine the labeling lists the following AEs (tremor 8%) 2% bradycardia QT prolongation (warning labeling suggests it's due to a DDI with thioridazine. AEs states no clinically significant ECG changes seen but listing of individual AEs by body system lists as rare).

High pre-dose asenapine concentrations are explained as due to carryover due to dextromethorphan but review indicates it may be due to suicide inhibition due to asenapine 2 weeks earlier.

5.6.3.2.8 Imipramine DDI Study - 25526

No serious AEs were listed, however there several cases of prolonged QT as well as elevated triglycerides similar to what was seen in other studies.

In this subject there was a subject who was found unconscious 1.3 days after dosing with imipramine 75 and 10 days after dosing with asenapine. Although it was not ascribed to asenapine the timing is similar to that seen in subject 37 in study 25525 and a drug interaction with one or more other drugs a week or two after a single dose of asenapine cannot be ruled out.

Structurally similar drugs manufactured by the sponsor that cause significant sedation like asenapine are specifically labeled to avoid alcohol and benzodiazepines due to excessive sedation. The manner of the labeling suggests that this was more than class effect labeling.

Figure 219 Text from Imipramine DDI Study 25526

Reason for subject narrative:
Adverse event (syncope e.c.i.).

Demographic data:
Healthy, non-smoking subject

Date of birth	: (b) (6)
Race	: Caucasian
Sex	: Male
Height	: 186 cm
Weight	: 75,6 kg

Exposure to trial medication:

Drug name and regimen	: Period 1 (Treatment C): A single sublingual dose of placebo asenapine (Org 5222) on 03-OCT-2005. A single sublingual dose of 5 mg asenapine and a single oral dose of 75 mg of imipramine on 04-OCT-2005. Period 2 (Treatment B): A single oral dose of 75 mg imipramine on 11-OCT-2005.
Treatment start	: 03-OCT-2005
Treatment stop	: 11-OCT-2005

Description event:
On Wednesday 12-OCT-2005 (day 2 of the second dosing period, treatment schedule: C, B, A), the subject discontinued the trial due to smoking. Smoking was prohibited during the trial. At screening, he had given incorrect information about his smoking habits.
Before discharge on Day 2, 12-OCT-2005 at 17:00 h, i.e.32.5 hours after dosing of imipramine only, vital signs were normal, and there were no adverse events. The trial CPRM agreed to discharge him on the afternoon of Day 2.

On 14-OCT-2005 investigator was notified that the subject was found unconscious at the Nijmegen train station at about 09:00 h on 13-OCT-2005. Another subject from this same trial reported that subject 08 regained consciousness spontaneously, the exact time is unknown, but within 5 minutes after falling. The subject was transported by ambulance to the (b) (4) Hospital in Nijmegen. Policemen were involved due to aggressive behaviour of the subject. The ambulance arrived at the emergency department at 09:50 h, the subject was conscious at that time. There is no information available about his state of consciousness during the ambulance ride. The start time of the syncope is 09:00 h, exact stop time unknown. On arrival at the hospital it was documented that the subject was conscious. Therefore, that time was chosen as the stop time of the event syncope. The subject was examined by a physician and released at 12:10 h with the diagnosis: collapse of unknown origin. ECG was normal, and comparable to the ones made at our site. The hospital physician stated that the subject smelled quite a bit, it is not specified which smell it was. As subject had been drinking, it was most probably the smell of alcohol. (On 14-OCT-2005, consent was given to retrieve this information.)

According to subjects' wife, he had called her at around 12:15 h on 13-OCT-2005 to inform her he was coming home. He told her that he had fainted that same morning due to the medication. Since then she had not heard from him and his whereabouts were unknown.

Before noon, on 14-OCT-2005, investigator was informed that subject 08 was again at the Nijmegen train station. He agreed to come to the trial site for medical examination.

Figure 220 Text from Imipramine DDI Study 25526 (Continued)

Subject said he drank a "few" beers, but denied drug abuse. However, we received reliable information that he did indeed use cannabis after discharge.
Subject 08 remembered passing out at the train station on 13-OCT-2005, 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.
He did not go home (as he had promised his wife) because: "He knew he was heading for trouble" because he had to inform her that he was dismissed for non-compliance.

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.

In consultation with our independent medical consultant, it was decided that it was not necessary to have this subject evaluated by a psychiatrist.

Conclusion:

- Syncope e.c.i., but most probably due to alcohol intoxication, possibly facilitated by cannabis abuse and imipramine dosing (on 11-OCT-2005 at 08:35)
- In agreement with the trials' CPRM, it was not filed as an SAE as it was not potentially life threatening, nor a prolonged hospitalization
- No reason for suspicion of cardiac of neurologic origin of the syncope
- Relation to the study medication imipramine: doubtful, asenapine: none.

5.6.3.2.9 Other Studies

An additional factor that's worrisome is that a number of subjects are listed in these single dose studies of 5 mg SL tablets as dropouts from the studies due to noncompliance, and in some cases it's clear that these are the subjects with the highest exposures. It's hard to understand how compliance would be an issue with a single dose, and without additional information including inspection of the raw case report forms these subjects should be considered as possibly experiencing serious AEs.

Although the QT Team acknowledged a number of AEs and worrisome indicators in their review including effects on calcium channels which are expected to result in conduction defects, these were not highlighted.

On April 14, 2008 at 3 PM this reviewer spoke with Suchitra Balakrishnan the medical officer on the QT review. She told me she was new and had taken over the QT review from another medical officer Dr. Grant. She had spoken to Dr. Norm Stockbridge and he had told her to only look at the QT review, the Integrated Summary of Clinical Safety and Investigator's Brochure. When I pointed out the serious nature and consequences in the elderly population she stated that she also had concerns. Consequently, I suggested that in the future she might wish to highlight any concerns for us that might need further review as medical officers typically don't review the phase I studies for safety.

She offered to do another review for other than QT effects, however I indicated that this would not be necessary presently but the medical division may decide to request a consult if another review cycle is needed.

Table 192 Summary of Selected Cardiac AEs

Study		Subj	Dose	Time	AE	
25506	IV study	1/2	0.7 mg IV over 30 min	15 min after end of infusion	Repeated Asystole with AV block responsive to Atropine Not vasovagel	Young healthy male. No cardiac illness found
25501	SD	1/6	30 mg PO SD	2.5 hrs	Asystole 8.7 sec with junctional escape rhythm	Young healthy male. No cardiac illness found
A7501015	Pivotal BE study		5 mg		2 subjects with "hypotension"	
A7501016	Pivotal BE study		5 mg	Telemetry monitoring	10 bradycardia 8 tachycardia 7 sinus pause 3 junctional rhythm 1 bradycardi with junctional rhythm	
41026	Pivotal BE Study		5 mg		At least 4 subjects effected Claimed that it's vasovagel orthostatic hypotension in 3 but 1 subject clearly not orthostatic in nature, and no description of another. Thus only 1 conceivably orthostatic.	
25525	Paroxetine DDI Study		5 mg SL BID		Afib requiring cardioversion with sotalol MI's (possibly 2) Hepatotoxicity Hypertension and inc HR	
25526	Imipramine DDI				Collapse and LOC of Unknown origin. Questionable relationship to asenapine, but possible.	
TQT Review					One subject died of cardiac failure in an ongoing trial	
25517						

5.6.3.3 Agranulocytosis and Pancytopenia

After finding serious AEs due to drug-drug interactions in clinical pharmacology studies this reviewer checked the deaths (and was going to check the serious AEs) in the overview of clinical safety. In the 'ongoing studies' this reviewer found two deaths with no cause listed and suspicious laboratory values. Figure 221 and Figure 222 show plots of the hematology lab values over time. Based upon visual inspection of the lab sheets it was initially thought that these were potential cases of aplastic anemia, upon plotting the data this needs to be revised to neutropenia with a developing pancytopenia with death likely due to agranulocytosis.

When the number of subjects who have been on drug for 52 weeks or longer are considered, the rough incidence of death due to agranulocytosis is 2 / 626 (or 1 in 313). There are also several other deaths attributed to respiratory arrest and pneumonia that need to be investigated. If these other suspicious deaths are considered it's even higher (~ 1 in 150).

Figure 221 Hematology Values Prior to Death for Subject 132017 -Study P25520

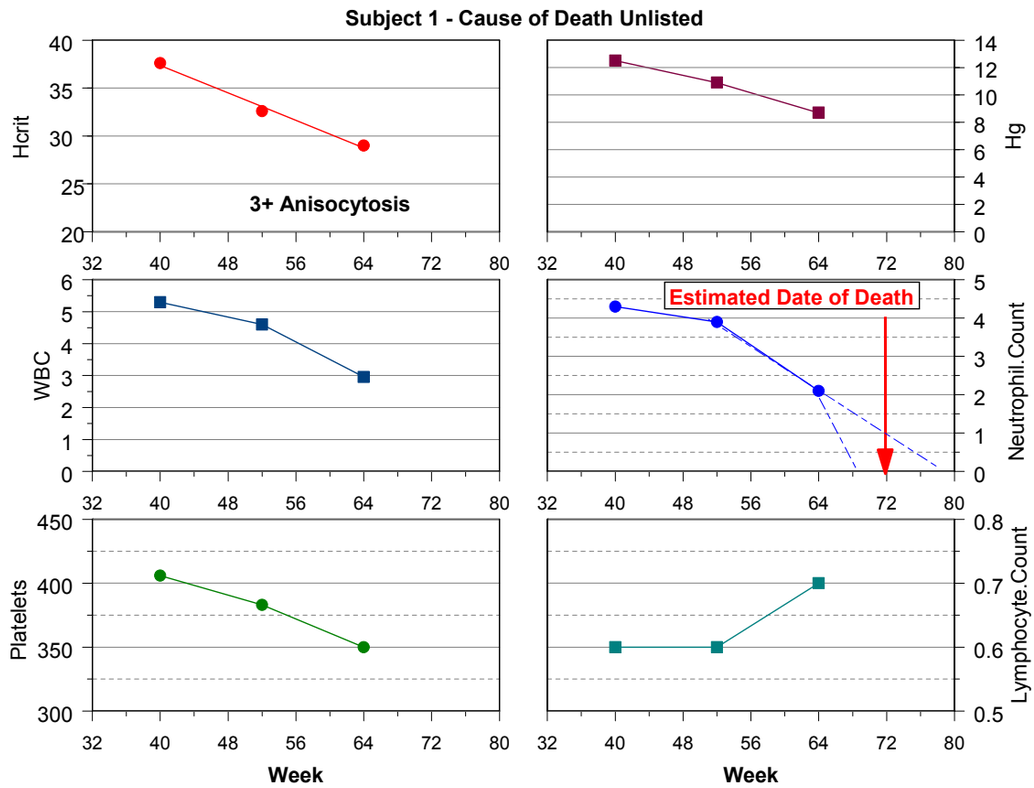
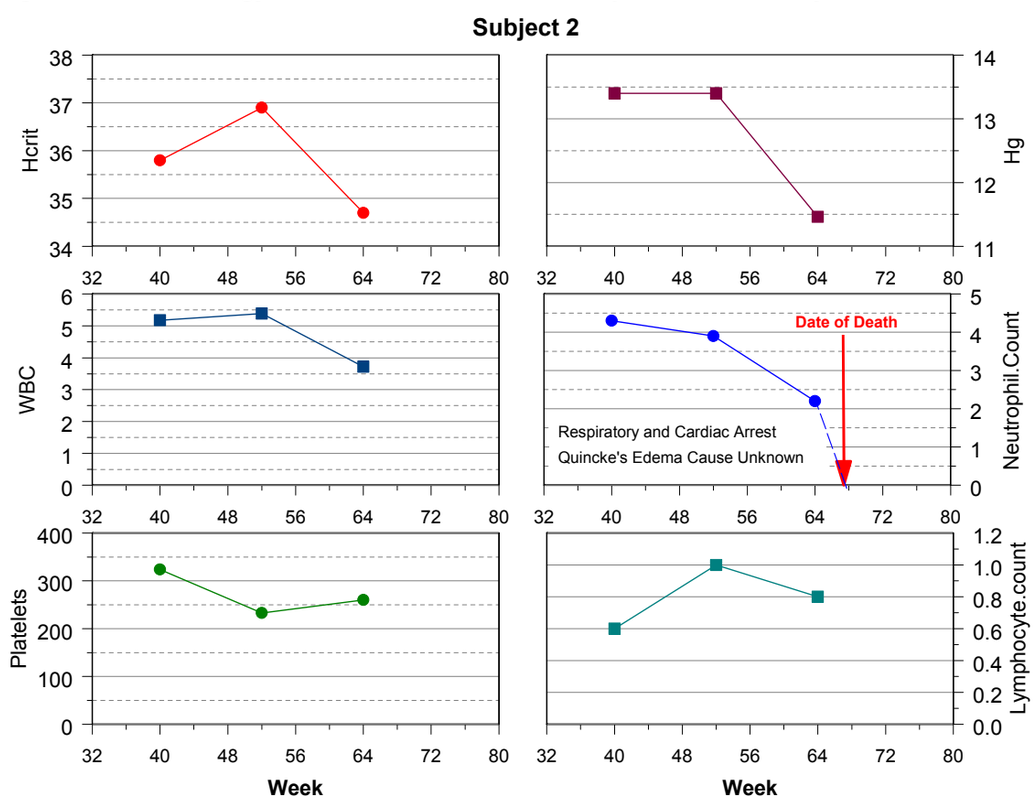


Figure 222 Hematology Values Prior to Death for Subject 241041 -Study P25520



5.6.3.4 Drug-Drug Interactions

Although not addressed in this review it was repeatedly observed that triglyderides were elevated with asenapine. In addition since asenapine has an N-oxide metabolite blood dyscrasias are a possibility. Both of these issues need to be addressed in future review cycles. For blood dyscrasias trends for trends for decreases in hematologic parameters may suggest the possibility and should be looked at.

In study 41009 one subject had an exascerbation of psychosis that may be due to an interaction between asenapine and over-the-counter allergy medications, specifically dextromethorphan and possibly pseudoephedrine. Other possibilities include an exascerbation of psychosis, also possibly due to these OTC drugs beginning prior to the treatment with the investigational agent, combined with use of a subtherapeutic dose or an experimental agent that would be ineffective for this patient.

STUDY AND TREATMENT DATA

Protocol number: 041009
Site Number: 01
Treatment: Org 5222, 10 mg
Test product: Org 5222, 5 mg

Subject number: **0012**
Subject initials: (b) (6)

REASON FOR SUBJECT NARRATIVE SUMMARY

Serious Adverse Event: SAE# 0218-01D **Schizophrenic Reaction** *(Bipolar Schizoaffective Disorder)*

BASELINE DEMOGRAPHIC DATA

Date of birth: (b) (6) (Age: 32 yrs)
Gender: Male
Height: 183 cm
Weight: 87.3 kg

EXPOSURE TO STUDY MEDICATION

Drug name	Total daily dose	Unit	Route	Day start	Day stop	Days on drug
Org 5222	10	mg	SL	24-Jun-01	02-Jul-01	9

DESCRIPTION OF EVENT

This 32-year-old Caucasian male took the study drug from 24-Jun-01 through 02-Jul-01. Current antipsychotic therapy was Geodon™. Prior to enrolment in the study, the subject presented with insomnia and increased anxiety. The symptoms were treated with Ambien® and Ativan®, respectively. Both symptoms continued until the follow-up period. The subject complained of having "racing thoughts" on 29-Jun-01, and on 30-Jun-01 was noted to be hyperverbal. On 01-Jul-01, the subject was reported to be intrusive and unable to maintain personal affairs outside a structured environment. The subject was admitted to the hospital with a diagnosis of bipolar schizoaffective disorder. The following day, the subject completed participation in the trial of Org 5222 and was restarted on Geodon™ at 40 mg BID. Moderate to severe increase in agitation and psychosis were noted in the follow-up period. In addition to Geodon™, treatment included Haldol®, Cogentin® and Depakote®. The event reportedly resolved on July 19, 2001.

ADDITIONAL RELEVANT INFORMATION

None

RELEVANT MEDICAL HISTORY

None

RELEVANT CONCOMITANT MEDICATION

Drug Name	Total Daily dose	Unit	Route	Start Date	Stop Date	Indication
Cardizem® CD	300	mg	PO	??-May-01	Cont	High Blood Pressure
acetylsalicylic acid	2	tab	PO	??-Jun-01	Cont	General body discomfort
ibuprofen	2	tab	PO	??-Apr-01	Cont	General body discomfort
Robitussin®	2	tsp	PO	??-??-1975	Unknown	Seasonal Allergies
Sudafed®	2	tab	PO	??-??-1975	20-Jun-01	Seasonal Allergies

Ativan®	2	mg	PO	23-Jun-01	Cont	Anxiety/Agitation
Ambien®	10	mg	PO	22-Jun-01	Cont	Insomnia
ziprasidone	80	mg	PO	??-Sep-99	21-Jun-01	Schizoaffective Symptoms

OTHER RELEVANT ADVERSE EXPERIENCES

Adverse experience	Day start	Day stop	Intensity	Action	Outcome	Causality
Insomnia	22-Jun-01	17-Jul-01	Moderate	None	Recovered	Unlikely
Increased anxiety	23-Jun-01	19-Jul-01	Moderate	None	Recovered	Unlikely
Racing thoughts	29-Jun-01	17-Jul-01	Moderate	None	Recovered	Unlikely
Hyperverbal	30-Jun-01	17-Jul-01	Moderate	None	Recovered	Unlikely
Increased agitation	14-Jul-01	14-Jul-01	Severe	None	Recovered	Unlikely
Increased psychosis	14-Jul-01	14-Jul-01	Severe	None	Recovered	Unlikely

RELATION TO STUDY DRUG
According to the investigator the event was **unlikely related** to trial medication.

Ziprasidone half-life 9 - 10 hr

There was also a neonatal death and a death due to complications 2 months status post of a hernia repair. No detailed information was submitted and needs to be requested however the possibility of interactions with narcotic analgesics and anesthetic agents needs to be kept in mind and evaluated.