5.4.3.3.2.2 Supersome Study NL0060848 (2005)

The objective of this study was to estimate and/or to confirm if human cytochrome P450 enzyme CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4 are involved in the Phase-I biotransformation of asenapine (Org 5222) *in vitro*. It was conducted from December 2005 to January 2006. It appears to have been conducted in response to the finding that asenapine is a potent CYP2D6 inhibitor in the *in vivo* paroxetine drug-drug interaction study, (25525), conducted from August to December 2005.

5.4.3.3.2.2.1 Turnover of Asenapine by Specific P450 Supersomes

Incubations of the asenapine were conducted with Supersomes selectively expressing human CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4 in order to select and/or confirm the enzymes involved in the metabolism of asenapine.

CYP1A2, CYP2B6, CYP2C19 and CYP3A4 (cytochrome P450 concentration: 100 pMol/mL) supersomes were incubated for 15 minutes at 37°C with two different concentrations of [^{14}C]-asenapine, approximately 2 and 20 µMol/L.

For CYP2D6 supersomes, [^{3}H]-asenapine was used at final concentrations of approximately 2 nMol/L and 2 µMol/L, the incubations with CYP2D6 were performed for 5 and 15 min at 37°C. The 2 nMol/L concentration is near the *in vivo* trough concentration.

Results are shown in Table 37.

Table 37 Biotransformation of Asenapine (%) by Supersomes[a] - NL0060848 (2005)

Supersome Isozyme	Asenapine Concentration	Biotransformation of Asenapine % of Baseline			
		Supersome Concentration			
		Control[b]	10 pMol	25 pMol	100 pMol
CYP1A2	1.84 µM		24.7	**53.5**	
	19.2 µM		10.7	15.6	
	2.16 µM	0.00			**82.3**
	20.7 µM	6.80			34.3
CYP2B6[c]		Control[b]	CYP2B6 Activity		
	2.05 µM	0.00	**48.8**		
	20.3 µM	6.72	42.5		
CYP2C19[c]		Control[b]	2C19 Activity		
	2.16 µM	0.00	**30.2**		
	20.7 µM	6.80	23.0		
CYP2D6[c]		5 min Control[b]	5 min CYP2D6	15 min Control[b]	15 min CYP2D6
	1.4 nMol	9.81	**27.0**	12.6	**67.6**
	2 µM	3.93	6.47	4.64	11.4
CYP3A4[c]		Control[b]	3A4 Activity		
	2.16 µM	0.00	12.5		
	20.7 µM	6.80	22.6		

a Biotransformation was expressed as percentage of total radioactivity not eluting as asenapine.
b Control Supersomes were Supersomes with no detectable cytochrome P450 activity. Incubations were performed in duplicate except for the incubations with control Supersomes.
c Experiments were performed with 100 pMol P450.

Table 37 shows that at supratherapeutic concentrations, (i.e. approximately 100 - 1000x *in vivo* concentrations of 10 – 70 nMol/L), CYP1A2 is the most important isozyme followed by CYP2B6 and then CYP2C19. However, at therapeutic concentrations CYP2D6 results in nearly as much turnover as CYP1A2 at supratherapeutic concentrations. In addition to this, the activity of CYP1A2, CYP2D6, and possibly CYP2C19 is lower at the higher asenapine concentration indicating the possible presence of an inhibitory metabolite.

Figure 21 to Figure 25 on the following page shows HPLC chromatograms for each supersome incubation at the high substrate concentration. CYP1A2 clearly shows the formation of the N-oxide, however it also shows a number of other metabolites. Consequently the degree on inhibition in a 15 minute incubation may not be predictive of more chronic administration. For CYP2B6, CYP2C19, and CYP3A4 it's clear there's activity but little evidence of N-oxide formation, whereas for CYP2D6 there's little metabolism and only the N-desmethyl metabolite is evident. Unfortunately without chromatograms from the lower substrate concentration incubations for comparison no conclusions can be reached based on these chromatograms.

Figure 21 CYP1A2 Supersomes & Asenapine 20 μM

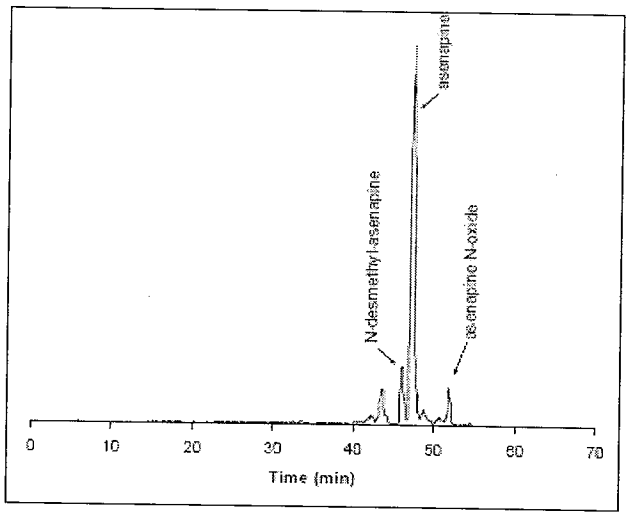


Figure 22 CYP3A4 Supersomes & Asenapine 20 μM

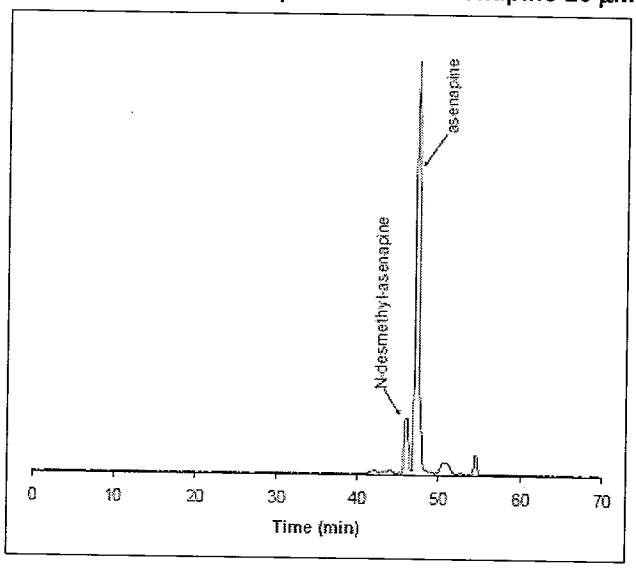


Figure 23 CYP2B6 Supersomes & Asenapine 20 μM

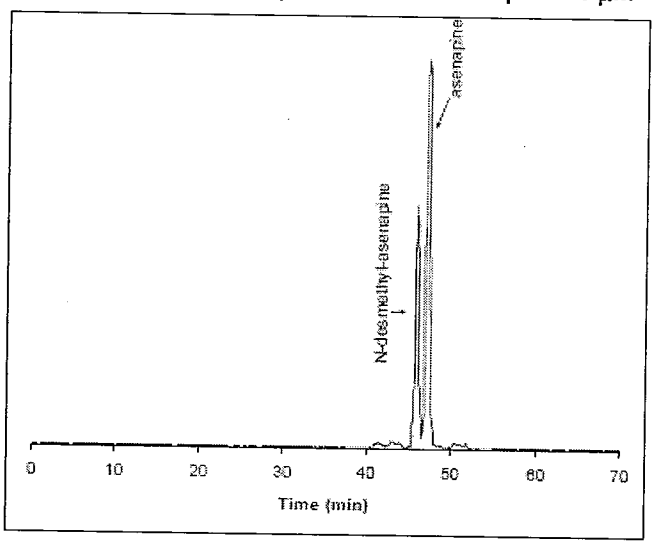


Figure 24 CYP2C19 Supersomes & Asenapine 20 μM

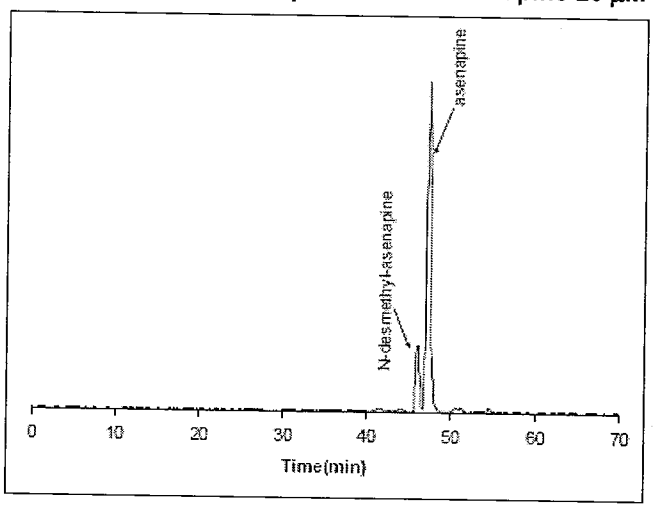
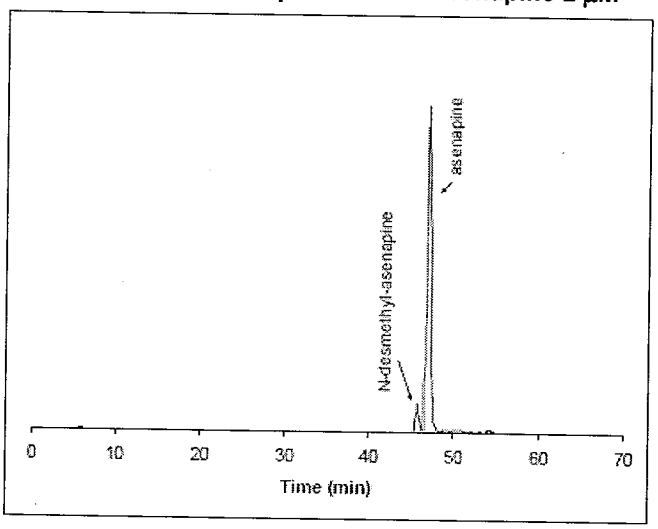


Figure 25 CYP2D6 Supersomes & Asenapine 2 μM



5.4.3.3.2.2.2 Protein Bound Metabolites with CYP2D6 Supersomes

For CYP2D6 the recovery of radioactivity was also determined by liquid scintillation counting (LSC) of the incubation fraction before the addition of acetonitrile and obtaining the supernatant. In each case recovery after centrifugation was less after incubation of CYP2D6, and even in the presence of CYP2D6 the recovery was greater at the higher asenapine concentration, (see Table 38).

Taken together this indicates binding of a reactive metabolite to the microsomal protein which is concentration dependent. The most likely candidate for a chemically reactive metabolite due to asenapine is the (N2-oxide).

Table 38 Radioactivity Bound to Microsomal Protein after Incubation of Asenapine with CYP2D6 - NL0060848 (2005)

Incubation Time (minutes)	Supersome	Asenapine Concentration	Replicate	Activity before acetonitrile (kBq)	Activity after centrifugation (kBq)	Recovery (%)
5 min	CYP2D6	1.4 nMol/L	A	1.5	1.2	77
			B	1.6	1.2	73
	Inactive Control	1.4 nMol/L	—	1.4	1.2	90
	CYP2D6	2 µMol/L	A	205.0	165.3	81
			B	206.1	166.3	81
	Inactive Control	2 µMol/L	—	206.1	183.9	89
15 min	CYP2D6	1.4 nMol/L	A	1.4	1.0	72
			B	1.5	1.0	70
	Inactive Control	1.4 nMol/L	—	1.3	1.2	88
	CYP2D6	2 µMol/L	A	199.0	156.0	78
			B	208.1	159.9	77
	Inactive Control	2 µMmol/L	—	197.8	167.5	85

Consequently, asenapine appears to be a suicide substrate inhibitor for CYP2D6 at supratherapeutic concentrations such as would occur on first pass after oral administration. As a suicide substrate, inhibition of CYP2D6 would be due to a decrease in the total amount of enzyme and would result in inhibition in CYP2D6 poor metabolizers as well as in extensive metabolizers and would not be overcome with increasing substrate concentrations. In addition, recovery might take several weeks until the enzyme has had time to regenerate, thus there would be issues with administering other CYP2D6 substrates even after asenapine could no longer be detected in plasma. This would make switching from asenapine to many other antipsychotics or addition of other psychoactive drugs problematic.

5.4.3.3.2.2.3 Supersome Enzyme Kinetic Parameters

Next the sponsor determined of the Km and Vmax using supersomes expressing selected human CYPs.

Km and Vmax determinations were performed for CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4. Supersomes were incubated for 15 minutes at 37°C with different concentrations of [^{14}C]-asenapine or [^{3}H]-asenapine in the case of CYP2D6. Asenapine concentrations used were as follows:

CYP1A2	0.5, 1, 2, 5, 10, 20, 50, and 100 µmol/L
CYP2B6	0.5, 1, 2, 5, 10, 20, 50, 100, 250, and 500 µmol/L
CYP2C19	0.5, 1, 2, 5, 10, 20, 50, and 100 µmol/L µmol/L
CYP2D6	1, 2, 5, 10, 20, 50, 100, 200, 500 and 2000 µmol/L
CYP3A4	0.5, 1, 2, 5, 10, 20, 50, 100, 250, and 500 µmol/L

Results are shown in Table 39. The sponsor only reported Vmaxs and Kms and since the same amount of microsomal protein was used in each experiment the sponsor only focused on the Km. However when intrinsic clearances are calculated the relative importance is more easily discernable. In addition when the relative abundance of these isozymes *in vivo* are considered CYP3A4 is likely to be even more important especially with oral administration.

Table 39 Enzyme Kinetic Parameters of Asenapine Disappearance in Supersomes – Study NL0060848 (2005)

Supersome Isozyme	Vmax (pMol/min x pMol P450^{-1})	Km (µMol/L)	Clint (L/min x pmol P450^{-1})
CYP1A2	10.2	24.5	**41,626**
CYP2B6	100.1	333.5	30,015
CYP2C19	15.9	68.5	23,212
CYP2D6	0.18	0.30	**60,000**
CYP3A4	139.7	936.6	14,916

5.4.3.4 Other Enzyme Systems

Other enzyme systems that might be expected to further metabolize asenapine and its metabolites based on the *in vivo* data and information from other drugs were not examined. These include:

Sulfation	Phenol Sulfotransferases
N-oxidation	Cytosolic N-Oxidases
Methylation	Catechol O-Methyl-Transferases.

Based on the *in vitro* information, NADPH independent oxidation by FMO does not appear to be a significant at clinical concentrations.

Other enzyme systems involved with detoxification of the N-oxide were also not examined.

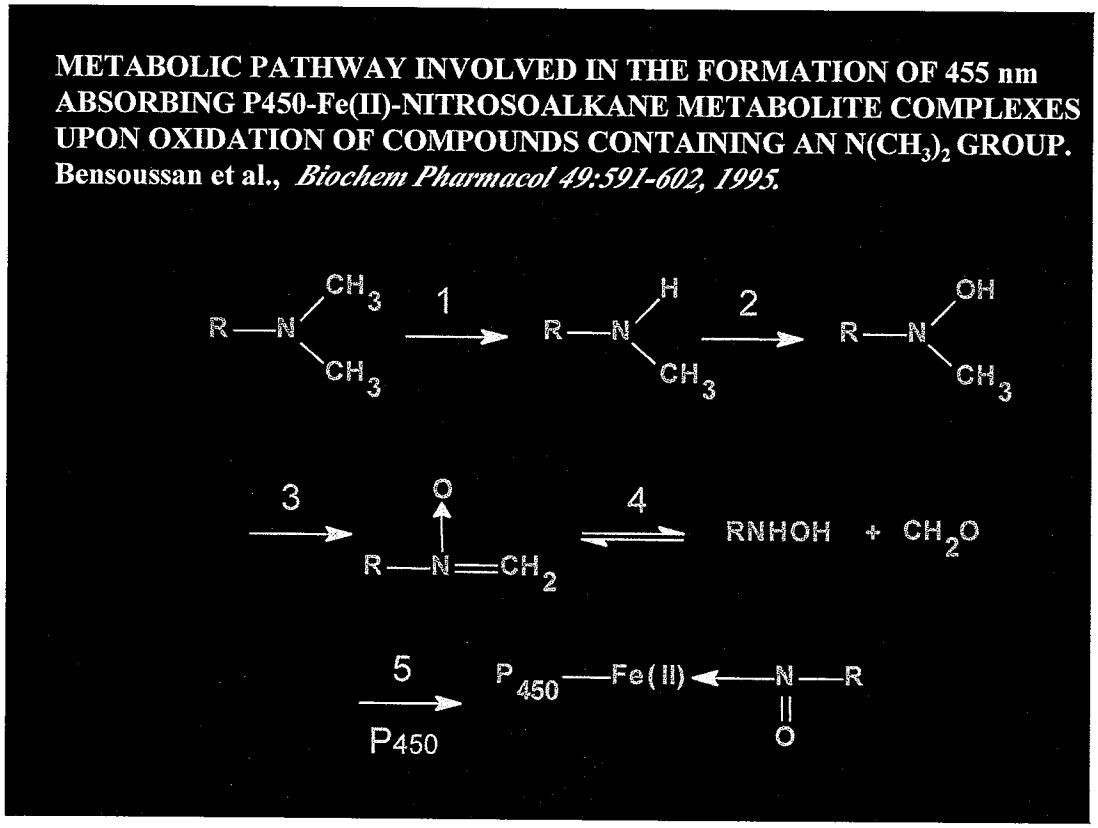
5.4.3.5 *In Vitro Inhibition by Asenapine and Metabolites*

Inhibition by asenapine and selected metabolites were examined *in vitro* in pooled human liver microsomes, (study DM2005-005222-009) and in GENTEST insect derived supersomes of human CYPs in studies NL0017588, NL0013163, NL0048836, NL0050059, and NL0050307.

Results of these studies indicate that asenapine, N-desmethyl-asenapine, and asenapine N-oxide, are all potent inhibitors of CYP2D6 with Ki's in the range of 6 – 85 nMol/L, which are at or somewhat above therapeutic concentrations. However, more important than the Kis is the fact that the N-desmethyl-metabolite is a noncompetitive inhibitor, i.e. a suicide substrate. Thus even with low doses inhibition will increase over time until a steady-state is reached. However if asenapine is swallowed the high concentrations achieved with such rapid delivery will result in a much greater degree of inhibition.

N-oxides are known to be potent suicide substrate inhibitors as shown by Figure 26. Although Figure 26 shows inactivation of by a nitrosoalkane whereas asenapine is a heterocyclic N-oxide, the evidence clearly points to suicide inactivation by asenapine regardless of whether the exact mechanism is the same or not.

Figure 26 Slide from FDA Presentation on N-Oxide Suicide Substrate Inhibition – Article from 1995



In addition a 1999[4] article on inhibition of CYP2D6 by antipsychotics, most of the antipsychotics examined were competitive inhibitors, although several were partial competitive and cis-thiothixene, and clozapine had greater inhibition with pre-incubation, and inhibition by metabolites was not examined.

[4] DMD (1999), Vol 27, no. 9 1078 – 1083.

This indicates that clozapine or a metabolite is also a mechanism based inhibitor of CYP2D6. See Figure 27 and Figure 28 for a comparison of the structures of these two dibenzo antipsychotics.

Figure 27 Structure of Asenapine

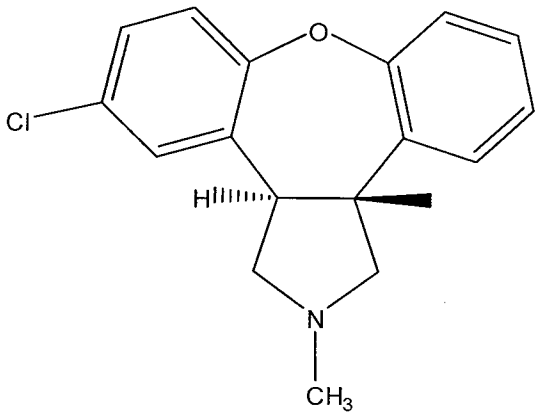
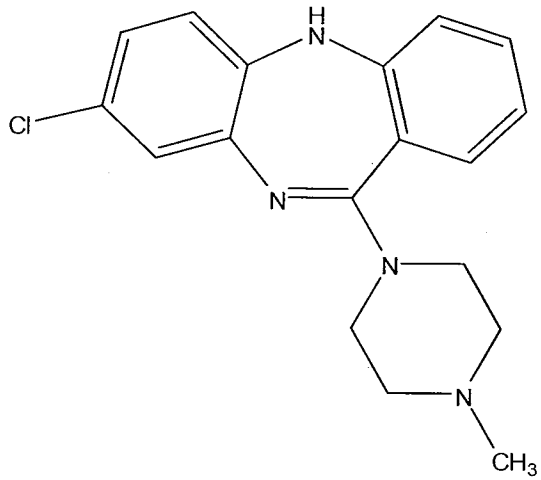


Figure 28 Structure of Clozapine



5.4.3.5.1 *In Vitro* Inhibition of P450 CYPs in Supersomes

A summary of the sponsor's results and the enzyme kinetic parameters reported may be found in Table 41 and Table 42 respectively.

It should be noted that no units were reported for Vmax. Consequently intrinsic clearances cannot be calculated.

In addition, since only 2 concentrations were examined and since high substrate inhibition is expected, fitting of the data to a Michaelis-Menton Model, the estimates of the apparent enzyme kinetic parameters, and the proposed mechanism of inhibition derived from nonlinear regression and the fit to a structural model cannot be considered reliable. However even if an adequate range of concentrations were studied this reviewer is uncertain of the advantages and disadvantages of the use of nonlinear regression as compared to other methods for determining the mechanism of inhibition, but believes that other methods would be preferable. In spite of this the totality of the data suggests that noncompetitive with CYP2D6 is likely.

In spite of the examination of the N-desmethyl-asenapine and asenapine N-oxide metabolites, the lack of information on the 11 and 7 – O asenapine metabolites limits the interpretability of the results.

Experimental conditions for supersomes were fairly similar across studies so they will be reviewed together rather than separately

GENTEST insect derived supersomes of human CYPs were incubated at 37 °C with their specific substrates in the presence or absence of asenapine, asenapine metabolites or specific reference inhibitors. The substrates and reference inhibitors used are shown in Table 40.

Table 40 CYP P450 Enzyme Specific Substrates and Reference Inhibitors used in Supersome Experiments

Study	Isozyme	Substrate	Product	Control Inhibitor
NL0017588	1A2	7-ethoxy-3-cyanocoumarin (CEC)	7-ethoxy-3-hydrocoumarin (CHC);	furafylline
NL0017588 NL0048836 NL0050307	2D6	3-[2-(N,N-diethyl-N-methylamino)-ethyl]-7-methoxy-4-methylcoumarin (AMMC)	3-[2-(N,N-diethylamino)-ethyl]-7-hydroxy-4-methylcoumarin (AHMC)	quinidine
NL0013163	2C19	mephenytoin	4-Hydroxy-mephenytoin	tranylcypromine
	3A4 (a) 3A4 (b)	testosterone	6ß-hydroxytestosterone	ketoconazole
NL0050059	1A2	7-ethoxy-3-cyanocoumarin (CEC)	7-ethoxy-3-hydrocoumarin (CHC)	furafylline
	2A6	Coumarin	7-hydroxycoumarin (7-HC)	tranylcypromine
	2C8	D benzylfluorescein (DBF)	fluorescein	quercetin
	2C9	7-methoxy-4-trifluoromethylcoumarin (MFC)	7-hydroxy-4-trifluoromethylcoumarin (HFC)	sulfaphenazole
	2C19	D benzylfluorescein (DBF)	fluorescein	tranylcypromine
	3A4 (1)	Benzyloxyresorufin (BzRes)	resorufin	ketoconazole
	3A4 (2)	7-benzyloxyquinoline (BQ)	7-hydroxyquinoline (7-HQ)	ketoconazole

An early study assessed linearity of CYP2D6 activity with different buffers, and experiments used different buffer systems. The final % of organic solvent used to dissolve substrates was generally not reported. In earlier experiments mentioned in previous sections this was a problem but it appears that this may have been taken care of for most of the supersome experiments.

For the most part information was not provided on the preliminary experiments to establish conditions, however it appears the sponsor was aware of the issues involved and even if the actual enzyme kinetic parameters are off this should not effect the general conclusions.

Studies NL0048836 and NL0050307 that assessed the ability of asenapine, N-desmethyl-asenapine, and asenapine N-oxide(s) to inhibit CYP2D6 utilized NADPH regenerating systems whereas other studies only used NADPH itself.

For study NL0013163 product formation of 4-OH-mephenytoin and 6ß-hydroxytestosterone were quantified by HPLC, whereas for other experiments the fluorescent products formed during the enzymatic incubation were quantified using a fluorometer to determine the initial formation rates.

In each study two sets of experiments were performed for each inhibitor.

First the IC_{50} values for asenapine, asenapine metabolites, and the reference inhibitors for the individual cytochrome P450 enzymes were determined using a series of increasing asenapine, metabolite or reference inhibitor concentrations, and then the IC_{50} was calculated by interpolation using the following formula:

IC50 = (50% Inhibition - % Inhibition at First Incubate concentration < IC50) / (%Inhibition at First Incubate Concentration > IC50 - % Inhibition at First Incubate concentration) x (Conc at First Conc > IC50 – Conc at First Conc < IC50) % Inhibition + Conc at First Conc < IC50

An example follows:

Figure 29 Example of IC_{50} Determinations in a Supersome Experiment

Table 8.1.1 IC50 determination Org 10968 for CYP2D6

Concentration Org 10968 (nmol·L^{-1})	Concentration AMMC (µmol·L^{-1})	AHMC production (units/pmol CYP2D6/min)	Inhibition (%)
250	1.5	50.667	88.9
125	1.5	108.07	76.3
62.5	1.5	201.37	55.8
31.3	1.5	301.08	33.8
15.6	1.5	377.84	17.0
7.8	1.5	406.63	10.6
3.9	1.5	410.52	9.8
2.0	1.5	427.97	6.0
0.98	1.5	421.28	7.4
0	1.5	455.09	0.0

Incubations were performed in duplicate.

IC50 calculation :

((50-33.8)/(55.8-33.8)x(62.5-31.3))+ 31.3 nmol·L^{-1} = **54.27 nmol·L^{-1}**

Based on these IC50 values, two asenapine or two asenapine metabolite and two reference inhibitor concentrations were chosen in the final inhibition experiments with increasing substrate concentrations for the CYP isozyme. An example of the type of data generated follows:

Figure 30 Example of the Type of Data Generated for Enzyme Kinetic Inhibition Parameter Estimates

Table 8.2.1 CYP2D6 inhibition by Org 10968

Concentration AMMC (µmol·L^{-1})	AHMC production (units/pmol CYP2D6/min)		
	0 nmol·L^{-1} Org 10968	2 nmol·L^{-1} Org 10968	20 nmol·L^{-1} Org 10968
10	796.03	875.10	722.42
5	666.33	677.18	582.11
2.5	564.74	567.88	469.61
1.25	458.76	436.23	351.03
0.625	318.93	323.30	246.92
0.313	219.45	202.08	160.22
0.156	130.39	129.38	91.083

Incubations were performed in duplicate.

From these final experiments the inhibition constants (Ki) as well as the type of inhibition (competitive, non- competitive, mixed competitive or uncompetitive) were determined using the curve-fitting program for the analysis of enzyme kinetic data "EZ-FIT"[5].

[5] Perrella FW (1988) EZ-FIT: A practical curve-fitting microcomputer program for the analysis of enzyme kinetic data on IBM-PC compatible computers. Analytical Biochemistry, 174(2):437-47.

Table 41 Summary of Results of *In Vitro* Cytochrome P450 Inhibition Studies with Asenapine and Selected Metabolites

Study	Date	Test System	Isozyme	Inhibitor	Ki	Claimed Type of Inhibition
NL0017588	Dec 1999	Supersomes	1A2	Asenapine	2.6 µMol	Competitive
			2D6		6.75 nMol	Competitive
NL0013163	April 1999	Supersomes	2C19	Asenapine	25.15	uncompetitive
			3A4 (a) 3A4 (b)		91.4 125.59	Mixed-competitive ? ?
NL0048836	Aug 2003	Supersomes	2D6	Asenapine	16.2 nMol	Competitive
				30526 N-Desmethyl	62.08 nMol	Noncompetitive
				31437 N-Oxide	82.62 nMol	Competitive
NL0050059	Oct 2003	Supersomes	1A2	Asenapine (N.B. CYP2D6 not studied)	1.5 µMol	Competitive
			2C8		360.44 µMol	Noncompetitive
			2C9		105.19 µMol	Uncompetitive
			2C19		2.0 µMol	Competitive
			3A4 (1)		33.24 µMol	Noncompetitive
			1A2	30526 N-Desmethyl-Asenapine (N.B. CYP2D6 not studied)	1.4 µMol	Noncompetitive
			2A6		70.31 µMol	Competitive
			2C8		80.33 µMol	Noncompetitive
			2C9		172.34 µMol	Noncompetitive
			2C19		1.78 µMol	Competitive
			3A4 (1)		3.53 µMol	Competitive
			1A2	31437 N-oxide (N.B. CYP2D6 not studied)	No inhibition	
			2A6			
			2C8			
			2C9			
			2C19			
			3A4 (1)			
			3A4 (2)			
NL0050307	Oct 2003	Supersomes	2D6	10968 N(2)-Oxide	26.72 nMol	Competitive
			2D6	10969 N(2)-Oxide	12.43 nMol	Competitive
DM2005-005222-009	Dec 2005	Pooled Human Liver Microsomes (HLM)	CYP1A2	Asenapine	6.9 µMol[a]	
			CYP2B6		> 30 µMol[a]	
			CYP2C8		> 30 µMol[a]	
			CYP2C9		> 30 µMol[a]	
			CYP2C19		> 30 µMol[a]	
			CYP2D6		44 nMol[a]	
			CYP3A		> 30 µMol[a]	
			CYP3A		> 30 µMol[a]	

a IC50

Table 42 Reported Enzyme Kinetic Parameters from *In Vitro* Cytochrome P450 Inhibition Studies with Asenapine and Selected Metabolites

Study	CYP	Substrate	Org 5222 (µmol/L)	Km (µmol/L)	Vmax (units/pmol CYP1A2/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP1A2/min)	Ki (µmol/L)	AIC	Runs test
NL0017588	1A2	Asenapine	0	2.69	157.9	***Competitive***	***3.08***	***165.9***	***2.06***	***119.3***	***Passes***
			1.5	7.92 a	196.7 b	***Non-Competitive***	***4.63***	***185.7***	***8.90***	***134.1***	***Fails***
			3	6.56 a	156.6 b	***Mixed Competitive***	***3.09***	***165.9***	***2.06***	***121.3***	***Passes***
						Uncompetitive	5.37	189.7	7.41 ***3916***	141.2	Fails
			Org 5222 (nmol/L)	**Km (µmol/L)**	**Vmax (units/pmol CYP2D6/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP2D6/min)**	**Ki (nmol/L)**	**AIC**	**Runs test**
	2D6	Asenapine	0	0.72	7.03	***Competitive***	***0.71***	***6.97***	***6.75***	***3.78***	***Passes***
			4	1.10 a	6.84 b	Non-Competitive	0.99	7.52	35.3	16.2	Passes
			6	1.35 a	7.03 b	Mixed Competitive	0.72	6.99	6.93 843.8	5.76	Passes
						Uncompetitive	1.08	7.56	32.7	21.8	Fails
NL0013163	2C19	Asenapine	**Org 5222 (µmol/L)**	**Km (µmol/L)**	**Vmax (pmol/pmol CYP2C19/min)**	**Model**	**Km (µmol/L)**	**Vmax (pmol/pmol CYP2C19/min)**	**Ki (µmol/L)**	**AIC**	**Runs test**
			0	33.87	0.37	Competitive	28.00	0.35	7.49	90.4	Passes
			5	36.02 a	0.33 b	Non-Competitive	38.67	0.38	30.83	92.0	Passes
			7.5	52.15 a	0.33 b	Mixed Competitive	33.02	0.37	12.98 50.43	91.6	Passes
						Uncompetitive	***43.97***	***0.39***	***25.16***	***88.4***	***Passes***
			Org 5222 (µmol/L)	**Km (µmol/L)**	**Vmax (pmol/pmol CYP3A4/min)**	**Model**	**Km (µmol/L)**	**Vmax (pmol/pmol CYP3A4/min)**	**Ki (µmol/L)**	**AIC**	**Runs test**
	3A4	Asenapine	0	29.54	1.67	Competitive	23.02	1.51	34.87	0.48	Passes
			25	36.49 a	1.49 b	Non-Competitive	31.45	1.70	114.27	1.8	Passes
			40	29.73 a	1.22 b	***Mixed Competitive***	***30.25***	***1.69***	***91.40*** ***125.59***	***0.21***	***Passes***
						Uncompetitive	36.98	1.76	86.44	1.3	Passes
NL0048836			**Org 5222 (µmol/L)**	**Km a (µmol/L)**	**Vmax b (units/pmol CYP2D6/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP2D6/min)**	**Ki (nmol/L)**	**GoF**	**Runs test**
	2D6	Asenapine	0	0.83	521.17	***Competitive***	***0.77***	***497.90***	***16.02***	***-0.05***	***Passes***
			2	0.87	483.36	Non-Competitive	0.90	518.97	66.00	-0.04	Passes
			8	1.03	483.81	Lin. Mixed Competitive	0.82	508.44	C C	0.98	Passes
						Uncompetitive	0.94	522.68	56.02	0.01	Passes
			Org 30526 (nmol/L)	**Km a (µmol/L)**	**Vmax b (units/pmol CYP2D6/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP2D6/min)**	**Ki (nmol/L)**	**GoF**	**Runs test**
	2D6	Org 30526 N-Desmethyl-Asenapine	0	1.41	665.71	Competitive	0.79	535.21	19.35	1.05	Passes
			10	0.59		***Non-Competitive***	***1.07***	***600.96***	***62.08***	***0.88***	***Passes***
			20	1.60	413.06	Lin. Mixed Competitive	0.79	535.23	C C	2.10	Passes
					542.47	Uncompetitive	1.26	625.65	45.15	0.89	Passes

	2D6	Org 31437 Asenapine N-Oxide	Org 30526 (nmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2D6/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2D6/min)	Ki (nmol/L)	GoF	Runs test
			0	0.90	531.46	***Competitive***	***0.95***	***542.66***	***82.62***	***0.62***	***Passes***
			40	1.42	549.46	Non-Competitive	1.29	582.14	419.8	0.77	Passes
			80	2.07	560.41	Lin. Mixed Competitive	0.95	542.69	82.67 C	1.2	Passes
						Uncompetitive	1.41	586.54	C	1.3	Passes
NL0050059	1A2	Asenapine	Org 5222 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP1A2/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP1A2/min)	Ki (µmol/L)	GoF	Runs test
			0	1.29	2479	***Competitive***	***1.42***	***2610***	***1.50***	***-1.010***	***Passes***
			0.3	1.62	2672	Non-Competitive	1.68	2667	c	-0.135	Passes
			0.6	2.40	2734	Lin. Mixed Inhibition	1.42	2610	1.50 C	-0.438	Passes
						Uncompetitive	1.71	2644	C	- 0.067	Passes
	2C8	Asenapine	Org 5222 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2C8/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2C8/min)	Ki (µmol/L)	GoF	Runs test
			0	0.51	268	Competitive	0.44	254	120.91	0.466	Passes
			10	0.52	265	***Non-Competitive***	***0.51***	***270***	***360.44***	***0.250***	***Passes***
			80	0.49	219	Lin. Mixed Inhibition	0.52	271	C c	1.297	Passes
						Uncompetitive	0.55	274	279.78	0.273	Passes
	2C9	Asenapine	Org 5222 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2C9/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2C9/min)	Ki (µmol/L)	GoF	Runs test
			0	14.76	536	Competitive	10.96	501	24.65	-0.108	Passes
			5	10.24	485	Non-Competitive	13.71	530	118.42	-0.187	Passes
			20	18.40	480	Lin. Mixed Inhibition	12.27	519	41.54 C	0.278	Passes
						Uncompetitive	14.56	533	105.19	-0.362	Passes
	2C19	Asenapine	Org 5222 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2C19/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2C19/min)	Ki (µmol/L)	GoF	Runs test
			0	1.18	104	***Competitive***	***1.22***	***103***	***2.00***	***-2.086***	***Passes***
			0.05	1.24	100	Non-Competitive	1.32	106	6.56	-1.779	Passes
			0.5	1.61	106	Lin. Mixed Inhibition	1.22	103	2.00 C	-1.420	Passes
						Uncompetitive	1.35	106	5.55	-1.579	Passes
	3A4	Asenapine	Org 5222 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP3A4/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP3A4/min)	Ki (µmol/L)	GoF	Runs test
			0	2.60	767	Competitive	2.24	736	9.77	-1.393	Passes
			1	2.47	747	***Non-Competitive***	***2.55***	***768***	***33.24***	***-2.749***	***Passes***
			4	2.59	686	Lin. Mixed Inhibition	2.54	768	31.10 (a=1.09)d	-2.655	Passes
						Uncompetitive	2.68	774	27.84	-2.474	Passes

[redacted]

	1A2	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP1A2/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP1A2/min)	Ki (µmol/L)	GoF	Runs test
			0	0.96	1919	Competitive	0.7	1722	0.30	0.383	Passes
			0.2	1.07	1683	***Non-Competitive***	***1.03***	***1935***	***1.40***	***-0.835***	***Passes***
			0.6	1.15	1396	Lin. Mixed Inhibition	0.96	1911	0.90 (a=1.77)c	-0.802 -	Passes
						Uncompetitive	1.18	1972	1.18	0.396	Passes
	2C8	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2C8/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2C8/min)	Ki (µmol/L)	GoF	Runs test
			0	0.58	243	Competitive	0.52	230	21.06	-0.502	Passes
			10	0.87	238	***Non-Competitive***	***0.71***	***255***	***80.33***	***-0.836***	***Passes***
			30	0.76	190	Lin. Mixed Inhibition	0.63	247	41.98 c	-0.371	Passes
						Uncompetitive	0.81	261	62.57	-0.465	Passes
	2C9	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2C9/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2C9/min)	Ki (µmol/L)	GoF	Runs test
			0	6.82	381	Competitive	5.00	352	c	1.994	Passes
			20	7.67	367	***Non-Competitive***	***6.92***	***388***	***172.34***	***1.152***	***Passes***
			40	6.09	300	Lin. Mixed Inhibition	7.15	389	C C	2.198	Passes
						Uncompetitive	7.67	393	149.58	1.161	Passes
	2C19	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2C19/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2C19/min)	Ki (µmol/L)	GoF	Runs test
			0	1.51	110	***Competitive***	***1.47***	***107***	***1.78***	***-1.753***	***Passes***
			0.04	1.46	103	Non-Competitive	1.55	109	4.82	-1.700	Passes
			0.3	1.70	107	Lin. Mixed Inhibition	1.47	107	C C	-0.531	Passes
						Uncompetitive	1.59	110	c	-1.063	Passes
	3A4	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP3A4/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP3A4/min)	Ki (µmol/L)	GoF	Runs test
			0	1.93	659	***Competitive***	***1.97***	***658***	***3.53***	***-0.068***	***Passes***
			0.8	2.57	659	Non-Competitive	2.35	679	c	0.545	Passes
			1.6	2.75	657	Lin. Mixed Inhibition	1.97	658	C C	0.980	Passes
						Uncompetitive	2.42	677	c	0.598	Passes
NL0050307	2D6	Org 10968 Asenapine N-Oxide (1)	Org 10968 (nmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2D6/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2D6/min)	Ki (nmol/L)	GoF	Runs test
			0	1.02	834.73	***Competitive***	***1.06***	***858.27***	***26.72***	***-0.593***	***Passes***
			2	1.34	924.83	Non-Competitive	1.25	900.75	104.15	-0.563	Passes
			20	1.53	796.19	Lin. Mixed Competitive	1.13	878.09	39.42 C	-0.100	Passes
						Uncompetitive	1.33	910.58	84.51	-0.386	Passes
		[redacted]									

			Org 10969 (nmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2D6/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2D6/min)	Ki (nmol/L)	GoF	Runs test
		Org 10969 Asenapine N-Oxide (2)	0	0.97	814.66	***Competitive***	***0.92***	***794.55***	***12.43***	***-0.791***	***Passes***
			3	1.21	804.28	Non-Competitive	1.16	847.30	51.94	-0.722	Passes
			11	1.43	742.33	Lin. Mixed Competitive	1.00	817.92	18.07 C	-0.321	Passes
						Uncompetitive	1.26	858.59	42.69	-0.488	Passes

a : apparent Km
b : apparent Vmax
c : Redundant
d : a = factor between inhibition constant 1(=Ki) and inhibition constant 2 in the linear mixed inhibition model
GoF : Goodness of Fit. The model giving the lowest value of GoF is considered the best fit.
Michaelis-Menten Model v = Vmax*([S]/(Km + [S]))

5.4.3.5.2 *In Vitro* Inhibition of P450 CYPs by Asenapine in Pooled Human Liver Microsomes- Study DM2005-005222-009

Asenapine was examined for effects on several drug metabolizing enzyme activities in pooled human liver microsomes. Seven concentrations ranging from 0.0952 - 30.0 µM or 0.00952 - 3.00 µM, including 0, were evaluated in duplicate and IC_{50}s were determined by interpolation. Other incubation conditions are shown in Table 43.

Table 43 Incubation Conditions with Human Liver Microsomes – Study DM2005-005222-009

Enzyme	Marker Substrate Activity	Substrate Concentration (µM)	Microsomal Protein Concentration (mg/mL)	Incubation Time (min)	Termination Solvent[a]
CYP1A2	Phenacetin O-Deethylase	50 µM	0.03	30	5/92/3
CYP2B6	Bupropion Hydroxylase	80 µM	0.05	20	5/92/3
CYP2C8	Amodiaquine N-Deethylase	1.9 µM	0.025	10	5/92/3
CYP2C9	Diclofenac 4'-Hydroxylase	4 µM	0.03	10	5/92/3
CYP2C19	S-Mephenytoin 4'-Hydroxylase	60 µM	0.2	40	5/92/3
CYP2D6	Dextromethorphan O-Demethylase	5 µM	0.03	10	5/92/3
CYP3A	Felodipine Oxidase	2.8 µM	0.01	10	50/47/3
CYP3A	Midazolam 1'-Hydroxylase	2.5 µM	0.03	4	92/5/3
CYP3A	Testosterone 6β-Hydroxylase	50 µM	0.03	10	5/92/3

a Termination solvent ratio = Acetonitrile/Water/Formic Acid

The percent activity remaining at the maximum concentration studied (30 mM) and the estimated IC_{50}s are shown in Table 44.

Asenapine demonstrated marked inhibition of CYP2D6 and moderate inhibition of CYP1A2 activities with respective IC_{50}s of 44 and 610 nMol/L, and little or no inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A. This suggests that the greatest potential for an interaction with asenapine is with compounds cleared by CYP2D6 followed by compounds cleared by CYP1A2, (see Table 44). However it should be remembered that metabolites have not been tested in this system.

Table 44 Summary of IC_{50} Data for Asenapine in Human Liver Microsomes – Study DM2005-005222-009

Enzyme	Marker Substrate Activity	% of control at [I] = 30 µM	IC50 (µM) Mean ± SE	IC50 (nM)
CYP1A2	Phenacetin O-Deethylase	6.9	0.61 ± 0.05	610
CYP2B6	Bupropion Hydroxylase	91	>30	
CYP2C8	Amodiaquine N-Deethylase	78	>30	
CYP2C9	Diclofenac 4'-Hydroxylase	95	>30	
CYP2C19	S-Mephenytoin 4'-Hydroxylase	84	>30	
CYP2D6	Dextromethorphan O-Demethylase	3.3a	0.044 ± 0.001	44
CYP3A	Felodipine Oxidase	65	>30	
CYP3A	Midazolam 1'-Hydroxylase	120	>30	
CYP3A	Testosterone 6β-Hydroxylase	58	>30	

a % of Control at 3 µM

5.4.3.6 Induction by Asenapine In Vitro

5.4.3.6.1 Induction of CYP1A2 and CYP3A4

In vitro experiments in 4 batches [2 fresh (HU cell lines) and 2 cryopreserved] of human hepatocytes were performed by Pfizer to evaluate the potential for asenapine to induce of CYPs 1A2 and 3A4. No evidence of induction was found. However, asenapine metabolites were not assessed nor were the effects on transporters or other enzyme systems, (e.g. glucuronosyl-transferases).

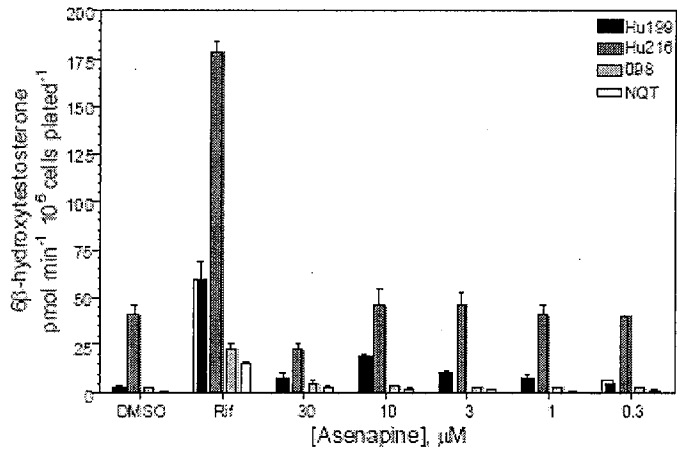
Results for CYP3A4 are shown in Figure 31 and Figure 32, and results for CYP1A2 are shown in Figure 33 and Figure 34.

The following information on the methodology used is from the sponsor:

'To evaluate the potential of a compound to induce drug metabolizing enzymes, we have implemented several assays to measure specific cytochrome P450 levels in vitro. These assays focus on induction of CYP3A4 and CYP1A2, and measure both enzyme activity and mRNA levels in freshly isolated and/or cryopreserved human hepatocytes. These assays include 10 µM rifampin as a positive control for CYP3A4 and 10 µM lansoprazole as a positive control for CYP1A2. Background controls treated with vehicle are included, and viability is measured at the conclusion of the experiment. Asenapine was tested at 5 concentrations (0.3 to 30 µM) in freshly isolated and cryopreserved hepatocytes from 4 separate donors. The rate of product formation was determined for each lot by LC-MS/MS, and results are normalized to percent of positive control using background (vehicle) as 0, and positive control as 100 (%control = (activity of test article mean background)/(mean activity of positive control - mean background) × 100). A compound is considered to be an in vitro inducer if it reaches 40% of the positive control with a dose-dependent increase in enzyme activity in 3 of the 4 hepatocyte lots tested.3 Measurement of CYP3A4 and CYP1A2 mRNA levels were performed using the TaqMan assays from Applied Biosystems, and fold increase over background (vehicle) was determined using relative quantification (RQ) based on cycle threshold (CT). Results of the TaqMan assay are not used alone to infer in vitro induction, but are used in support of enzyme activity data.'

Figure 31 A) Rate of 6β−Hydroxytestosterone Formation for Controls and Asenapine at 0 to 30 μM in Human Hepatocytes; B) Fold Induction for CYP3A4 for Controls and Asenapine at 0 to 30 μM in Human Hepatocytes - Study RR 764-04914

A)



B)

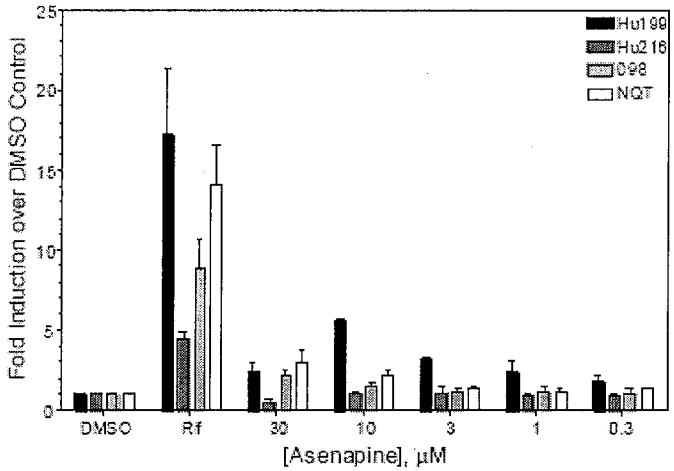
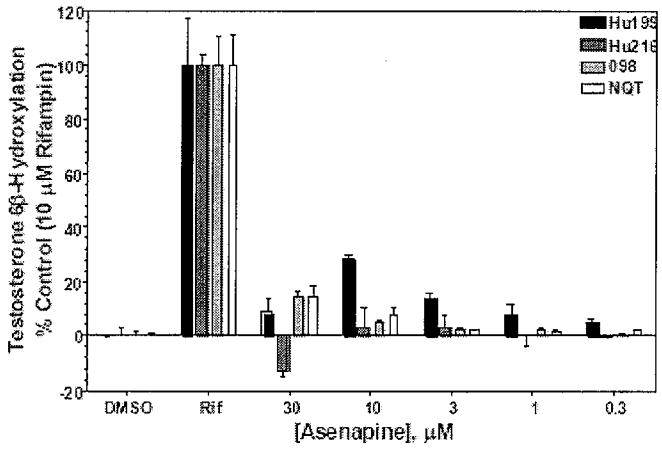


Figure 32 A) Rate of 6β-Hydroxytestosterone Formation Normalized to Percent of Positive Control for Controls and Asenapine at 0 to 30 μM in Human Hepatocytes; B) Mean Rate of 6β-Hydroxytestosterone Formation Normalized to Percent of Positive Control and Relative Quantitation (RQ) Values of CYP3A4 mRNA for Controls and Asenapine at 0 to 30 μM in Human Hepatocytes - Study RR 764-04914

A)



B)

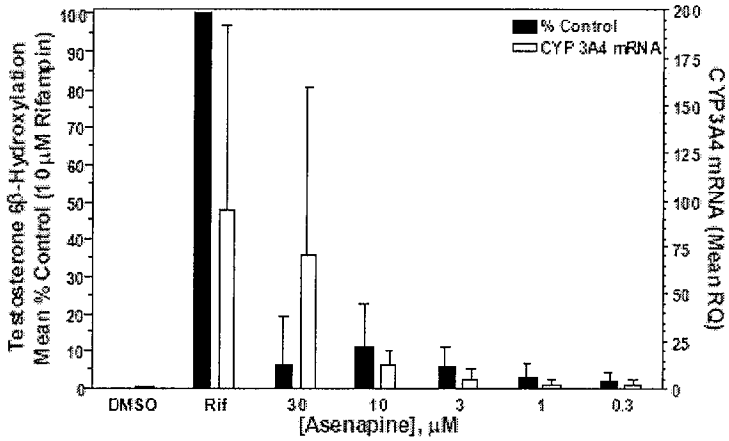
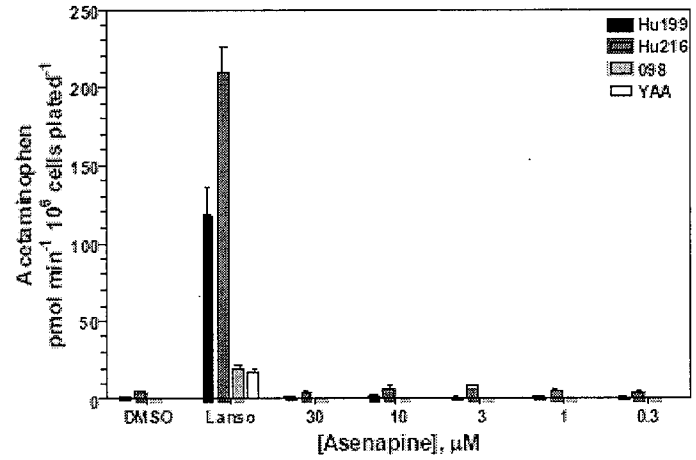


Figure 33 A) Rate of Acetaminophen Formation for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes; B) Fold Induction for CYP1A2 for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes

A)



B)

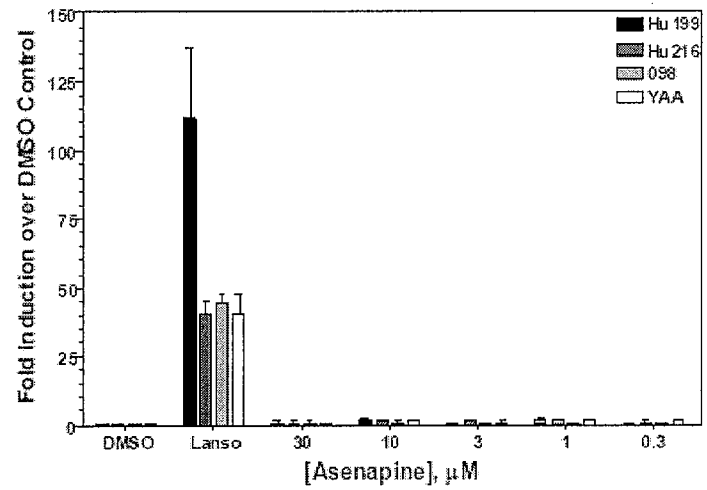
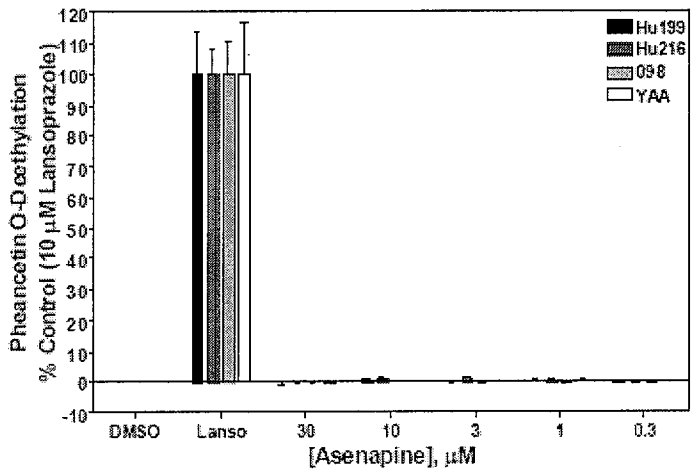


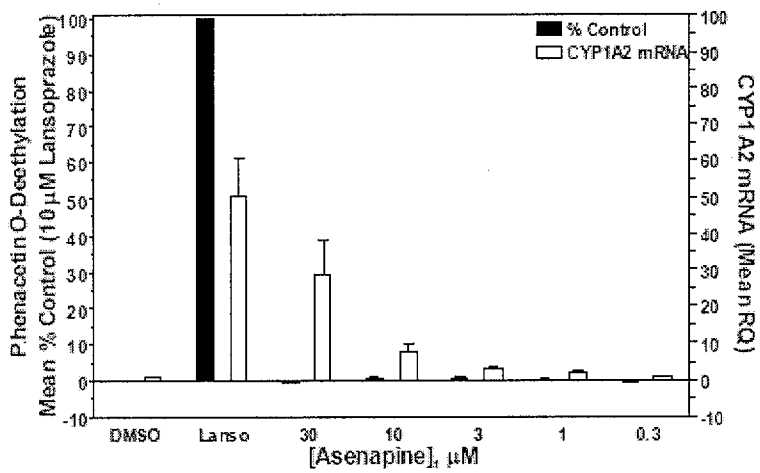
Figure 34 A) Rate of Acetaminophen Formation Normalized to Percent of Positive Control for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes; B) Mean Rate of Acetaminophen Formation Normalized to Percent of Positive Control and

Relative Quantitation (RQ) Values of CYP1A2 mRNA for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes

A)



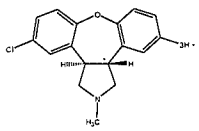
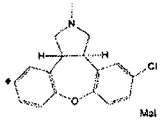
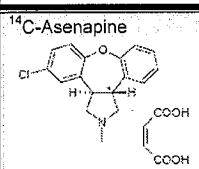
B)

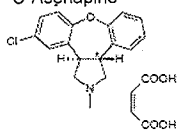


5.4.3.7 *Cross Species Comparison of Metabolites Detected In Vitro*

The following table was created for the scoping meeting to respond to a request from the Pharmacology/Toxicology reviewer in order to determine whether all human metabolites have been observed in toxicology studies. Coding for metabolites are per each individual study report. In general H*i* or M*i* stands for the ith metabolite by retention time from hepatocytes or microsomal incubations respectively. Where identification of metabolites was possible they are nominally shown below the metabolite code, in addition when metabolites with different codes (e.g. H15 and M7 can be identified in different experiments as the same metabolite they have been lined up.Species in red are human metabolites that can be matched to an animal metabolite and pink species are human metabolites that cannot be matched to animal metabolites. Species in blue are animal metabolites that were also detected as human metabolites in the same study and experimental conditions, whereas green indicates an animal metabolite that was also detected as a human metabolite in the same study but not under the same experimental conditions. Species in brown are amimal metabolites that cannot be matched to a human metabolite. Where available, the % recovery is included otherwise an X indicates the metabolite was detected and a **bold X** indicates that this was one of the dominant species recovered. By looking across columns it appears that most of the human metabolites here have been seen in animal species. In addition at the midcycle meeting held at the end of Janurary 2008 the pharm/tox reviewer again requested if there was any any new metabolism information that would be of interest to the pharm/tox reviewer. A few days later OCP was able to identify that 99.9% of the circulating radioactivity in humans had not been identified and that there were a number of unidentified metabolites that accounted for greater than 10% of the circulating exposures to asenapine.

Table 45 Cross Species Comparison of Metabolites Detected *In Vitro*

Study	System Studied	Radiolabeled Substrate	Conc	Species	Metabolite																	
							H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13 H14	H15	As	H16
2874	Hepatic Microsomal incubation	7,11 ^{3}H, ^{14}C - Asenapine 	[redacted]		Met 2	Met 3	11-O-SO_4(?)												N-oxide (diasteromers 1 & 2) Org 31437	N(2)-desmethy Org30526		
				Human	5.4 – 8.3	3.5 – 4.5													3.6 - 5.8	8.1 - 12.7		
			25 nMol/ml	Wistar Rat															74.8	5.8		
			25 µM	Dog															31.7	32.2		
5067	Hepatocyte Cell Medium	7 ^{3}H-Asenapine 	149 ng/ml	Human			37.7	9.3	3.2	**12.5**			2.8	6.9	11.9	1.1			9.1	4.0	1.6	
			219 ng/ml	Rat			10.8	7.1	5		2.8	1.7			6.0	2.7	1.7		6.8	5.4	49.4	1.2
	Hepatocyte Cell Extract		149 ng/ml	Human			3.1					2.1	3.9	8.2	12.0			3.9	10.4	46.7	9.6	
			219 ng/ml	Rat			1.9												2.7	31.5	60.7	3.4
INT 00003054	Hepatic Microsomes	^{14}C-Asenapine 	A1 5% EtOH 5.5 nMol		M1	M2	M3	M4	M5	M6	M9	M11	M12	M13	M14	M15	M16		M10	M7	M8	
				Human				X											X	X	**94.5**	
				Mouse ICR/CD-1				X			X	X	X	X	X				X	X	X	
				SD Rat				X			X	X		X	X				X	X	X	
				NZ White Rabbit				X				X		X	X				X	X	X	
				Beagle Dog	X	X	X	X	X	X	X	X	X	X	X				X	X	X	

			B1 5% EtOH 22.3 nMol	Human																	100	
				Mouse								X		X					X	X	X	
				Rat							X	X		X	X				X	X	X	
				Rabbit										X	X				X	X	X	
				Dog							X	X							X	X	X	
			A 2 1% EtOH 5.3 nMol	Human			X	X											X	X	81.7	
				Mouse										X					X	X	X	
				Rat			X							X					X	X	X	
				Rabbit			X	X	X										X	X	X	
				Dog				X											X	X	X	
			B2 1% EtOH 18.8 nMol	Human				X			X									X	X	63.8	
				Mouse			X												X	X	X	
				Rat															X	X	X	
				Rabbit			X	X						X					X	X	X	
				Dog															X	X	X	
					H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15	H16	H17	
									O-SO4	O-SO4	N-Gluc	OH-N-DesMe			Org30526 N(2) desMe	As	N(2) formyl hydroxy	Org 31437	Org 31437 N(2) oxide	N(2) formyl		
NL 0060905	Cyropreserved Hepatocytes	^{14}C-Asenapine 	B	Mouse ICR/CD-1									X	X	X	X		X	X	X	X	
				Rat SD											X	X		X	X	X	X	
				Rabbit NZ white									X		X	X		X	X	X	X	
				Dog Beagle	X	X							X	X	X	X		X	X			
				Human			X	X	X	X	X	X	X	X	X	X	X					
			A	Mouse									X	X	X	X		X	X	X	X	
				Rat											X	X		X	X	X	X	
				Rabbit									X		X	X		X	X	X	X	
				Dog	X	X							X	X	X	X		X	X	X	X	
				Human			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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

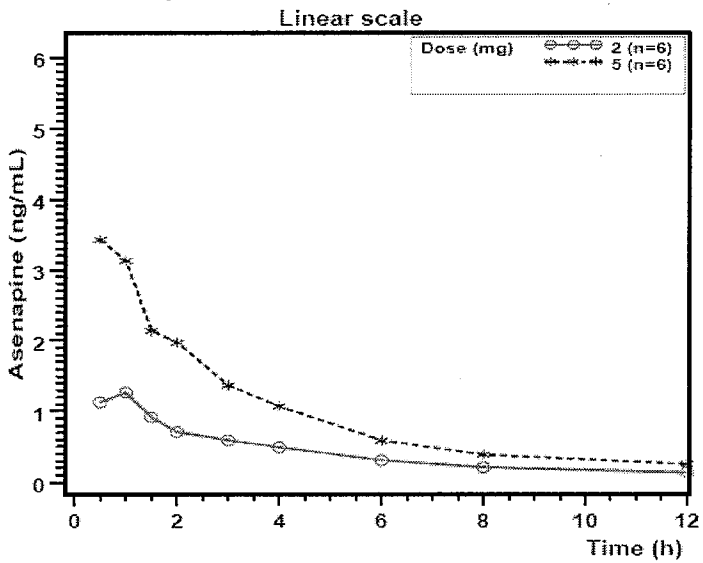


Figure 36 Mean Single Dose Asenapine Dose-Normalized Concentration vs. Time Profiles – Study 25542

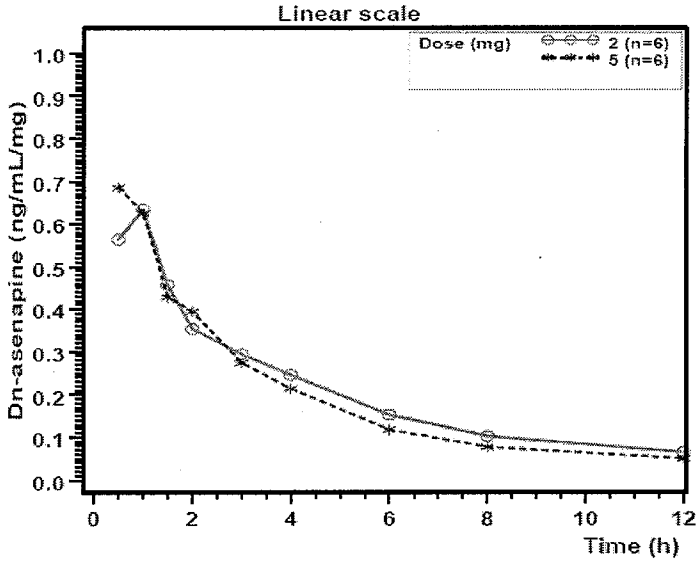


Figure 37 Mean Single Dose Asenapine Semi-log Concentration vs. Time Profiles – Study 25542

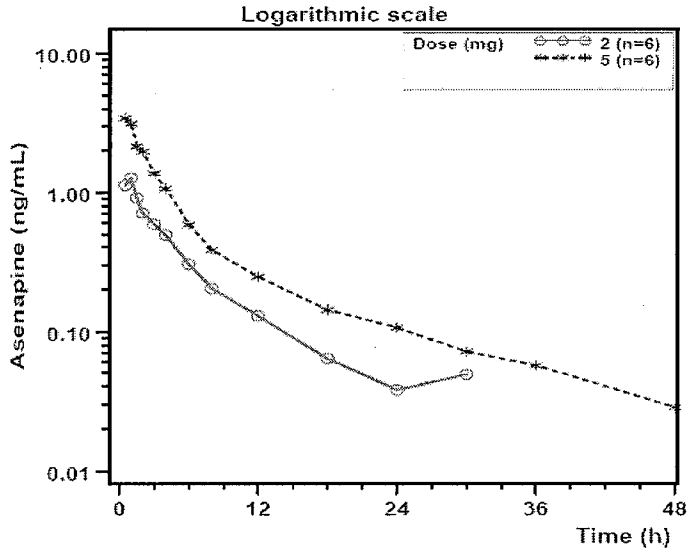


Figure 38 Mean Single Dose Asenapine Semi-log Dose-Normalized Concentration vs. Time Profiles – Study 25542

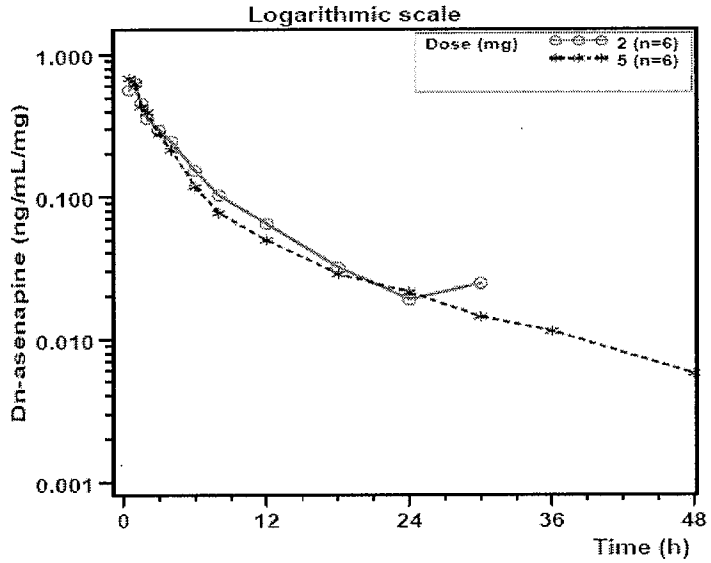

Logarithmic scale
Dose (mg)
2 (n=6)
5 (n=6)
1.000
0.100
0.010
0.001
Dn-asenapine (ng/mL/mg)
0
12
24
36
48
Time (h)

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

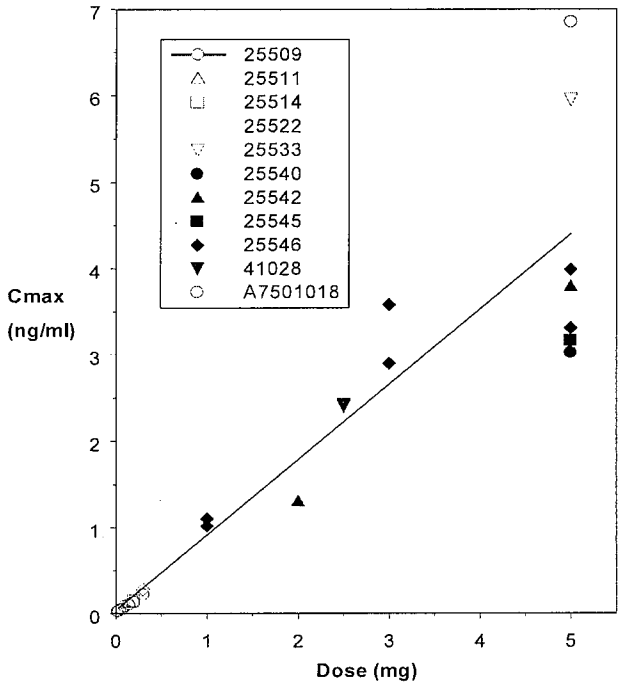


Figure 40 Asenapine Single Dose Mean AUC vs. Dose from Multiple Studies

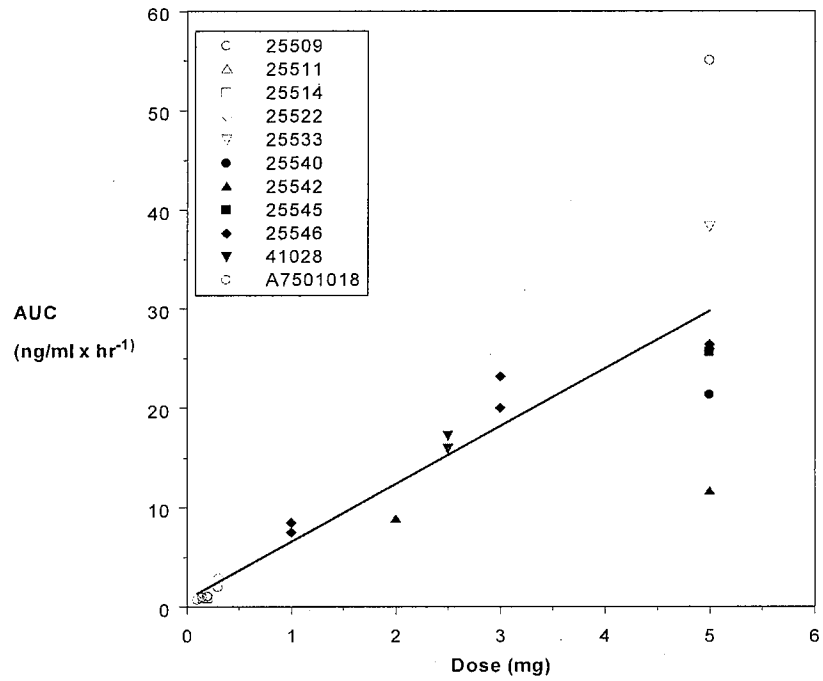


Figure 41 Pharmacokinetic Metrics (Mean ± SD) for Single Rising Doses of Sublingual Asenapine in Healthy Young Males - Study 25509

Dose group (µg)	C_{max} (pg/ml)	t_{max} (h)	$AUC_{0-\infty}$ (pg·h/ml)	AUC_{0-tlx} (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±11.13	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	Evening	Morning	Evening	Morning	Evening
		(n=5)	(n=5)	(n=6)	(n=6)	(n=5)	(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

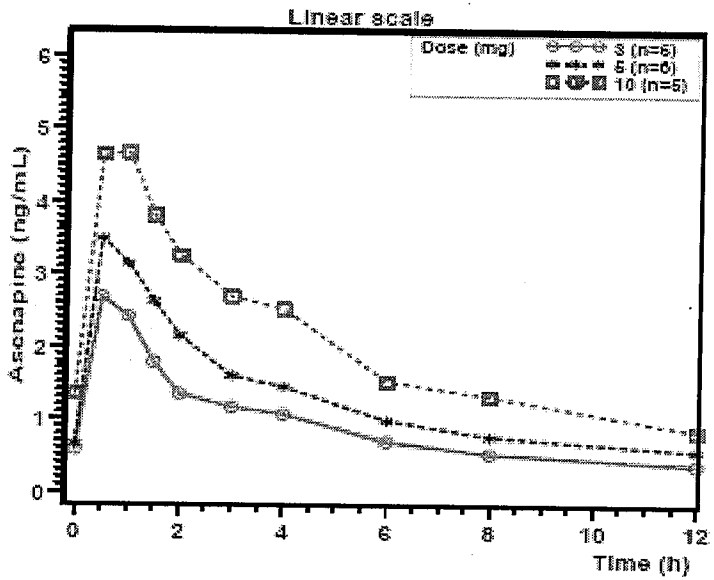


Figure 43 Mean Steady-State Asenapine Semi-log Concentration vs. Time Profiles after a Morning Dose – Study 25542

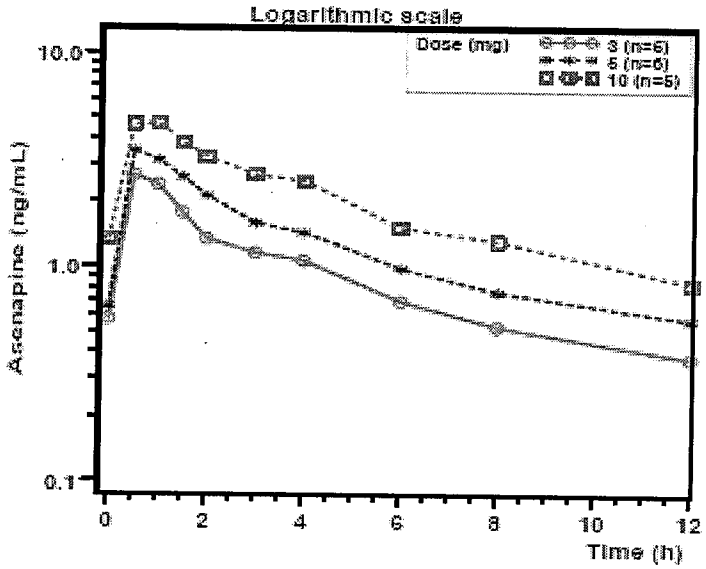


Figure 44 Mean Steady-State Asenapine Concentration vs. Time Profiles after an Evening Dose – Study 25542

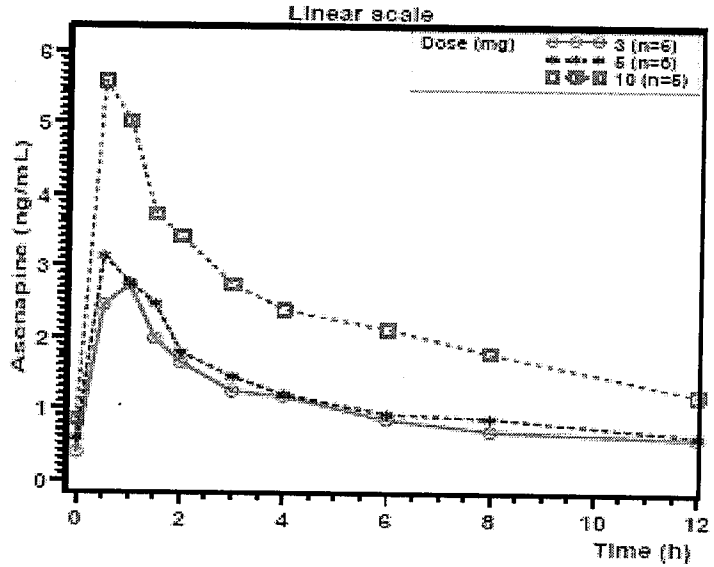


Figure 45 Mean Steady-State Asenapine Semi-log Concentration vs. Time Profiles after an Evening Dose – Study 25542

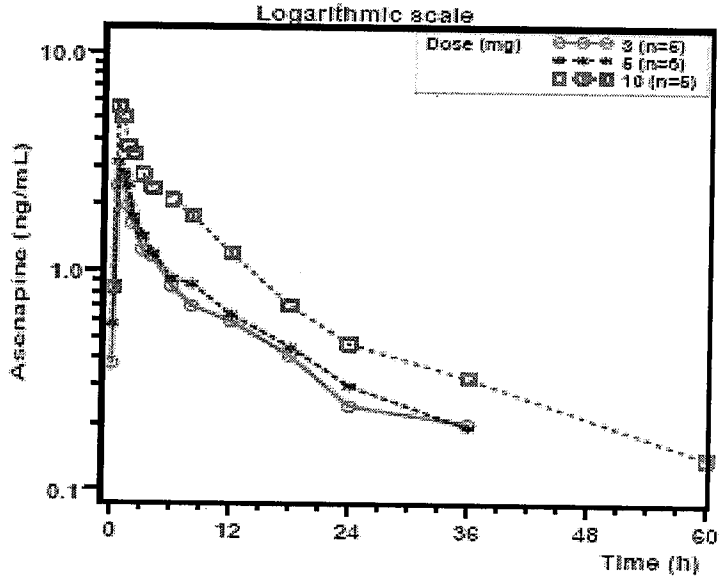


Figure 46 Mean Steady-State Desmethyl-Asenapine Concentration vs. Time Profiles after a Morning Dose – Study 25542

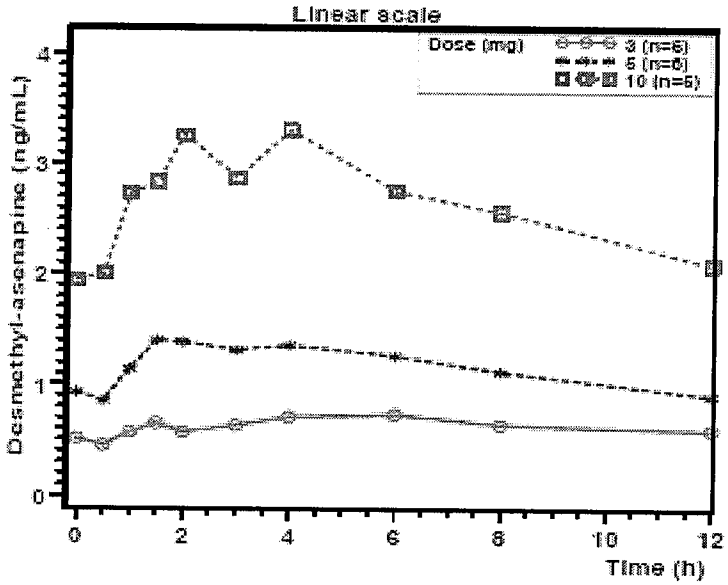


Figure 47 Mean Steady-State Dose-normalized Asenapine Concentration vs. Time Profiles after a Morning Dose – Study 25542

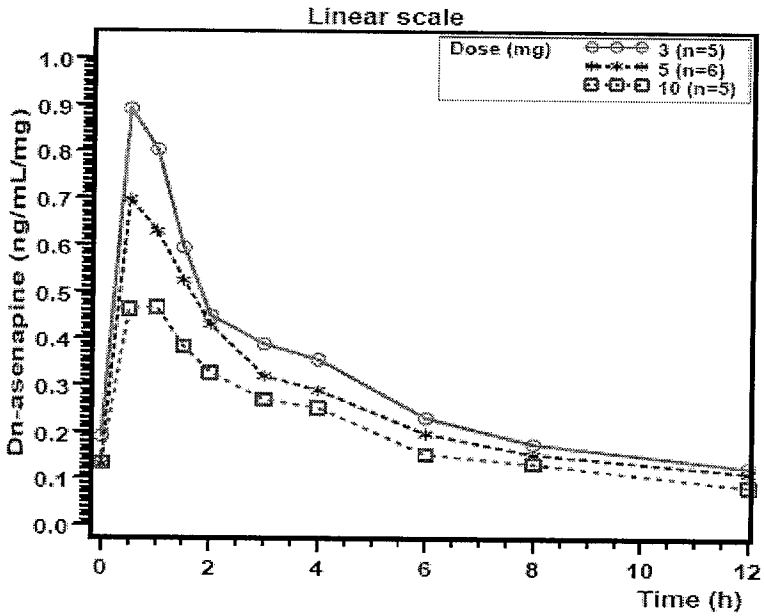


Figure 48 Mean Steady-State Desmethyl-Asenapine Semi-log Concentration vs. Time Profiles after a Morning Dose – Study 25542

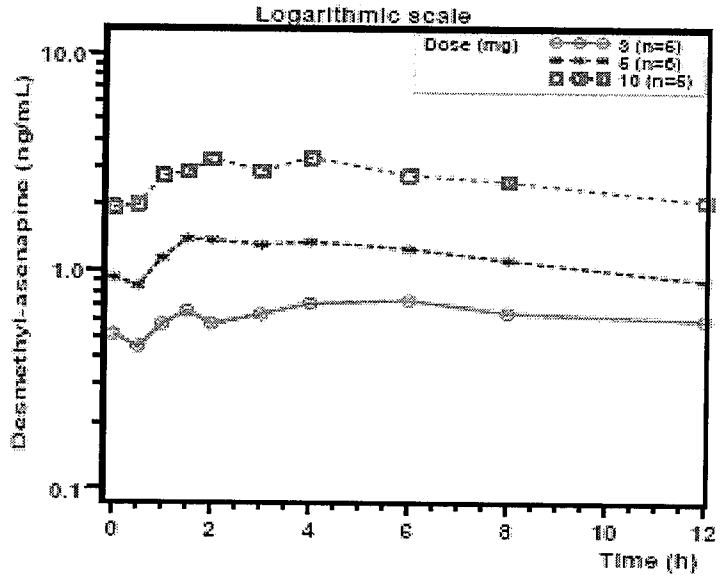


Figure 49 Mean Steady-State Dose-normalized Asenapine Concentration vs. Time Profiles after an Evening Dose – Study 25542

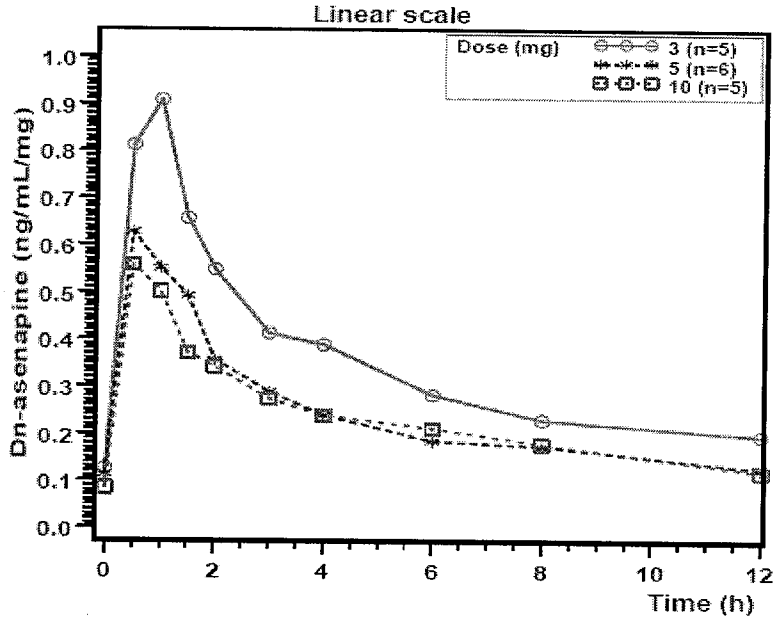
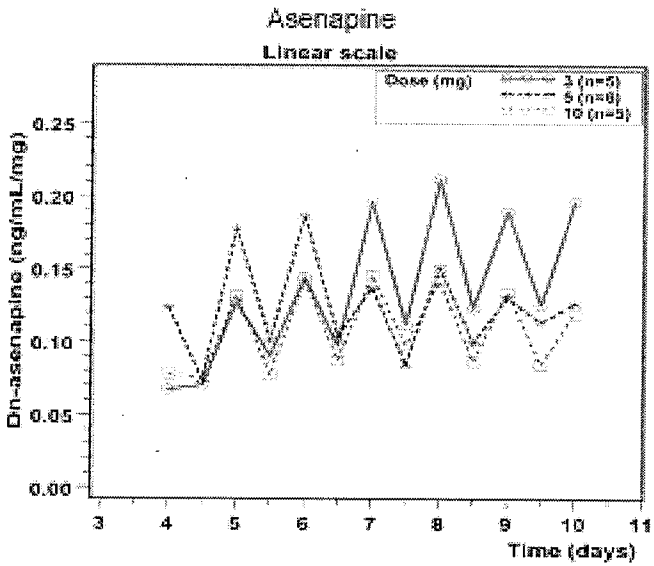


Figure 50 Mean Dose-Normalized Asenapine and Desmethyl-Asenapine pre-Dose Concentration Fluctuations from Days 4 to 10 of Dosing – Study 25542



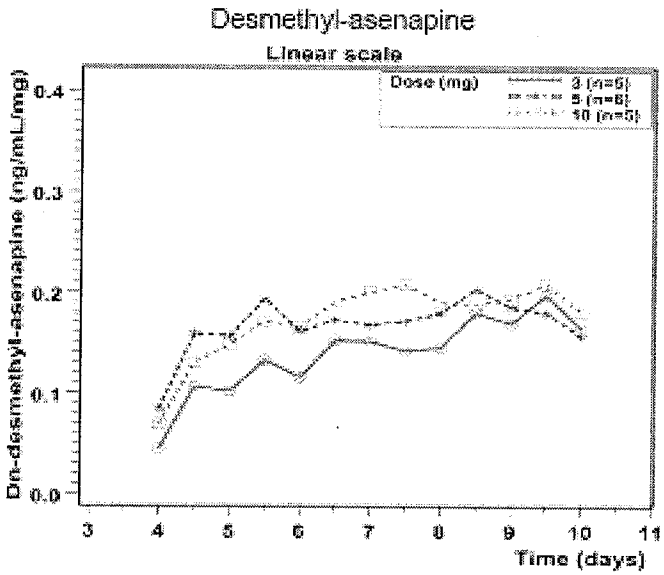


Table 55 Multiple Dose Asenapine Pharmacokinetic Metrics –Study 41012

	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

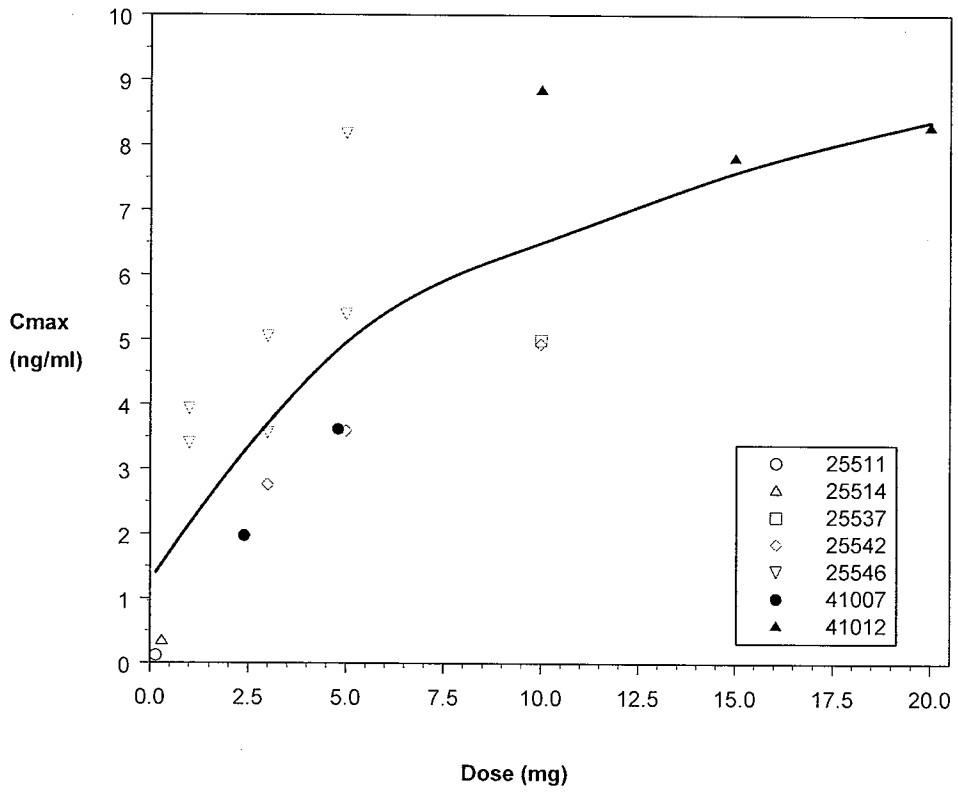


Figure 52 Mean Asenapine Multiple Dose AUCs vs. Dose from Various Studies

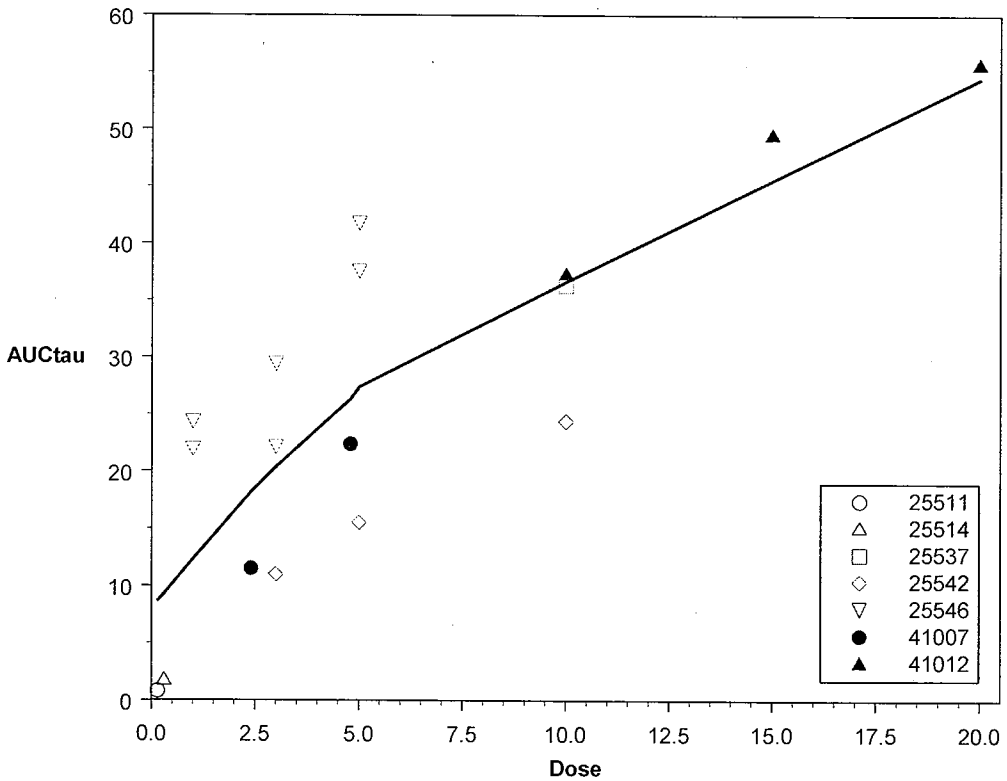


Figure 53 Mean Asenapine Dose Normalized Cmaxs and AUCs vs. Dose from Various Multiple Dose Studies

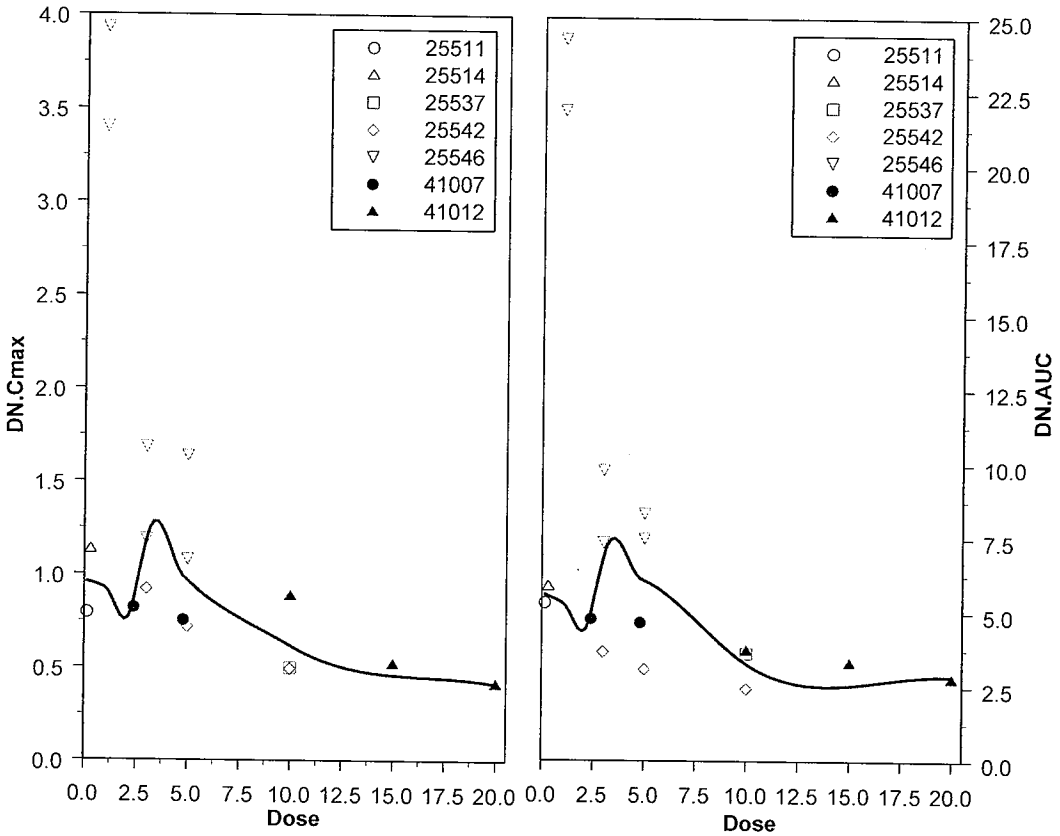


Table 56 Asenapine SL Multiple Dose Pharmacokinetic Metrics in Young Healthy Male Volunteers - Studies 25511 and 25514

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

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, Ithough 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	—
AUC0 – tlast (ng·h/mL)	37.0 (24.2) 19.6 - 44.6	—	7.76 (21.70 6.08 - 11.0	—
AUC0 – 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

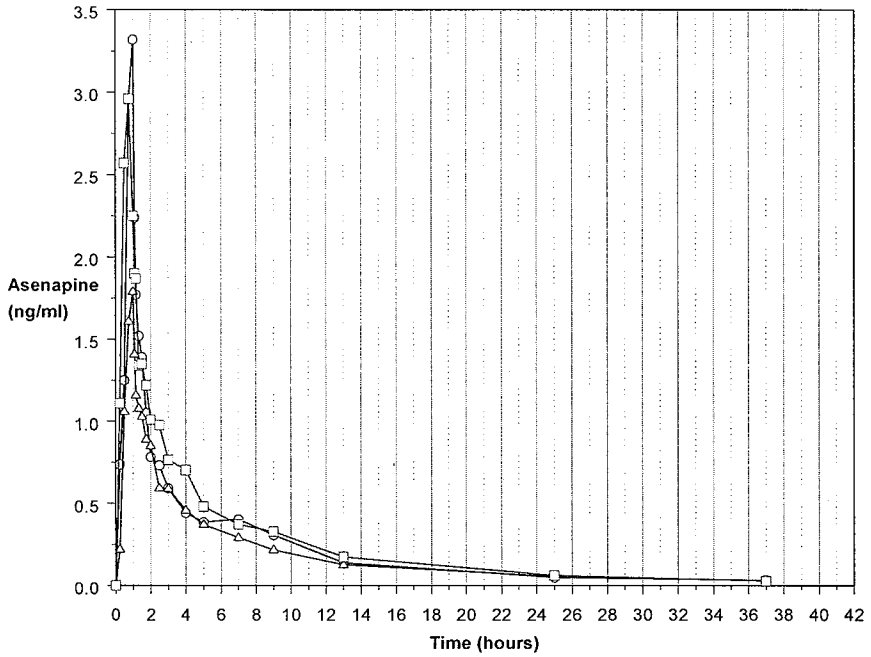
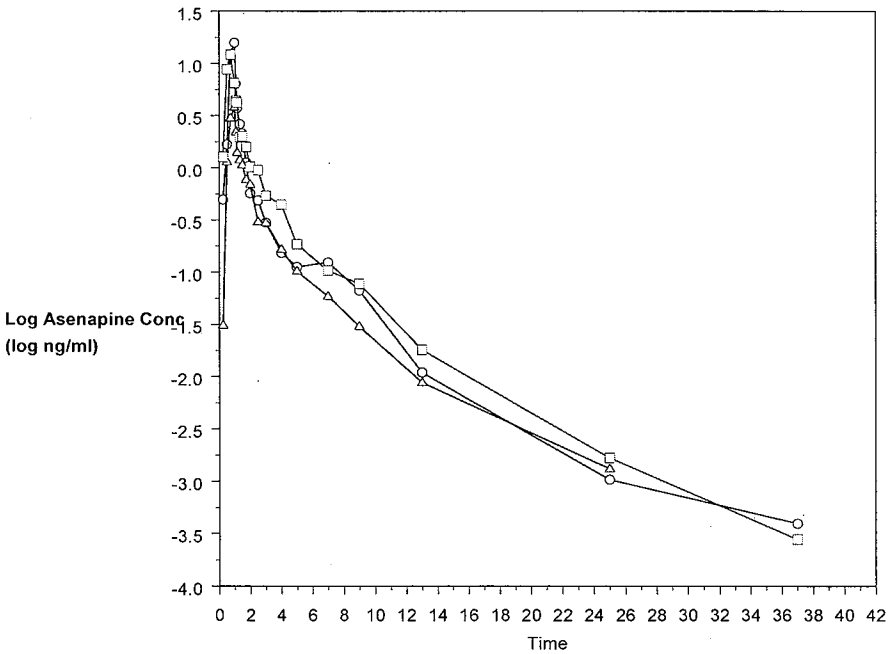


Figure 55 Asenapine Natural Log- Concentration vs. Time Profiles after 0.5 mg IV over 1 hour – Study 41036



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.

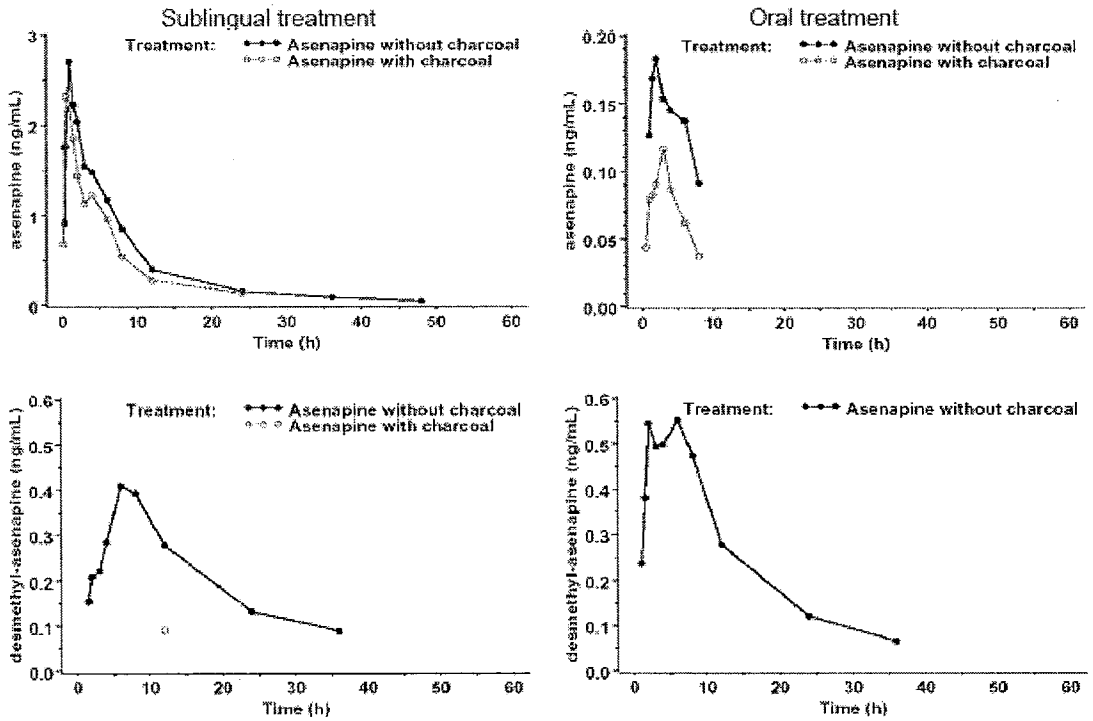
Subjects in Group 1 were administered asenapine sublingually and subjects in Group 2 were administered asenapine tablets orally dissolved in 150 ml of water. After an interperiod wash-out of 7 days subjects received the same asenapine treatment as previously, however it was administered 10 minutes after 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
	t½ (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
	t½ (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.

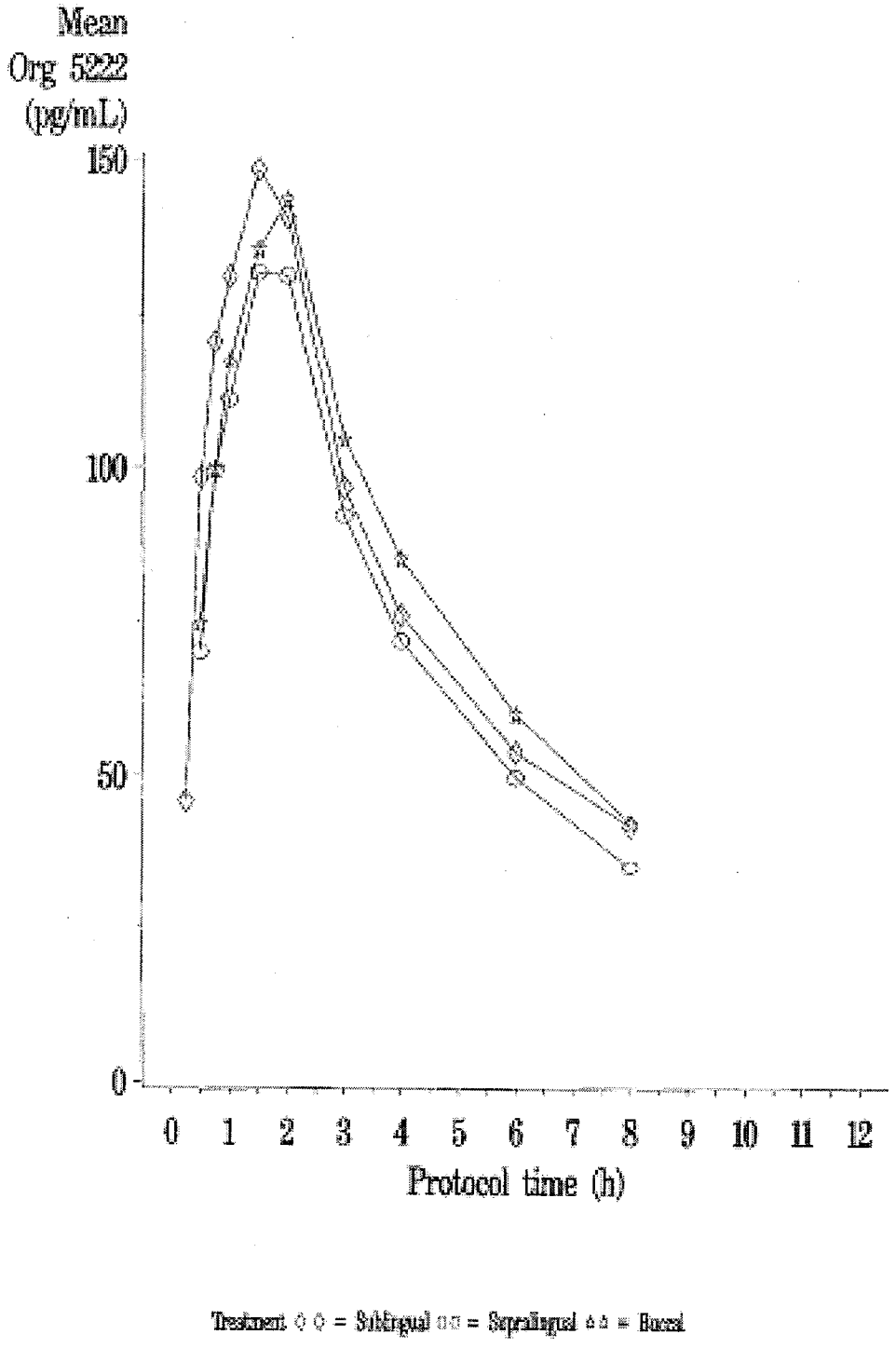
Both the lingual and buccal routes had lower Cmaxs, AUCs and delayed Tmaxs as compared to the sublingual route, with absorption via the supralingual route being less than the buccal route. The supralingual route was bioinequivalent to sublingual administration and although the buccal route met the criteria 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)a
(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 [illegible] and With Supplied by [illegible] Formulation (Test 1) and a [illegible] Formulation (Test 2) - Study A7501015 b(4)

(b) (4)	Least-Squares Mean Parameter Values[a]		Ratio	90% Confidence Interval
	(b) (4) (Test1)	(b) (4) (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)	
	(Test2)	(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) in Pivotal BE Study A7501015

(b) (4)

Figure 59 Individual Desmethyl-Asenapine Cmax and AUCs by Treatment for (b) (4) (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 differen (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)d Tablets (Test) - Study A7501016

Parameter	Least-Squares Mean Parameter Values[c]		Ratio	90% Confidence Interval
	(b) (4) Tablet (Test)	(b) (4)d 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)

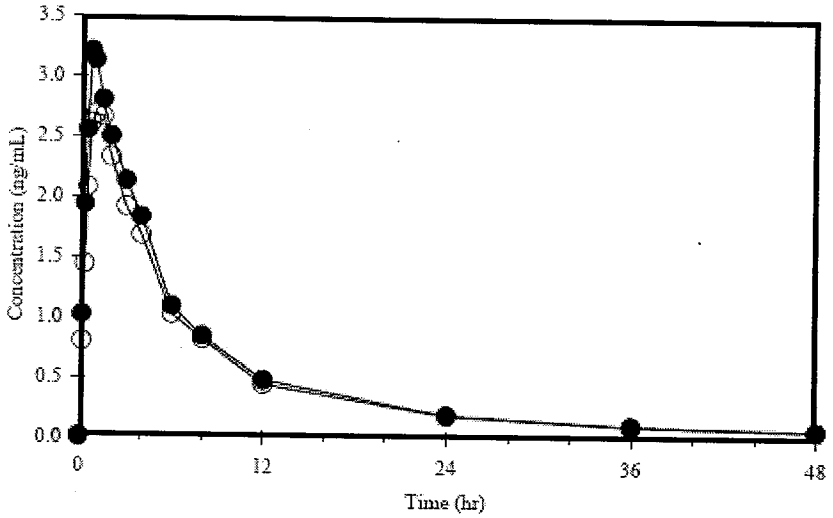


Figure 61 Mean Plasma Asenapine Concentration-Time Profiles Following Administration of Asenapine 5 mg (b) (4) Tablets (Filled Circles; Reference) and 5 mg (b) (4) Tablets (Open Circles, Test) (Study A7501016)

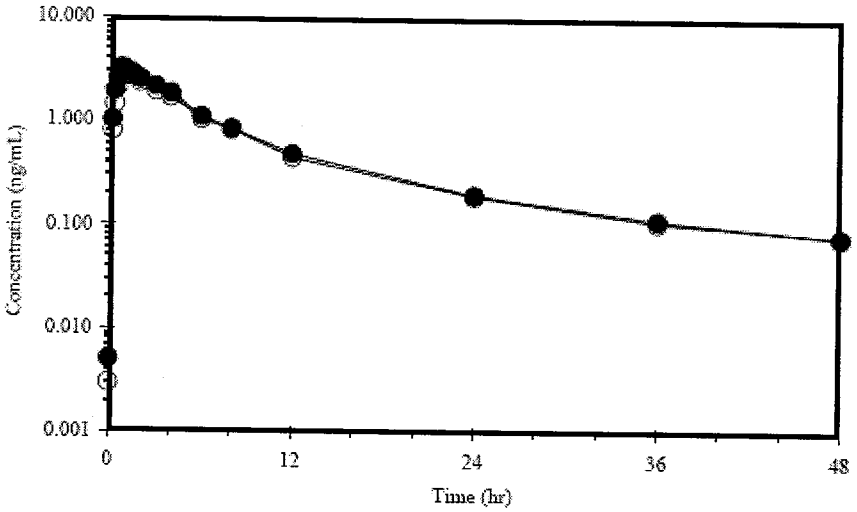


Figure 62 Asenapine Cmax Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) (Study A7501016)

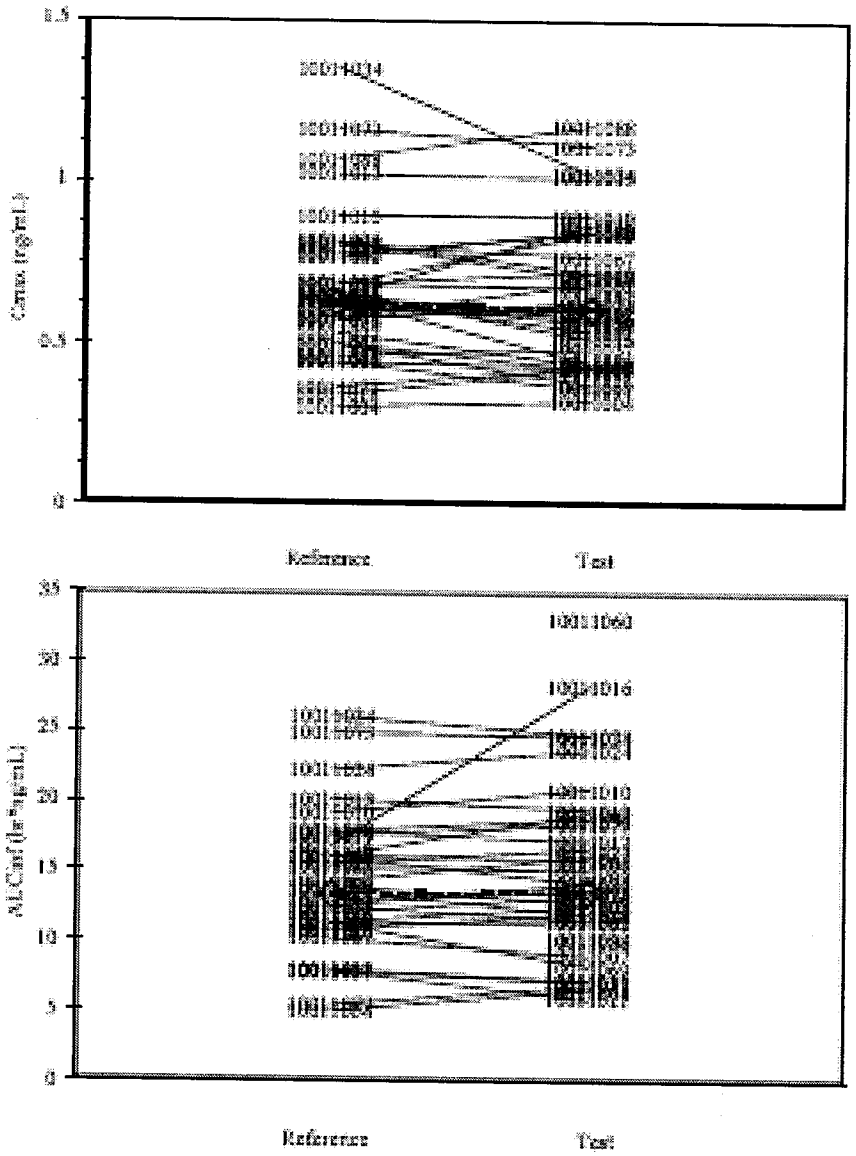
(b) (4)

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 — 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). b(4)

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) AND (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) AND M (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
--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	DGF (b) (4)
Test	Asenapine	05-024604	D0501720	5 mg	DGF (b) (4)

No information was provided on the actua (b) (4)s 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) (b) (4)

In this review the stated
asenapine maleate drug substance varies 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 specification was and no information was included in the batch analyses submitted.

b(4)

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 (b) (4). *Batch AT had a* (b) (4) (b). *A deviating* (b) (4) *was intentionally obtained to support manufacturability and bioavailability studies.*

(b) (4)

The (b) (4)*e distribution is determined* (b) (4). (b) (4) (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) (b), and all efficacy and safety data was generated with (b) (4) (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) - 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). The taste of the (b) (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 – Study 41026

b(4)

	Test	Ref	Geometric Mean Parameter		Conclusion
	(b) (4) (dc)	(b) (4) (fd)	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 BID	3 mg SD 5 mg BID	5 mg SD 10 mg BID	1 mg SD 3 mg BID	3 mg SD 5 mg BID	5 mg SD 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-$AUC_{0\text{-tlast}}$	1.10	0.83 - 1.46	1.33	0.91 - 1.94	1.14	0.80 - 1.62
	dn-$AUC_{0\text{-inf}}$	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-$AUC_{0\text{-}12}$	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	15.2 (67.9)	9.65 (38.9)	+58%
	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

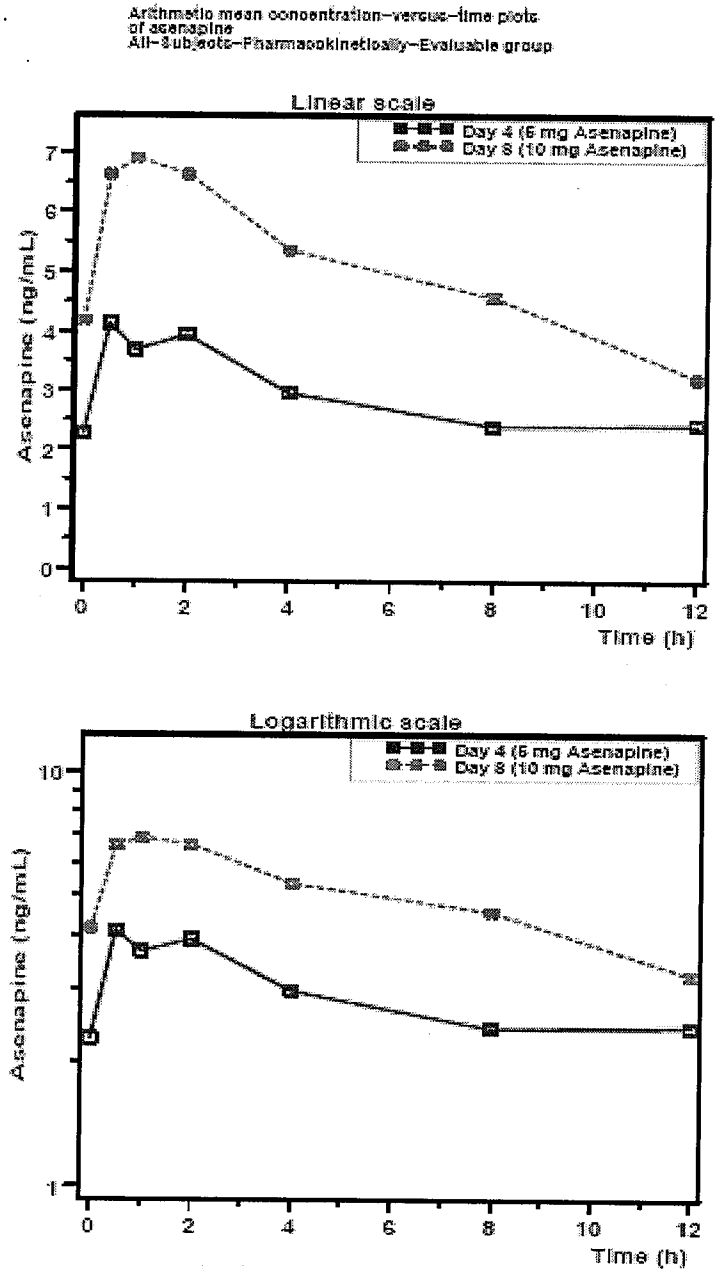
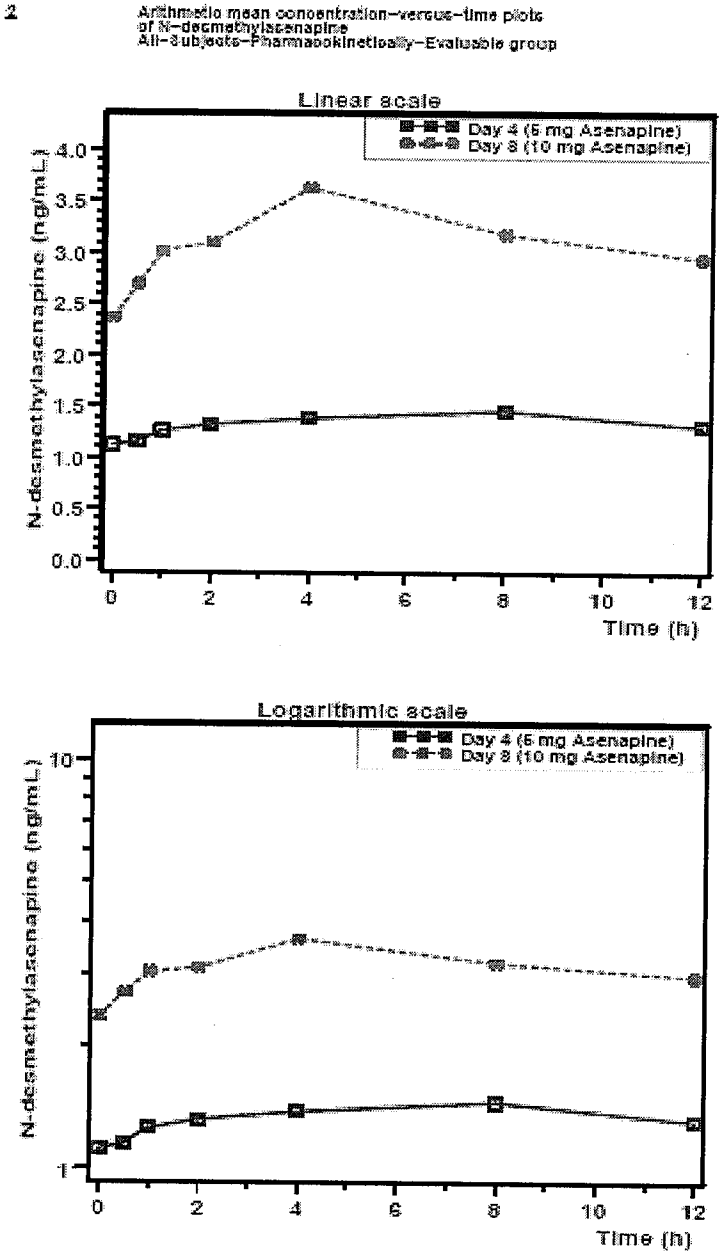


Figure 68 Mean Desmethyl-Asenapine Steady-State Concentration vs. Time Profiles in the Elderly – Study A7501021



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

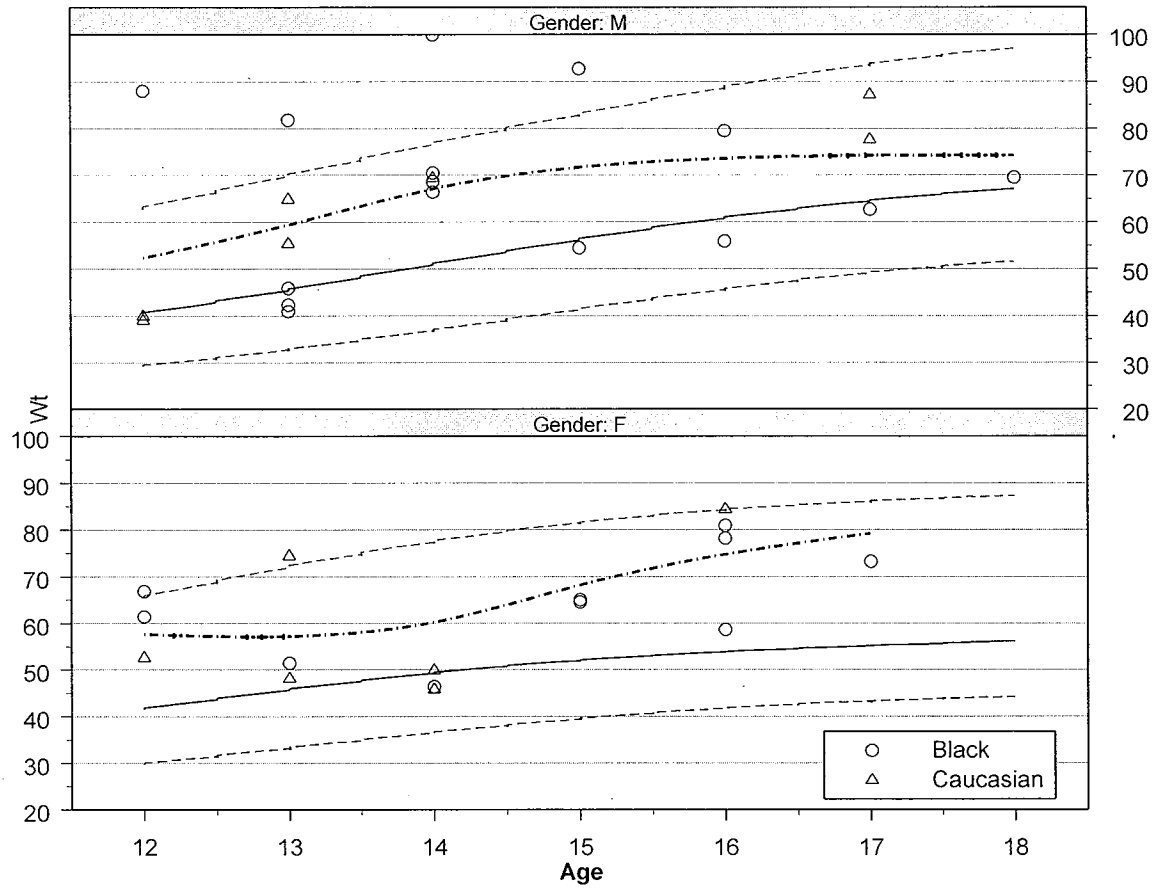
Asenapine Dose	1 mg	3 mg	5 mg	10 mg
N (n)	8 (5)	8 (5)	8 (8)	8 (6)
Tmax (hr)	3.04 (0.50 - 12)	1.82 (0.28 - 6.0)	4.00 (0.0 - 11)	3.59 (0.78 - 4.0)
Cmax (ng/mL)	0.430 (67.7)	1.04 (63.2)	1.40 (37.4)	2.96 (74.5)
Cmin (ng/mL)	0.219 (57.5)	0.621 (67.8)	0.800 (37.6)	1.07 (83.5)
AUC(0-τ) (ng/mL x hr^{-1})	4.03 (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	

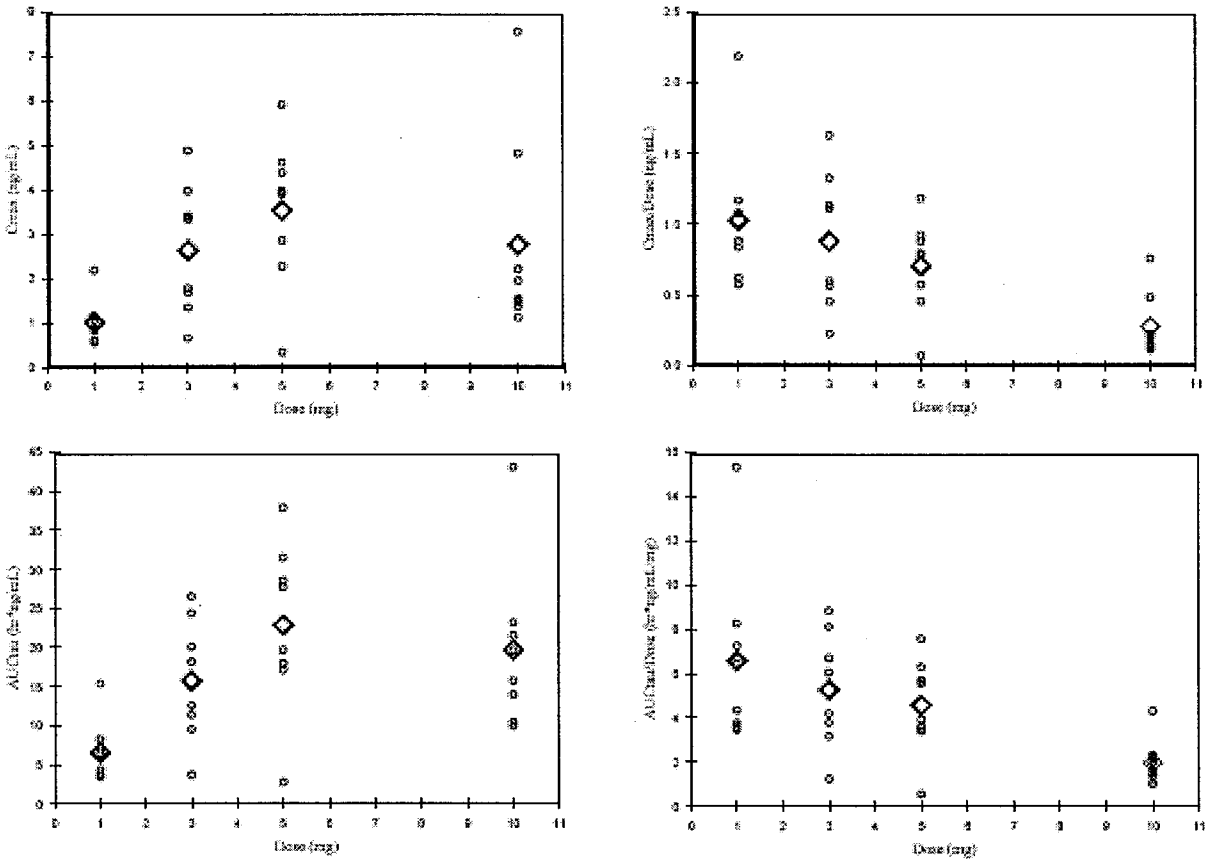
Figure 69 Adolescent Subjects Body Mass (kg) vs. Age (years) by Gender and Race, with Superimposed Curves for Population Medians and 95% Confidence Intervals along with a Cubic Spline Fit to the Subject's Data – Study A7501022



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.