

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-117

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 22117	Sponsor : Organon USA
Drug: Asenapine (ORG5222)	
Formulation:	Sublingual Tablets
Proposed Indication:	Schizophrenia Acute Mania Associated w/Bipolar Disorder
Correspondence Date:	July 25, 2008 September 4, 2008 September 23, 2008
Reviewer:	Andre Jackson

Review History of Additional Plasma Metabolic Profile Data Submitted by the Firm

HISTORY

The firm submitted a letter on July 25th 2008 making the following points related to the clarification of the metabolite profile for Asenapine (see Appendix I).

- Nearly 50% of the drug-related material in human plasma has been unequivocally identified and/or quantified by LC-MS/MS.
- The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile.
- A significant percentage (~71%) of the excreted radioactivity has been characterized by LC-MS.

The FDA responded to that July 25th correspondence with comments in the format of a review (see Appendix II).

The amount of information presented by the firm related to metabolite analysis required an in depth re-analysis of all submitted data which was completed and is presented in Appendix III.

Questions were sent to the firm on September 3, 2008 seeking further clarification (see Appendix IV).

The firm's response is presented in Appendix V.

The firm's response response to FDA questions is presented in Appendix VI.

Information presented at the internal meeting on September 15, 2008 (see Appendix VII).

The firm's final response and data summary are presented in Appendix VIII.

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OVERALL COMMENT:

The metabolite data presented by the firm is acceptable to OCP and has been included in the label text.

OCP LABEL

Metabolism and Elimination

In a mass balance study about 50% of the circulating species in plasma have been identified and they are asenapine-N-glucuronide (34%), N-desmethyiasenapine (5%), N-desmethyiasenapine N-carbamoyl glucuronide (7%) and unchanged asenapine (4%). There are other non-identified metabolites which account for 32% of the plasma circulating species.

SIGNATURES

Andre Jackson_____

RD/FT Initialed by Raymond Baweja, Ph.D.

Team Leader _____

Cc-NDA 22117, HFD-860(Jackson, Baweja,Mehta), Central Documents
Room(Biopharm-CDR)

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APPENDIX 1 July 25th 2008 LETTER FROM FIRM

Org 5222 (asenapine) Sublingual Tablets
July 2008

NDA 22-117

Nearly 50% of the drug-related material in human plasma has been unequivocally identified and/or quantified by LC-MS/MS. The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile. Metabolites eluting in this region have been characterized by LC-MS and correspond mostly to Phase II (sulfate, glucuronide and methylated) products. Overall more than 70% of circulating radioactivity is associated with conjugated metabolites. In addition, it should be noted that a significant percentage (~71%) of the excreted radioactivity has been characterized by LC-MS. Given the well-characterized biotransformation pathways for asenapine in the mouse, rat, rabbit, and dog, we believe that we have adequately exposed non-clinical safety species to all relevant human metabolites. A more detailed discussion of these points can be found below.

Metabolite profiling was studied in human volunteers using state-of-the-art LC-MS, LC-MS/MS and liquid scintillation techniques. All samples were derived from four healthy male subjects who had received a single radiocarbon dose (10 mg) after having been previously administered unlabeled drug for 10 days.

- The most representative profile which illustrates total exposure to plasma metabolites and unchanged drug comes from a pooled (1.5-12 hr) plasma sample. Referring to the radiochromatogram (**Figure 1**), we can see that asenapine (PC20) is extensively metabolized. While >9% the circulating radioactivity can be accounted for by asenapine and the desmethyl metabolite (PC19), an additional 40.5% is associated with asenapine N⁺-glucuronide (PC12/13; 33.6%) and N-desmethylenapine N-carbamoyl glucuronide (PC16; 6.9%). The N⁺-glucuronide, N-desmethylenapine and asenapine-11-hydroxysulfate metabolites have also been quantified by validated bioanalytical assays in clinical PK trial 25546 (included in the dossier). These results reproduced the ratios found in the human ¹⁴C-AME study. With the exception of the N-carbamoyl glucuronide, these metabolites have also been tested pharmacologically and showed decreased activity and/or no entrance into the brain.
- The remaining radioactivity which elutes between 13 and 25 min (**Figure 1**) corresponds to at least 15 different peaks, none of which represent more than 6% of the plasma radioprofile. As determined in urine by LC-MS, most peaks eluting before PC12/13 consisted of more than 3 metabolites, resulting in the characterization of greater than 40 metabolites. It is important to note that the majority (**Table 1**) of these metabolites correspond to phenolic sulfate and/or glucuronide conjugates and as per FDA guidance most likely pose little safety concern. The remaining unconjugated metabolites result from 10- and/or 11-hydroxylation and N-oxidation and represent no obvious structural alert. Each of these minor metabolites in turn have been detected in at least one preclinical safety species.

- In addition to very acceptable total recovery (>90%) of the radioactive dose within 7 days, a significant percentage (~71%) of the excreted radioactivity has been characterized by LC-MS. There were no major human-specific biotransformation pathways identified in plasma, urine and feces (**Figure 2**).

In summary, a majority (>70%) of the drug-related material in human plasma following sublingual administration of asenapine is associated with conjugated metabolites. Other than desmethyl-asenapine, for which adequate exposure multiples have been established with validated LC-MS/MS methods, any other unconjugated metabolite likely represents less than 6.0% of the total plasma profile. The known metabolites of asenapine have much reduced affinity for CNS receptors considered to be involved in mediating the pharmacological effects of asenapine or have low brain penetration and are thus unlikely to contribute towards the pharmacodynamic properties of asenapine. In addition, all metabolic pathways as observed in human have been observed in preclinical species. In conclusion, given the well-characterized metabolic pathways and their respective identified metabolites there is strong evidence that we have adequately exposed non-clinical safety species to all relevant human metabolites.

Figure 1. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.

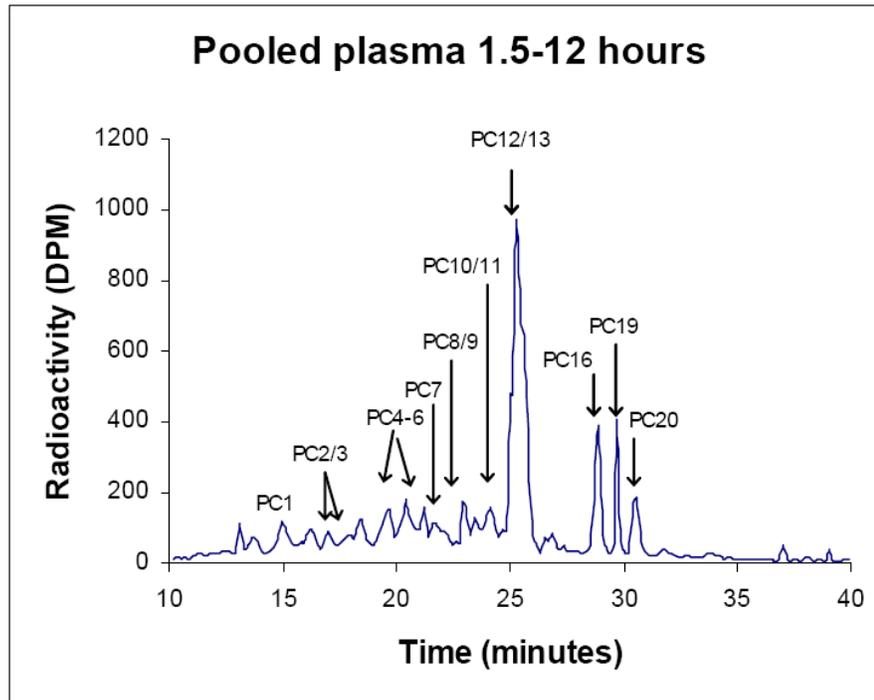
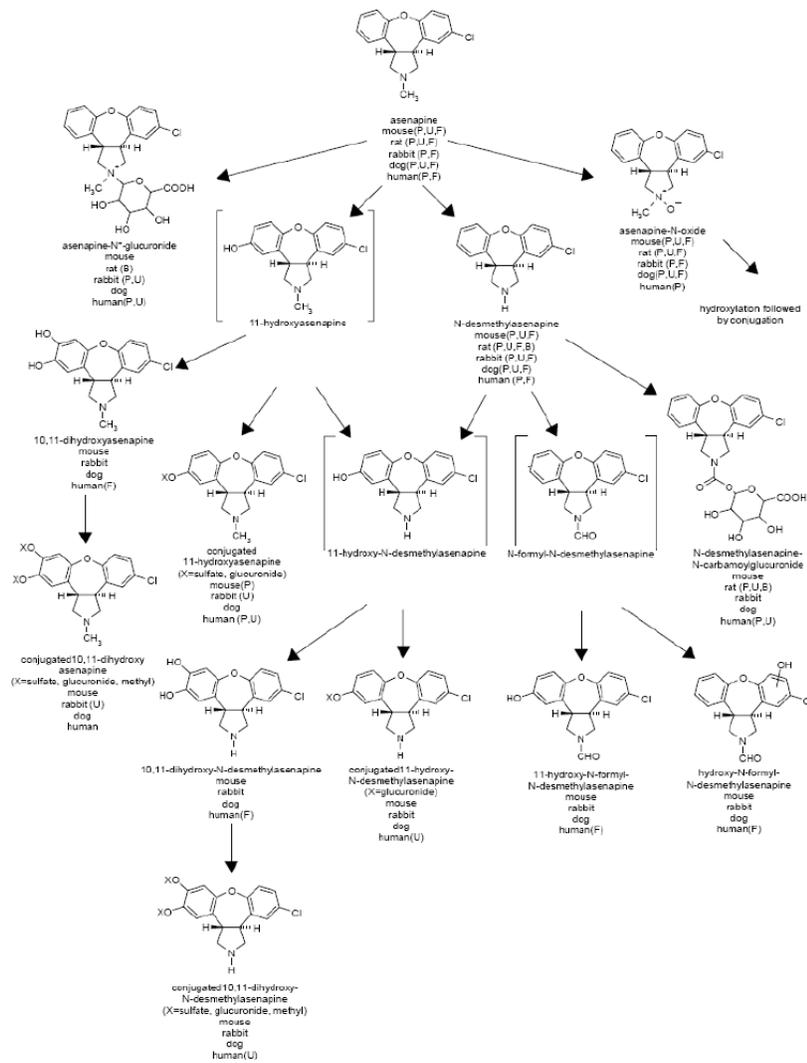


Figure 2. Major biotransformation pathways of asenapine in human and preclinical species



P= plasma, U = urine, F = feces, B = bile

Table 1: Summary of Radioactive peaks found in human plasma and urine after sublingual administration of asenapine (Org 5222 plus [¹⁴C]-Org 5222) to male volunteers.

Peak Number (human)	Identity	Retention time	% radioactivity of run, corrected for noise	Presence verified in at least one preclinical species (excreta or plasma)
PC1	Unknown	15.2	3.6	+
PC2 PC3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethyiasenapine, with the positions of the conjugates 10,11 and reverse	16.6-17.6	5.1	+
PC4-PC6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethyiasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethyiasenapine; other conjugates (sulfates/glucuronides)	18.5-22.0	13.3	+
PC7	Unknown	22.7	2.7	+
PC8-9	Sulfates and glucuronides	23.3-23.6	5.9	+
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	25.1 25.6	7.4	+
PC12 PC13	N+ glucuronide	26.8 27.2	33.6	+
PC16	N-desmethyiasenapine N-carbamoyl glucuronide	28.7	6.9	+
PC19	N-desmethyiasenapine	29.7	5.1	+
PC20	Asenapine	30.2	4.3	+

APPENDIX II- FDA RESPONSE TO FIRM JULY 25TH LETTER

TITLE RESPONSE TO FIRM JULY 25, 2008 LETTER CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA	22117
Sponsor :	Organon USA
Drug:	Asenapine (ORG5222)
Formulation:	Sublingual Tablets
Proposed Indication:	Schizophrenia Acute Mania Associated w/Bipolar Disorder
Correspondence Date:	July 25, 2008
Reviewer:	Andre Jackson

Review of Additional Plasma Metabolic Profile Data Submitted by the Firm

The firm has submitted a document with additional information related to the metabolite issues. This review will only focus on metabolite identification and quantitation in plasma. Feces and urine will not be discussed.

Firm Comment 1.

Nearly 50% of the drug-related material in human plasma has been unequivocally identified and/or quantified by LC-MS/MS. The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile.

FDA Reply:

OCP agrees that, “nearly 50% of the drug-related material in human plasma has been unequivocally identified and that The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile.” However OCP does not agree with the use of the word quantified. The profiles were a mixture of plasma samples from (1.5-12hrs) and the firm has stated in (see Module 5.3.3.1, CTR 25532, Table 4, page 31), “At a later stage the remainder of the plasma samples 1.5-12h of all four subjects was pooled. The same was done for the 1h plasma sample. Both pooled samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively and therefore these chromatograms were only evaluated in a qualitative way.” What is being reported is a mixture of times so one can not be sure of how much is parent and how much are metabolites. The statement “6% of the plasma radiocarbon profile” is non-informative related to the parent drug.

Firm Comment 2.

Metabolites eluting in this region have been characterized by LC-MS and correspond mostly to Phase II (sulfate, glucuronide and methylated) products. Overall more than 70% of circulating radioactivity is associated with conjugated metabolites.

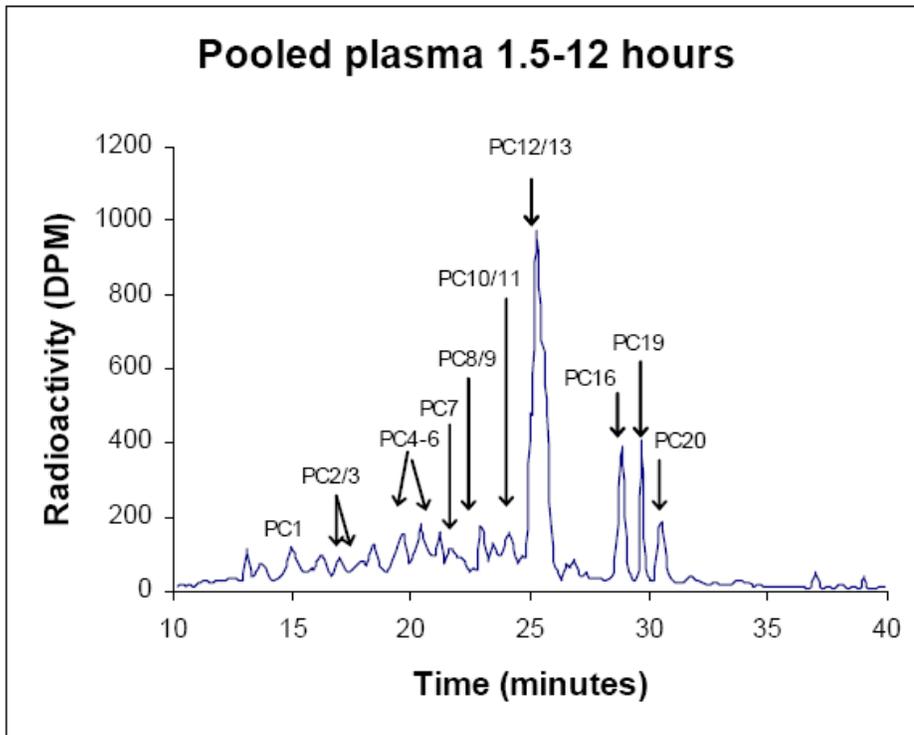
FDA Reply:

OCP agrees with this statement but it is **not quantitative** relative to the parent and the major metabolites and the time course is unknown.

Firm Comment 3.

- The most representative profile which illustrates total exposure to plasma metabolites and unchanged drug comes from a pooled (1.5-12 hr) plasma sample. Referring to the radiochromatogram (**Figure 1**), we can see that asenapine (PC20) is extensively metabolized. While >9% the circulating radioactivity can be accounted for by asenapine and the desmethyl metabolite (PC19), an additional 40.5% is associated with asenapine N+-glucuronide (PC12/13; 33.6%) and N-desmethylenapine N-carbamoyl glucuronide (PC16; 6.9%). The N+-glucuronide, N-desmethylenapine and asenapine-11-hydroxysulfate metabolites have also been quantified by validated bioanalytical assays in clinical PK trial 25546 (included in the dossier). These results reproduced the ratios found in the human ¹⁴C-AME study. With the exception of the N-carbamoyl glucuronide, these metabolites have also been tested pharmacologically and showed decreased activity and/or no entrance into the brain.
- The remaining radioactivity which elutes between 13 and 25 min (**Figure 1**) corresponds to at least 15 different peaks, none of which represent more than 6% of the plasma radioprofile.

Figure 1. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.



FDA Reply:

OCP agrees but there is no quantitation of the major species other than the desmethyl metabolite (PC19) and the N-oxide. What is required is a quantitative time course for the identified species (i.e., asenapine, desmethyl metabolite (PC19), asenapine N⁺-glucuronide, N-oxide and N-desmethyiasenapine N-carbamoyl glucuronide as a function of time. This will allow for a quantitative assessment of the contribution of each species which is not possible from pooled plasma samples.

Overall FDA Comment:

The accepted good scientific standard for NME metabolites adhered to by the FDA is that a quantitative assessment of metabolites as a function of time is done so that any relevant exposure response can be determined. For Asenapine only a total quantitation for pooled samples (2-12 hr) but not a true metabolic profile for parent and major metabolites has not been done over time.

SIGNATURES

Andre Jackson _____

RD/FT Initialed by Raymond Baweja, Ph.D.
Team Leader_____

Cc-NDA 22117, HFD-860(Jackson, Baweja,Mehta), Central Documents
Room(Biopharm-CDR)
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APPENDIX III-IN DEPTH RE-ANALYSIS OF ALL SUBMITTED DATA

TITLE: INITIAL REVIEW ASENAPINE DEFINING STUDY INFORMATION PRESENTED IN THE NDA DOSING

TABLE 1. Dosing schedule1: SOURCE(Module 4.2.2.5, Report INT00003211)),PAGE 2/94

Day-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Plac.	0.3 mg	1 mg	3 mg	5 mg	10 mg+[14C]					

FDA COMMENT :DOSING SCHEDULE-INFORMATION ONLY

HPLC SYSTEMS

HPLC system 1-SOURCE(Module 4.2.2.5, Report INT00003211)),PAGE 23/94

Radioactivity in the HPLC effluent was determined on-line (urine and feces (partly)) using a flow-through detector or off-line by the collection of fractions (plasma and feces (partly)) followed by Solid Scintillation Counting (SSC). Radioactive peaks in the HPLC metabolite profiles were assigned by visual inspection.

Gradient : 5% B isocratic during 5 minutes
5 to 35% B in 30 minutes (linear)
35 to 90% B in 20 minutes (linear)
90 to 100% B in 1 minutes (linear)
100% B isocratic during 9 minutes
100% to 5% B in 5 minutes (linear)

HPLC system 2(Module 4.2.2.5, Report INT00003211)),PAGE 24/94

Gradient : 10% B isocratic during 3 minutes
10 to 40% B in 17 minutes (linear)
40 to 90% B in 30 minutes (linear)
90 to 95% B in 1 minute (linear)
95% B isocratic during 3 minutes or 8 minutes
95 to 10% B in 1 minute (linear)

Radioactive peaks in the HPLC profiles were numbered assigned on the basis of retention time.

FDA COMMENT : The systems will have different elution patterns. Based upon information from the firm only HPLC System 1 gives a quantitative analysis. On the other hand, “HPLC system 2 was considered to achieve the best separation and ended up being used for all (plasma, urine and fecal) human samples so that direct comparison of radiochromatographic profiles among these matrices can be made. In addition to the qualitative information (correspondence with standard retention times and mass spectral data) embedded in these analyses, quantitative determinations from the radioactivity contained within individual peaks and total radioactivity eluted during the run were also made.”

METABOLITE PROFILING

METABOLITE PROFILING-SOURCE(Module 4.2.2.5, Report INT00003211)),PAGE 2/94

Blood samples for the determination of the concentration of radioactivity in plasma (coded B) were taken from day 10 onwards at 0 (=pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72 h post dosing and blood samples for the metabolite profiling (coded C) were taken at day 1 at 0 h (=pre-dose (just before the first dose of asenapine)) and on day 10 at 1, 1.5, 2, 4, 8, 12 and 24 h post dosing.

They were extracted after which the metabolite profiles of [¹⁴C]-asenapine in plasma, urine and feces samples were determined by HPLC analysis using HPLC system 1 and 2 followed by Liquid Scintillation Counting (LSC) or Solid Scintillation counting (SSC). Afterwards metabolites of asenapine were isolated from plasma, urine and feces. Identification of the isolated metabolites was performed by MS and/or NMR

(Module 4.2.2.5, Report INT00003211)),PAGE 31/94

At first plasma samples (1.5-12h) were measured per time point per subject on HPLC system 1. These data are used to give quantitative data. At a later stage the remainder of the plasma samples 1.5-12h of all four subjects was pooled. The same was done for the 1h plasma sample. Both pooled samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively and therefore these chromatograms were only evaluated in a qualitative way.

FDA COMMENT : These statements by the firm are confusing since they are using HPLC system 2 to profile but clearly state “ The same was done for the 1h plasma sample. Both pooled samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively and therefore these chromatograms were only evaluated in a qualitative way.” OCP has interpreted this to mean that for HPLC system 2 only radioactivity was quantified.

RADIOACTIVE RECOVERY

Table 2. Radioactive recovery.

SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 3/94

	Excreted Radioactivity (% of the radioactive dose)					
	Subject 1	Subject 2	Subject 3*	Subject 4	Mean ± SD	Mean ± SD (excluding subject 3)*
Urine	50.7	58.8	37.0*	49.0	48.9 ± 9.0	52.8 ± 5.3
Feces	36.2	37.1	34.8	47.0	38.8 ± 5.6	40.1 ± 6.0
Total	86.9	95.9	71.8	96.0	87.7 ± 11.4	93.0 ± 5.2

a: Due to a technical error (most probably loss of urine between 0-12h) the urine value of subject 3 was lower than of the other 3 subjects.

FDA COMMENT : The table clearly shows the percentage of radioactivity (ie mass balance for asenapine recovered ~90%).

RAW DATA USED FOR PLASMA PROFILES IN FIGURE 1

Table 3. Concentrations of individual peaks in HPLC chromatograms (HPLC system 1) of plasma samples per time point of male human volunteers after sublingual administration of asenapine (Org 5222 plus [¹⁴C]-Org 5222) SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 47/94

Peak no	Mean retention time (minutes)	Peaks (ng equivalents·mL ⁻¹ plasma)									
		Subject 1					Subject 2				
		1.5 h	2.0 h	4.0 h	8.0 h	12.0 h	1.5h	2.0 h	4.0 h	8.0 h	12.0 h
10	38.7	-	-	-	-	-	2.0	-	-	-	-
11	40.8	-	-	6.3	3.5	-	13.2	12.5	10.1	-	-
13	44.8	-	-	2.6	2.9	-	1.9	-	-	-	-
15	47.5	2.2	2.2	-	-	-	2.8	3.1	-	-	-

Peak no	Mean retention time (minutes)	Peaks (ng equivalents·mL ⁻¹ plasma)									
		Subject 3					Subject 4				
		1.5 h	2.0 h	4.0 h	8.0 h	12.0 h	1.5h	2.0 h	4.0 h	8.0 h	12.0 h
10	38.7	-	-	-	-	-	4.5	2.3	-	-	-
11	40.8	7.6	10.7	15.9	10.5	3.4	12.0	11.8	9.3	6.7	-
13	44.8	-	-	-	-	-	3.8	3.0	3.3	-	-
15	47.5	3.8	-	-	-	-	2.1	1.4	3.0	-	-

Peak 10 contains at least the sulfate of the 11-hydroxy of asenapine.

Peak 11 is identified as the quaternary glucuronide of asenapine

Peak 13 is identified as the carbamate glucuronide of N(2)-des-methyl of asenapine

Peak 15 is identified as asenapine

- Not detected

FDA COMMENT: The data in Table 3 is incomplete however the firm has used this data to construct Figure 1 below which is **misleading** since it is composed of the observed values from Table 3 which clearly show that none of the subjects has a complete profile not even for peak # 15 asenapine. They have only connected the dots with the limited data collected. OCP could not locate data that would support the graph past 12 hrs as shown in Table 3. The firm needs to give the location of that data.

REPRESENTATIVE MEAN PLASMA GRAPH HPLC SYSTEM 1

INDIVIDUAL ASSAY HPLC SYSTEM 1 –SOURCE (Module 4.2.2.5, Report INT00003211),PAGE 3/94

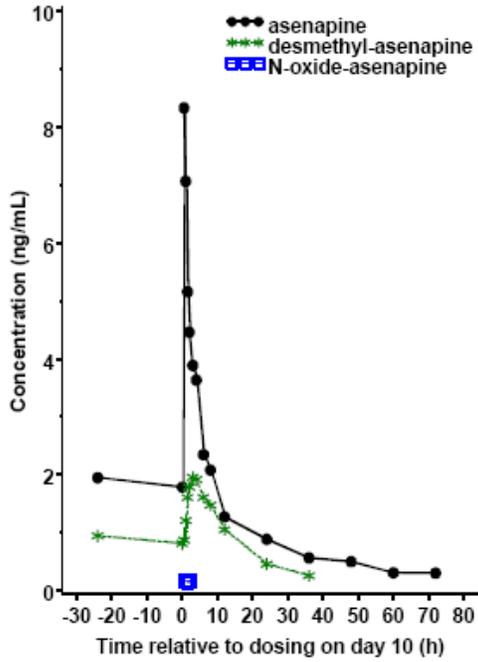
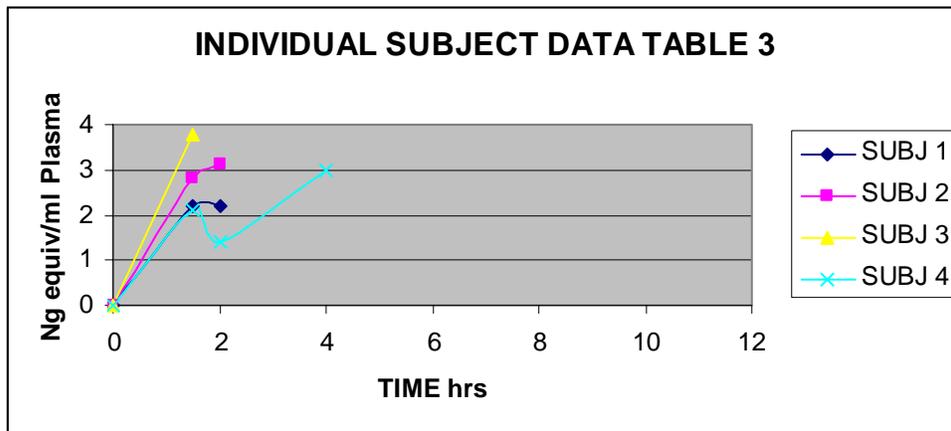


Figure 1. Profile obtained from HPLC system #1.



FDA COMMENT-See comments on Table 3.

TOTAL RADIOACTIVITY IN PLASMA

Figure 2. Profile obtained for total radioactivity. SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 46/94

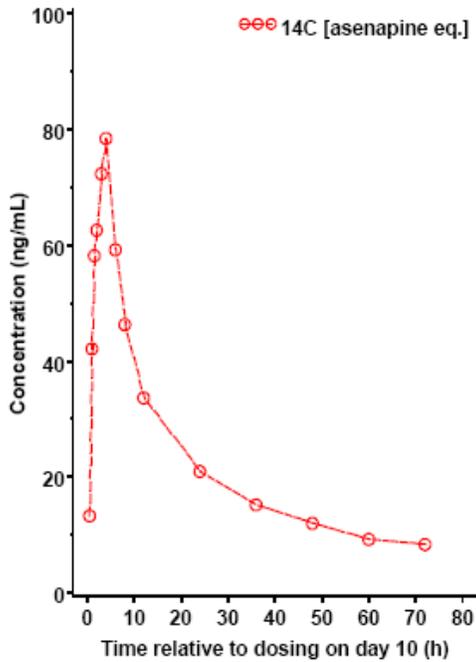


Table 4 Concentration of radioactivity in plasma samples after sublingual administration of asenapine (Org 5222 plus [14C]-Org 5222) to male human volunteers

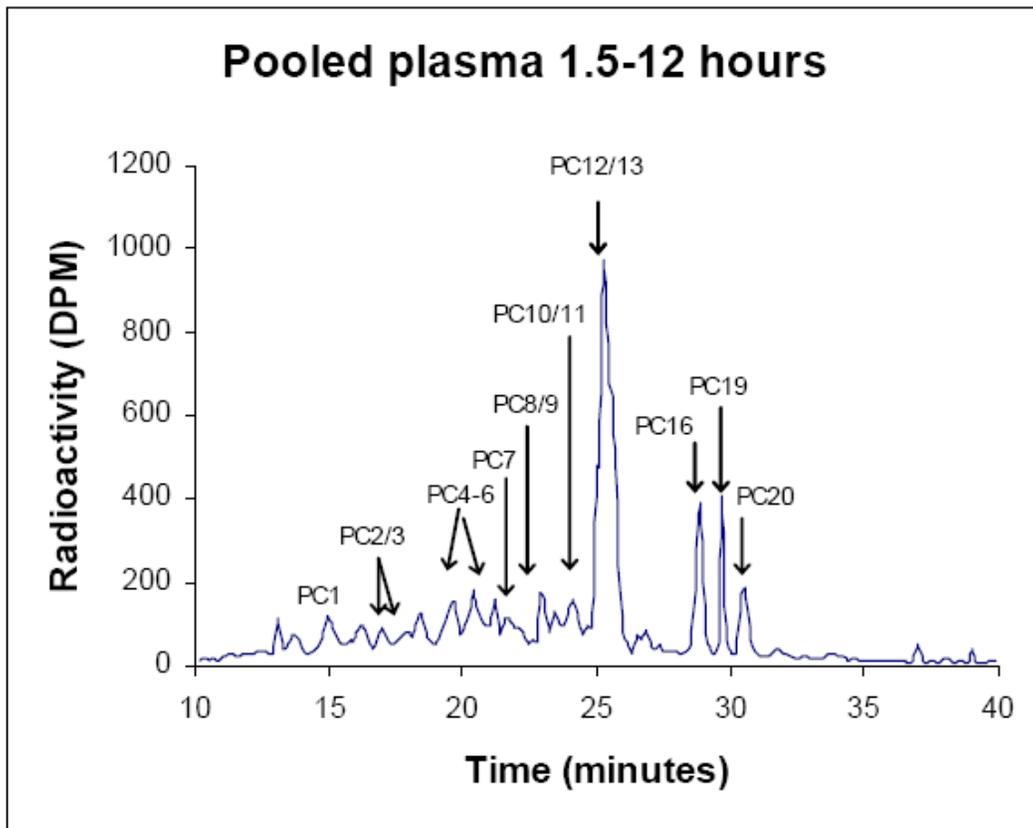
time (h)	Plasma Radioactivity (ng equivalents.mL-1)													
	0.5	1.0	1.5	2.0	3.0	4.0	6.0	8.0	12	24	36	48	60	72
Subject 1	6.68	13.7	23.6	39.8	65.7	69.7	60.5	46.9	36.1	22.9	16.2	10.9	9.01	7.00
Subject 2	19.6	53.6	64.7	64.0	61.7	64.7	43.7	30.9	27.0	16.2	13.0	10.2	7.28	8.35
Subject 3	15.1	45.2	75.3	77.4	84.4	91.4	77.1	62.1	40.9	24.6	18.1	16.2	13.5	11.3
Subject 4	11.7	55.6	69.2	68.8	77.1	87.8	55.4	45.0	30.5	19.9	13.4	10.7	7.03	6.69
Mean	13.3	42.0	58.2	62.5	72.2	78.4	59.2	46.2	33.6	20.9	15.2	12.0	9.2	8.3
SDa	5.5	19.4	23.5	16.1	10.4	13.2	13.9	12.8	6.1	3.7	2.4	2.8	3.0	2.1

a SD = standard deviation

FDA COMMENT : Figure 2 is consistent with the data in Table 4, however this is **only total radioactivity data as a function of time. There is no information on individual metabolites.**

REPRESENTATIVE CHROMATOGRAM

Figure 3. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects. HPLC SYSTEM 2. SOURCE POOLED ASSAY 1.5-12HR SUBMITTED JULY 25 2008



FDA COMMENT : Chromatogram is acceptable to OCP.

**PEAKS IDENTIFIED BASED UPON CHROMATOGRAM IN
FIGURE 3.**

TABLE 5. Metabolites identified in plasma and urine. SUBMITTED BY THE FIRM DATE:
JULY 25 2008 HPLC SYSTEM 2

Peak Number (human)	Identity	Retention time	% radioactivity of run, corrected for noise	Presence verified in at least one preclinical species (excreta or plasma)
PC1	Unknown	15.2	3.6	+
PC2 PC3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylenapine, with the positions of the conjugates 10,11 and reverse	16.6-17.6	5.1	+
PC4-PC6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylenapine; other conjugates (sulfates/glucuronides)	18.5-22.0	13.3	+
PC7	Unknown	22.7	2.7	+
PC8-9	Sulfates and glucuronides	23.3-23.6	5.9	+
PC10 *	11-O-sulfate asenapine;	25.1	[7.4]	+
PC11 *	other sulfates and glucuronides of the N-oxide asenapine	25.6		
PC12 *	N+ glucuronide	26.8	[33.6]	+
PC13 *		27.2		
PC16 *	N-desmethylenapine N-carbamoyl glucuronide	28.7	[6.9]	+
PC19 *	N-desmethylenapine	29.7	[5.1]	+
PC20 *	Asenapine	30.2	[4.3]	+

Sum of plasma metabolites in brackets=57.3%

PEAKS IDENTIFIED BASED UPON CHROMATOGRAM IN FIGURE 3.

TABLE 6. Metabolites identified in plasma and urine. TABLE SUBMITTED BY THE FIRM IN SEPTEMBER 2008 TO MY REQUEST FOR INFORMATION HPLC SYSTEM 2

Peak	Name	% of total radioactivity
PC2/3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylenapine	5.1
PC4-6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylenapine; other conjugates (sulfates/glucuronides)	13.3
PC8-9	Sulfates and glucuronides	5.9
PC10	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide	7.4
PC11	asenapine	
PC12	N+ glucuronide	33.6
PC13		
PC16	N-desmethylenapine N-carbamoyl glucuronide	6.9
PC19	N-desmethylenapine	5.1
PC20	Asenapine	4.3
SUM		81.6

Note: "BOLDED" metabolites have been unequivocally identified.

Please note that the total for those bolded the PC10 and PC 11 have been excluded so the total now becomes 57.3%-7.4%=49.9%. Nonbolded metabolites have not been found in plasma.

FDA COMMENT ON Tables 5-7 and Figure 3. OCP agrees with Figure 3 for the chromatogram. However, the firm changes the metabolites which they believe they can identify between the July and September submissions. In July P10 and P11 were included whereas in September they were excluded. This is very inconsistent and not explained by the firm. Based upon the firms statements related to the performance of HPLC System2, the results are at best semi-quantitative. Summed identifiable material in plasma for AUC 1.5-12h is either 57.3% or 49.9%. Most notable is that neither the 57.3% or 49.9% values is defining a profile only a 1.5 to 12 AUC window for a drug with a half-life of 27 hrs.

PRESENCE OF QUANTIFIED CHROMATOGRAM PEAKS AT SAMPLED TIMES

SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 48/94

Table 7. Peaks found in HPLC chromatograms (HPLC system 2) of the pooled plasma samples of male human volunteers after sublingual administration of asenapine (Org 5222 plus [¹⁴C]-Org 5222)

Peak code	Mean retention time (minutes)	Present yes (+)/no (-)	
		Plasma 1h	Plasma 1.5-12h
^a	16.8	+	-
^a	20.1	+	-
PC10/11	22.4	+	-
^a	23.8	+	-
PC12/13	25.0	+	+
PC16	28.7	+	+
PC19	29.7	-	+
PC20	30.2	+	+

^a No peak code was assigned because the linkage between the plasma, urine and feces metabolite profiles could not be made for these peaks.

PC10/11 is identified as the sulfate of the 11-hydroxy of asenapine plus some other conjugated metabolites (sulfates and glucuronides) of most probably the N(2)-oxide of asenapine.

PC12/13 is identified as the quaternary glucuronide of asenapine.

PC16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine.

Peak PC19 co-elutes with the N(2)-des-methyl of asenapine

Peak PC20 is identified as asenapine

FDA COMMENT-Table 7 shows the level of confusion that exists related to the time profile for asenapine and its metabolites. For example, metabolite PC10/11 is present at 1hr but is not found in the 1.5-12 hr pooled sample. On the other hand PC19 is not present at 1 hr but is present in the pooled sample from 1-5-12 hr. These results are very confusing.

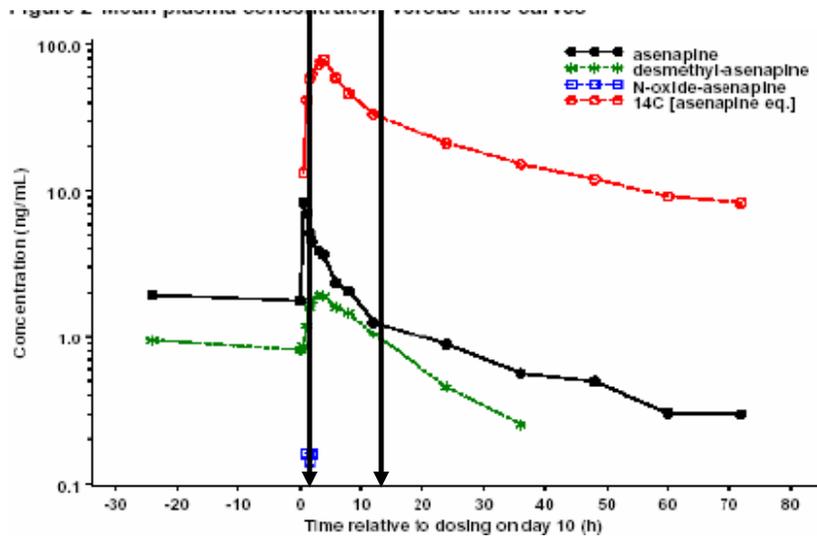


Figure 4.

↓ ↓
 ↓ ↓ 1.5 -12 hrs pooled sampling time for “quantitation” of asenapine and metabolites using HPLC System 2. Source module 5.3.3.1.1 page 56

THE FIRM NEEDS TO REPEAT THE METABOLISM STUDIES WITH A QUANTITATIVE ASSAY AND COLLECT COMPLETE PROFILES.

C:\Data\REVIEWS\NDA\ASENAPINE_NDA22117ORGANON\METABOLITERE V2.doc

APPENDIX:

Results from study 25511 :
 Dose-0.15 mg/BID
 Cmax :0.127 ng/ml on Day 1

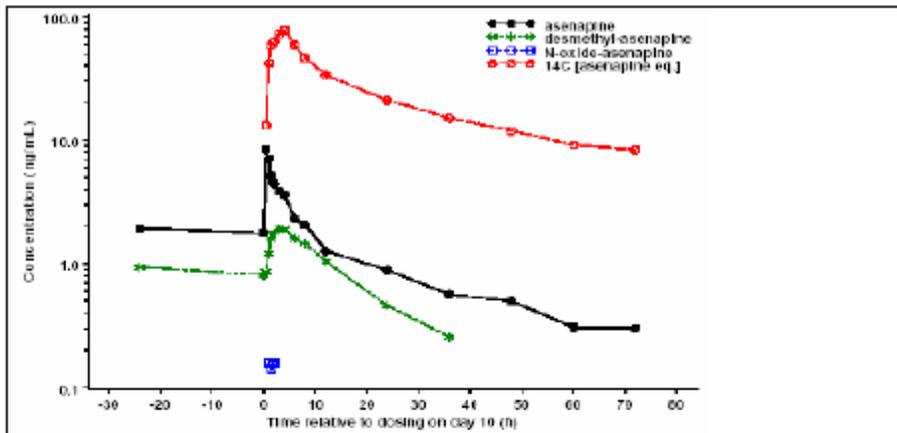
APPENDIX IV: MEAN ORG 5222 PLASMA LEVELS (pg/ml)

Table 1: Mean Org 5222 concentrations (pg/ml) in subjects receiving 150 µg sublingual Org 5222 twice daily for 6.5 days (Block 1)

Day	Protocol Time (h)	Mean	SD	N	ND	NS
1	0	-	-	0	6	0
1	0.083	-	-	0	6	0
1	0.25	32.41	10.32	4	2	0
1	0.5	74.78	22.79	5	1	0
1	0.75	92.86	41.47	6	0	0
1	1	94.08	33.12	6	0	0
1	1.5	127.89	40.81	6	0	0
1	2	94.61	38.00	6	0	0
1	3	89.15	19.68	6	0	0
1	4	71.98	14.66	6	0	0
1	6	49.79	7.20	6	0	0
1	8	32.33	6.32	6	0	0
1	12	23.58	4.99	2	4	0
3	0	41.93	10.11	5	0	1
5	0	48.47	4.32	5	0	1
7	0	44.64	13.83	5	0	1
7	0.083	48.81	15.76	5	0	1
7	0.25	86.88	29.75	5	0	1
7	0.5	134.29	35.89	5	0	1
7	0.75	134.28	42.00	5	0	1
7	1	150.40	57.08	5	0	1
7	1.5	152.62	49.99	5	0	1
7	2	129.30	32.88	5	0	1
7	3	109.48	34.48	5	0	1
7	4	98.97	33.56	5	0	1
7	6	66.17	21.99	5	0	1
7	8	46.50	6.74	5	0	1
7	12	34.42	9.99	5	0	1
8	24	24.54	-	1	4	1
8	36	-	-	0	5	1
9	48	-	-	0	5	1

Study 25532
 Dose-0.27 mg
 Cmax :78 ng/ml on Day 1

[¹⁴C]-labeled asenapine was provided to PBR as an alcohol containing solution. The responsible pharmacist was to drop a volume corresponding to 50 µCi and 0.27 mg asenapine on a 10 mg tablet according to instructions provided by Organon. A test batch was prepared and analyzed prior to the final preparations.



A summary of the main pharmacokinetic parameters is presented in the following table.

Parameter (unit)*	¹⁴ C [asenapine equivalents]	asenapine	desmethyl-asenapine	N-oxide-asenapine
C _{max} (ng/mL)	78.4 (13)	8.40 (3.9)	2.07 (0.76)	0.211 (0.054)
t _{max} (h)	4.0 (1.5-4.0)	0.75 (0.5-1.0)	3.5 (2.0-4.0)	0.75 (0.50-1.50)
t _{1/2} (h)	39.3 (7.6)	27.5 (5.0)	12.9 (4.5)	n.c.
AUC _{0-12h} (ng·h/mL)	n.a.	36.9 (9.7)	17.9 (6.9)	n.c.
AUC _{0-∞} (ng·h/mL)	2020 (467)	n.a.	n.a.	n.a.

Presented are median (minimum-maximum) for t_{max}; arithmetic mean (SD) for other PK parameters.
 *:n=4; n.a.:Not applicable; n.c.:Not calculated.

Statistical analysis showed that plasma levels of asenapine and desmethyl-asenapine had reached steady state on the day of the radioactive dose. The plasma concentrations of ¹⁴C (asenapine equivalents) greatly exceeded those of asenapine and its measured metabolites from the first time point (0.5 h) onwards. The peak concentration of ¹⁴C was reached 4 h after dosing, which is later than for asenapine (0.75 h) and comparable to desmethyl-asenapine (3.5 h). These data indicate that asenapine is metabolized rapidly and that desmethyl- and N-oxide-asenapine constitute only a small fraction of the total of asenapine metabolites in plasma. The mean terminal half-life of plasma radioactivity was 39 h, which is longer than for asenapine (28 h) and desmethyl-asenapine (13 h).

ASSAY

6.4 METABOLITE PROFILES

6.4.1 General

Since the resolution of the obtained metabolite signals of urine and feces samples obtained on HPLC system 1 (Section 3.3.6) was sub-optimal, the integration of the metabolite profiles appeared to be non-conclusive. The resolution on HPLC system 2 (Section 3.3.6) was much better and therefore the metabolite profiles of urine and feces, obtained with HPLC system 2 were used to give quantitative data. Indication of major or minor metabolites is done by visual inspection.

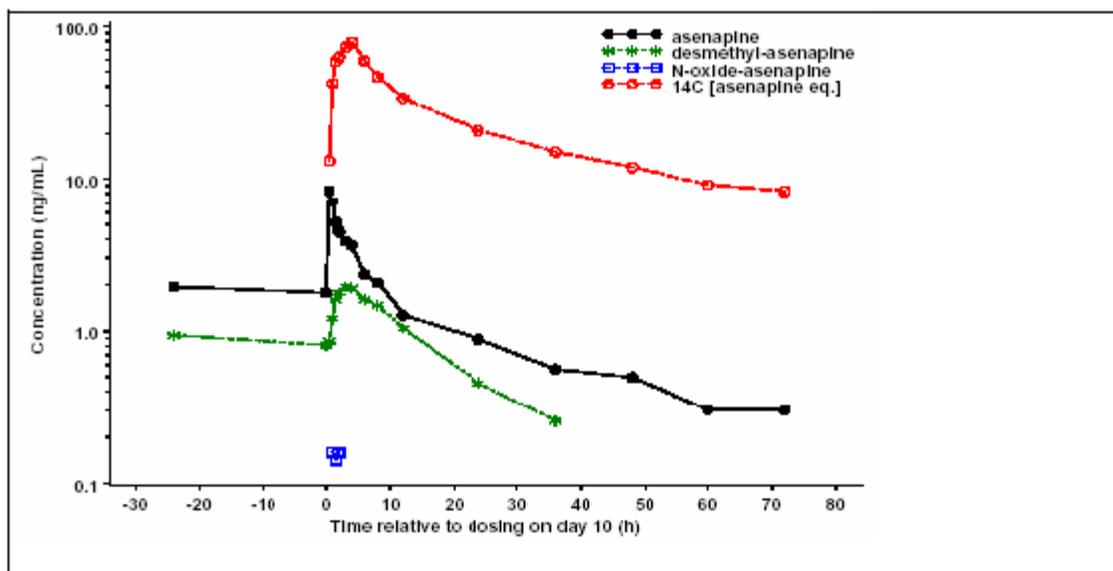
At first plasma samples (1.5-12h) were measured per time point per subject on HPLC system 1. These data are used to give quantitative data. At a later stage the remainder of the plasma samples 1.5-12h of all four subjects was pooled. The same was done for the 1h plasma sample. Both pooled samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively and therefore these chromatograms were only evaluated in a qualitative way.

APPENDIX IV QUESTIONS SENT TO THE FIRM

TITLE- REQUEST OF INFORMATION FROM THE FIRM

I have been reviewing your submission related to the identity of plasma metabolites and I need some clarification.

In the study Clinical Trial Report for study 25532 you produced the following graph which appears in your synopsis page 5 of 612:



A summary of the main pharmacokinetic parameters is presented in the following table.

Parameter (unit) [#]	¹⁴ C [asenapine equivalents]	asenapine	desmethyl-asenapine	N-oxide-asenapine
C _{max} (ng/mL)	78.4 (13)	8.40 (3.9)	2.07 (0.76)	0.211 (0.054)
t _{max} (h)	4.0 (1.5-4.0)	0.75 (0.5-1.0)	3.5 (2.0-4.0)	0.75 (0.50-1.50)
t _{1/2} (h)	39.3 (7.6)	27.5 (5.0)	12.9 (4.5)	n.c.
AUC _{0-12h} (ng·h/mL)	n.a.	36.9 (9.7)	17.9 (6.9)	n.c.
AUC _{0-∞} (ng·h/mL)	2020 (467)	n.a.	n.a.	n.a.

It is not clear to me how this graph was constructed. What I would like to have from you would be an **example calculation** based upon any standard curves and dpm dated employed for all of the species represented. Please start from the raw cpm/dpm data. You can reference any data submitted in the NDA giving its location so that it can be located.

Please give all formulas. Make sure you list whether it is based upon HPLC system 1 or 2. Please base your example only upon C_{max} which would be the same procedures for the area calculation.

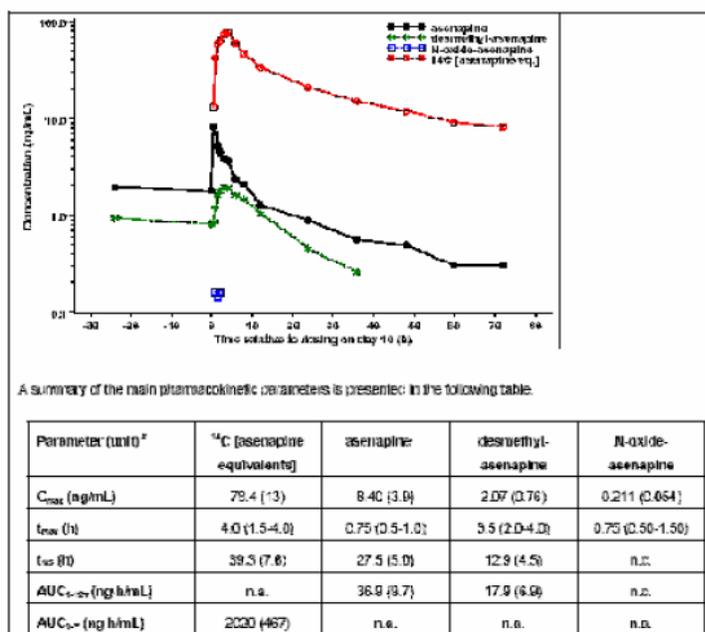
C:\Data\REVIEWS\NDA\ASENAPINE_NDA22117ORGANON\Questiontofirm_9-3-08.doc

APPENDIX V FIRM'S RESPONSE TO OCP QUESTIONS

Comment 1:

I have been reviewing your submission related to the identity of plasma metabolites and I need some clarification.

In the study Clinical Trial Report for study 25532 you produced the following graph which appears in your synopsis page 5 of 612:



It is not clear to me how this graph was constructed. What I would like to have from you would be an **example calculation** based upon any standard curves and dpm dated employed for all of the species represented. Please start from the raw cpm/dpm data. You can reference any data submitted in the NDA giving its location so that it can be located.

Please give all formulas. Make sure you list whether it is based upon HPLC system 1 or 2. Please base your example only upon C_{max} which would be the same procedures for the area calculation.

Response 1:

First, we would like to point out that in the human ADME study different methods have been used for: 1) determination of ¹⁴C in plasma, 2) determination of asenapine, N-desmethyiasenapine and asenapine N-oxide concentrations in plasma and 3) metabolite profiling. Samples for the different assessments were taken at the same time points in each subject (see Module 5.3.3.1, CTR 25532, Table 4, page 32).

The asenapine (black symbols/curve), N-desmethyiasenapine (green symbols/curve) and N-oxide asenapine (blue symbols/curve) plasma concentration data as presented in this graph have been quantified bioanalytically, i.e. by means of LC-MS, as described in the bioanalytical report for this study (Module 5.3.3.1, CTR 25532, Appendix BII-1, page 125), and are not based on radioactivity data. These LC-MS methods are different methods than those used for metabolite profiling (as described in the metabolite profiling report (Module 4.2.2.5, Report INT00003211)), but are the exact same methods as have been applied for the determination of plasma concentrations of these compounds throughout the clinical program for asenapine (Module 2.7.1, Section 2.7.1.1.2.2, page 13).

In other words, the concentration data for the different analytes presented in the above graph are a direct reflection of the bioanalysis results, and no calculations have been performed on them (other than averaging by time point). Further, it should be noted that these 'cold', bioanalytical concentration data reflect the complete multiple dose (10 mg BID) asenapine regimen, whereas the radioactivity data are associated with the final, single ¹⁴C-labeled asenapine dose of 10 mg.

The ¹⁴C total radioactivity data in the above graph (red symbols/curve) are based on liquid scintillation counts of the plasma samples. A calculation has been made on these count data to translate them into 'asenapine equivalents'. This has been done using the specific activity of the administered radiolabeled asenapine, which was 0.08296 ng/dpm. All individual count data (corrected for baseline radiation) were transformed into asenapine equivalent plasma concentrations as follows:

$$C_{\text{asenapine equiv.}} [\text{ng/mL}] = \frac{\text{counts [dpm]}}{\text{aliquot analyzed [mL]}} \cdot \text{specific activity [ng/dpm]}$$

As an example, the calculation of the C_{max} of total radioactivity in asenapine equivalents (concentration at 4 h) for subject 1 is presented below. For reference, see also the table below from the bioanalytical report on ¹⁴C (Module 5.3.3.1, CTR 25532, Appendix BII-2, page 173) with the ¹⁴C data from this particular subject.

$$C_{\text{asenapine equiv.}} = \frac{210 \text{ dpm}}{0.25 \text{ mL}} \cdot 0.08296 \text{ ng/dpm} = 69.7 \text{ ng/mL}$$

Table ^{14}C radioactivity in plasma at individual time points for subject 1 (Trial 25532)

29-Oct-04

ANALYSIS RESULT REPORT - PLASMA ^{14}C -RADIOACTIVITY

Title (short) : [^{14}C]-Asenapine mass balance study
Pharma Bio-Research code : PBR-043723 (Clinical code: PBR-041201)
Sponsor code : 25532
Sponsor : N.V. Organon, The Netherlands

Subject: Number : 01 Initials : NM

Technician(s) : XBo

Conversion factor dpm to ng equivalent : 0.08296

Apparatus: Liquid Scintillation Analyzer (Tri-Carb 3100TR)

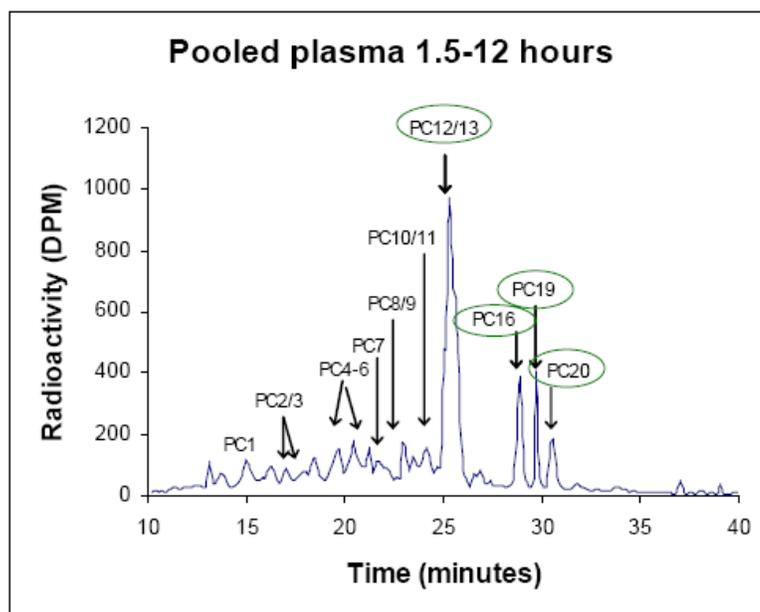
Sample Identification		Analysis Date	Analytical Run Number	Analysed Aliquot (mL)	Background (cpm)	Count Number	^{14}C -Radioactivity			
Sample Number	Scheme Time (h)						Measured Counts ¹⁾ (dpm)	Derived Counts (dpm.mL ⁻¹)	Calculated (Bq.mL ⁻¹)	Calculated (ng eq.mL ⁻¹)
B-4	0.00	31Aug04	AN-01	0.250	3.42	5	1.40	< LLQ	< LLQ	< LLQ
B-5	0.50	31Aug04	AN-01	0.250	3.42	6	20.1	80.6	1.34	6.88
B-6	1.00	31Aug04	AN-01	0.250	3.42	7	41.2	165	2.75	13.7
B-7	1.50	31Aug04	AN-01	0.250	3.42	8	71.2	285	4.75	23.6
B-8	2.00	31Aug04	AN-01	0.250	3.42	9	120	479	7.99	39.8
B-9	3.00	31Aug04	AN-01	0.250	3.42	10	198	792	13.2	65.7
B-10	4.00	31Aug04	AN-01	0.250	3.42	11	210	840	14.0	69.7
B-11	6.00	31Aug04	AN-01	0.250	3.42	12	182	730	12.2	60.5
B-12	8.00	31Aug04	AN-01	0.250	3.42	13	141	566	9.43	46.9
B-13	12.00	31Aug04	AN-01	0.250	3.42	14	109	435	7.25	36.1
B-14	24.00	31Aug04	AN-01	0.250	3.42	15	89.0	276	4.60	22.9
B-15	36.00	31Aug04	AN-01	0.250	3.42	16	49.0	196	3.26	16.2
B-16	48.00	31Aug04	AN-01	0.250	3.42	17	32.9	131	2.19	10.9
B-17	60.00	31Aug04	AN-01	0.250	3.42	18	27.2	109	1.81	9.01
B-18	72.00	31Aug04	AN-01	0.250	3.42	19	21.1	84.3	1.41	7.00

¹⁾ corrected for background radiation

Identity of plasma metabolites (metabolite profiling):

In addition to the quantitative LC-MS bioanalytical measurements of asenapine, N-desmethylenapine and N-oxide asenapine metabolites, qualitative metabolite profiling of a representative pooled (0.5-12 hr) plasma sample was completed. As can be seen from the following figure and table, greater than 80% of the plasma drug-derived radioactivity has been identified in this sample: approximately 50% unequivocally and approximately 30% based upon retention time comparison with urinary metabolite profiling chromatograms.

Figure: Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.



Peak	Name	% of total radioactivity
PC2/3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylenapine	5.1
PC4-6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylenapine; other conjugates (sulfates/glucuronides)	13.3
PC8-9	Sulfates and glucuronides	5.9
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	7.4
PC12 PC13	N+ glucuronide	33.6
PC16	N-desmethylenapine N-carbamoyl glucuronide	6.9
PC19	N-desmethylenapine	5.1
PC20	Asenapine	4.3
SUM		81.6

Note: "Circled" metabolites have been unequivocally identified.

APPENDIX VI :RESPONSE FROM FIRM ON SEPTEMBER 18, 2008 FOR FDA QUESTIONS AND FDA REPLY

TITLE-RESPONSE TO FIRM 9-19-08

1. The representative chromatogram presented for the pooled 1.5-12h plasma sample has several major peaks i.e., PC10/11, PC12, PC13, PC16, PC19, and PC20 which accounts for 57% of the observed AUC (0-72h) based upon the total radioactivity profile presented in Module 4.2.2.5.1, Report INT00003211, page 57/94. We would like to know what percent of the total radioactivity in plasma is represented by the other peaks in the chromatogram. Do the peaks account for 43% of the AUC?

Firm Response:

No, the linking between the radioactive profile and the AUC(0-72h) is not valid. The above mentioned peaks in the pooled plasma (1.5-12 hr) metabolite profile, (PC10/11, PC12, PC13, PC16, PC19 and PC20) collectively account for 57% of the total chromatographic radioactivity detected within this sample rather than the observed AUC(0-72h).

FDA RESPONSE A-

I don't quite understand their point but it is not essential to the other problems presented by the data.

Firm Response:

Additional characterization, totaling 25% (PC2/3, PC4-6, PC8-9) of the total chromatographic radioactivity, was accomplished and is described below. The remaining radioactivity is unknown and represents multiple compounds throughout the 0-40 min run time chromatogram.

Figure: Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.

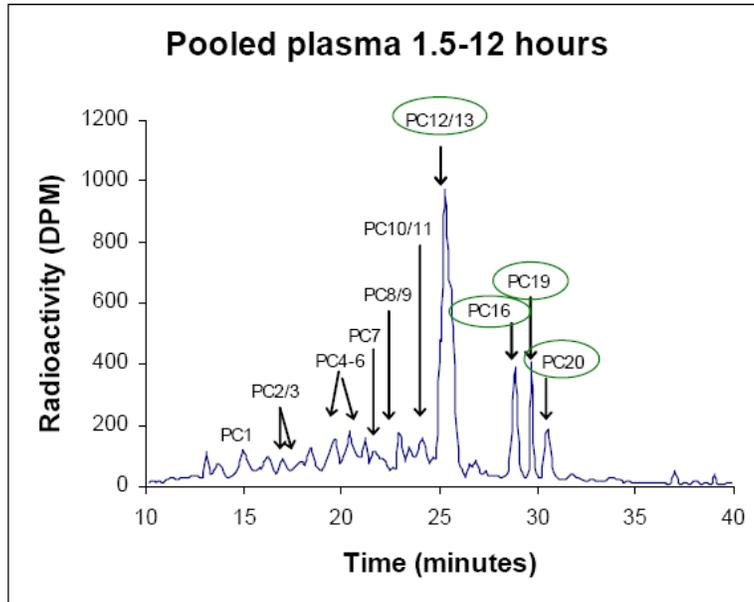


Table 1: Summary of Radioactive peaks found in human plasma and urine after sublingual administration of asenapine (Org 5222 plus [¹⁴C]-Org 5222) to male volunteers.

Peak Number (human)	Identity	Retention time	% radioactivity of run, corrected for noise	Presence verified in at least one preclinical species (excreta or plasma)
PC1	Unknown	15.2	3.6	+
PC2 PC3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylenapine, with the positions of the conjugates 10,11 and reverse.	16.6-17.6	5.1	+
PC4-PC6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylenapine; other conjugates (sulfates/glucuronides)	18.5-22.0	13.3	+
PC7	Unknown	22.7	2.7	+
PC8-9	Sulfates and glucuronides	23.3-23.6	5.9	+
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	25.1 25.6	7.4	+
PC12 PC13	N+ glucuronide	26.8 27.2	33.6	+
PC16	N-desmethylenapine N-carbamoyl glucuronide	28.7	6.9	+
PC19	N-desmethylenapine	29.7	5.1	+
PC20	Asenapine	30.2	4.3	+

FDA RESPONSE B-

This response was interpreted to mean that for the pooled 1.5-12 h chromatogram that an additional 25% of the total chromatographic radioactivity could be described by (PC2/3, PC4-6, PC8-9). The only point of concern was that the firm's statement "of the total chromatographic radioactivity" **did not** refer specifically to the pooled 1.5-12 h chromatogram. However that was the inference taken by FDA. If they are referring to the pooled 1.5-12 h chromatogram then the total per cent in the sample quantified is 57% + 25% = 82% which is a good quantitation.

2. A Table was presented in Module 4.2.2.5 Report INT00003211, page 48/94 which shows if a peak was present or absent at 1h or in the 1.5-12h pooled sample. We would like for you to explain why these peaks at 1 h were not quantified since they do appear in the 1h chromatogram in Module 4.2.2.5.1, Report INT00003211, page 57/94. A quantitative profile for the 1 hr sample as was provided for the 1.5 - 12 h pooled sample would be helpful.

Table 7 SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 48/94
Table 7. Peaks found in HPLC chromatograms (HPLC system 2) of the pooled plasma samples of male human volunteers after sublingual administration of asenapine (Org 5222 plus [¹⁴C]-Org 5222)

Peak code	Mean retention time (minutes)	Present yes (+)/no (-)	
		Plasma 1h	Plasma 1.5-12h
*	16.8	+	-
*	20.1	+	-
PC10/11	22.4	+	-
*	23.8	+	-
PC12/13	25.0	+	+
PC16	28.7	+	+
PC19	29.7	-	+
PC20	30.2	+	+

* No peak code was assigned because the linkage between the plasma, urine and feces metabolite profiles could not be made for these peaks.

PC10/11 is identified as the sulfate of the 11-hydroxy of asenapine plus some other conjugated metabolites (sulfates and glucuronides) of most probably the N(2)-oxide of asenapine.

PC12/13 is identified as the quaternary glucuronide of asenapine.

PC16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine.

Peak PC19 co-elutes with the N(2)-des-methyl of asenapine

Peak PC20 is identified as asenapine

Firm Response:

The three peaks observed at retention time 16.8 min, 20.1 min and 23.8 min in the 1 hr pooled plasma metabolite profile sample could not be identified or characterized by LC-MS. Therefore, no additional analysis of these peaks was completed, including quantification.

FDA RESPONSE

This is **not** consistent with the statement from #1, “Additional characterization, totaling 25% (PC2/3, PC4-6, PC8-9) of the total chromatographic radioactivity, was accomplished and is described below”. The peaks can not total 25% if they could not be analyzed nor quantified. The firm needs to explain this inconsistency in their description

of the quantitation of these peaks and if “characterization” means quantitation or something else?

Firm Response:

All other identified peaks in the 1 hr sample were observed in the corresponding pooled (1.5-12hr) plasma sample as well as additional drug-derived metabolites which were identified or characterized by comparison to urine and fecal metabolite profiles.

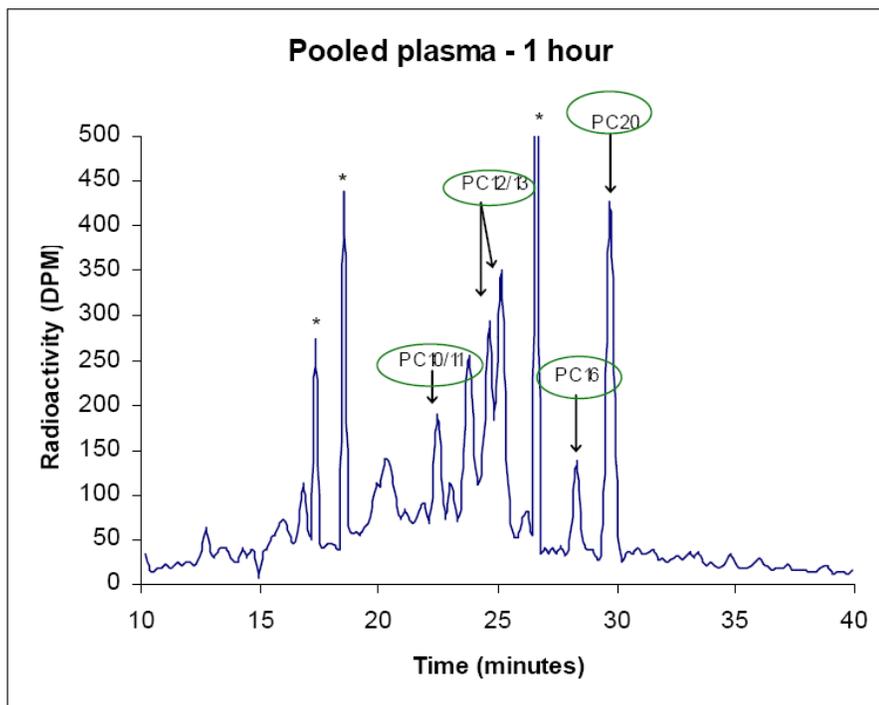
FDA RESPONSE

This statement is okay but there was peak PC 19 which was not seen at 1h but present in the 1.5-12h pooled sample. The firm should address this discrepancy since they stated, “All other identified peaks in the 1 hr sample were observed in the corresponding pooled (1.5-12hr) plasma sample.” OCP does not want to consider urine and feces at this time.

Firm Response:

Figure 1, below shows the radiochromatographic profile of pooled 1 hr plasma and the percent of total chromatographic radioactivity of the peaks detected.

Figure 1. Radiochromatographic profile of a pooled (1 hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.



Peak nr	Name	% of Total Chromatographic radioactivity
RT=16.8	Unknown	3.3
RT=20.1	Unknown	9.5
RT=23.8	Unknown	8.0
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	5.7
PC12 PC13	N+ glucuronide	17.7
PC16	N-desmethyiasenapine N-carbamoyl glucuronide	3.6
PC20	Asenapine	10.8
SUM		58.6

Prominent radioactive spikes identified with an asterisk in the 1 hr pooled plasma sample are artifactual peaks and are not related to asenapine based upon LCMS analysis of the fractions. These appeared during solid scintillation counting used for measuring radioactivity in the plasma fractions and are thus not relevant.

FDA RESPONSE

The table shows that you have quantified 37.8% of the metabolites at 1h. However, you can not use the RT 16.8 , RT 20.1 and RT 23.8 peaks for your total since it was pointed out previously that this is not consistent with Table 7 above. You have stated, with a subscripted 'a' " No peak code was assigned because the linkage between the plasma, urine and feces metabolite profiles could not be made for these peaks." The firm needs to explain this statement.

3. We would like you to provide information specifying that the metabolites quantified in the 1.5-12 h pooled sample is representative/quantitative for the (0-1 h) and (12-72 h) time intervals (i.e. not sampled).

Response:

We believe that the 1.5-12 hr pooled plasma is most representative of the plasma metabolic profile because it encompasses the greatest, feasible time interval of samples with sufficient radioactivity concentrations to allow metabolite profiling. Because only low levels of radioactivity were detected in plasma at 24, 36, 48, 60 and 72 hr post-dose, plasma obtained from these timepoints was not included in the pooled sample to minimize any dilution of the radioactivity signal. The 1.5 - 12 hr sample represents the most technically feasible and representative plasma metabolite profile.

FDA RESPONSE

OCP agrees with this response.

Response:

All identified peaks in the 1 hr sample were observed in the corresponding pooled (1.5-12hr) plasma sample as well as additional drug-derived metabolites which were identified or characterized. Because the 1.5-12 hr pooled plasma metabolite profile was determined using the remaining plasma volumes (i.e. 79 mL, not necessarily equal volumes from each subject at each timepoint contributed to the pooled sample), a direct quantitative comparison to the 1 hr plasma metabolite profile is not appropriate. Also, because of the low levels of radioactivity in the plasma after 12 hr, neither a qualitative or quantitative assessment was possible.

FDA RESPONSE

The firm's Table 9-5 Module 4.2.2.5 page 48/94 (i.e., Table 7 above) clearly refutes this statement. Peaks at retention times of 16.8 min, 20.1 min and 23.8 min have 'plus' signs at 1h but 'minus' signs at 1.5-12h meaning that they were not present. Furthermore the firm has labeled a superscript 'a' meaning ,” No peak code was assigned because the linkage between the plasma, urine and feces metabolite profiles could not be made for these peaks. This statement is clearly contradictory to the firm's response and should be clarified by the firm.

C:\Data\REVIEWS\NDA\ASENAPINE_NDA22117ORGANON\RESTOFIRM_9-19-08.doc

APPENDIX VII: INFORMATION PRESENTED AT INTERNAL FDA MEETING

ON 9-15-08

TOTAL RADIOACTIVITY IN PLASMA

Figure 1. Profile obtained for total radioactivity. SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 46/94

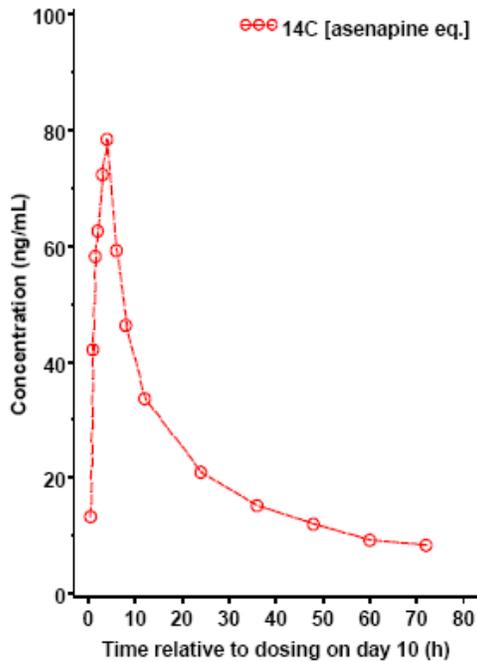


Table 1 Concentration of radioactivity in plasma samples after sublingual administration of asenapine (Org 5222 plus [14C]-Org 5222) to male human volunteers

time (h)	Plasma Radioactivity (ng equivalents.mL-1)													
	0.5	1.0	1.5	2.0	3.0	4.0	6.0	8.0	12	24	36	48	60	72
Subject 1	6.68	13.7	23.6	39.8	65.7	69.7	60.5	46.9	36.1	22.9	16.2	10.9	9.01	7.00
Subject 2	19.6	53.6	64.7	64.0	61.7	64.7	43.7	30.9	27.0	16.2	13.0	10.2	7.28	8.35
Subject 3	15.1	45.2	75.3	77.4	84.4	91.4	77.1	62.1	40.9	24.6	18.1	16.2	13.5	11.3
Subject 4	11.7	55.6	69.2	68.8	77.1	87.8	55.4	45.0	30.5	19.9	13.4	10.7	7.03	6.69
Mean	13.3	42.0	58.2	62.5	72.2	78.4	59.2	46.2	33.6	20.9	15.2	12.0	9.2	8.3

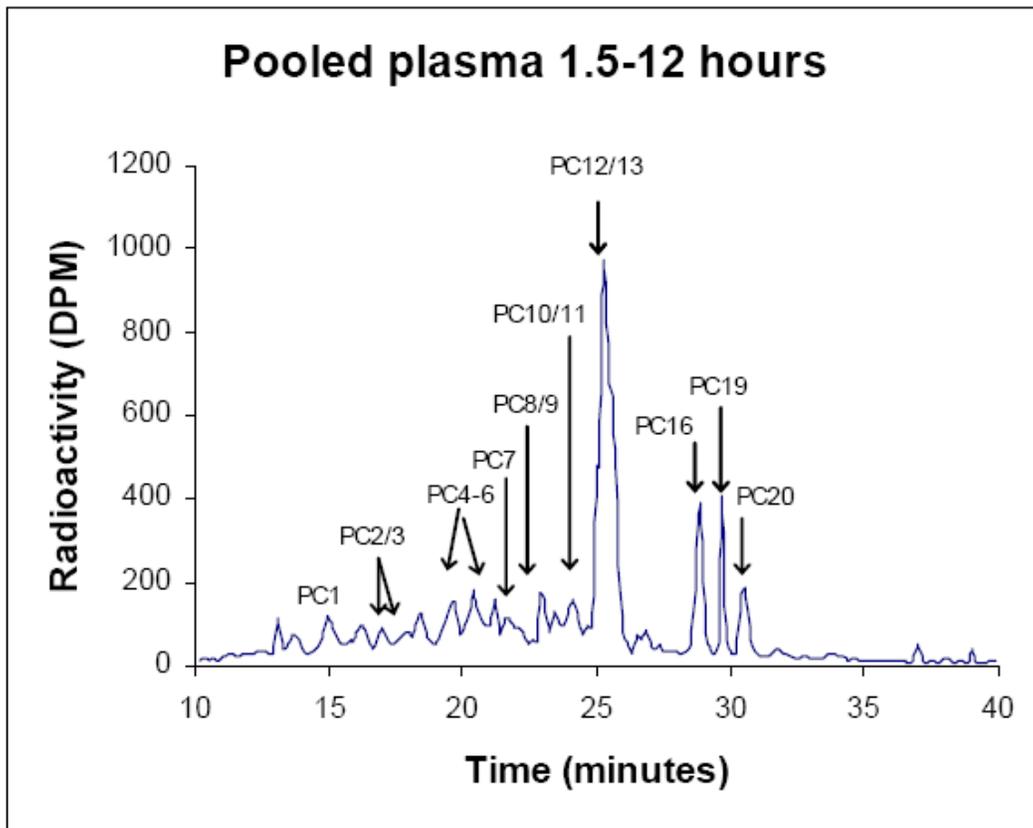
SDa	5.5	19.4	23.5	16.1	10.4	13.2	13.9	12.8	6.1	3.7	2.4	2.8	3.0	2.1
-----	-----	------	------	------	------	------	------	------	-----	-----	-----	-----	-----	-----

a SD = standard deviation

FDA COMMENT : Figure 1 is consistent with the data in Table 1, however this is **only total radioactivity data as a function of time. There is no information on individual metabolites.**

REPRESENTATIVE CHROMATOGRAM

Figure 2. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects. HPLC SYSTEM 2. SOURCE POOLED ASSAY 1.5-12HR SUBMITTED JULY 25 2008



FDA COMMENT : Chromatogram is acceptable to OCP.

**PEAKS IDENTIFIED BASED UPON CHROMATOGRAM IN
FIGURE 2.**

TABLE 2. Metabolites identified in plasma and urine. SUBMITTED BY THE FIRM DATE:
JULY 25 2008 HPLC SYSTEM 2

Peak Number (human)	Identity	Retention time	% radioactivity of run, corrected for noise	Presence verified in at least one preclinical species (excreta or plasma)
PC1	Unknown	15.2	3.6	+
PC2 PC3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylenapine, with the positions of the conjugates 10,11 and reverse	16.6-17.6	5.1	+
PC4-PC6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylenapine; other conjugates (sulfates/glucuronides)	18.5-22.0	13.3	+
PC7	Unknown	22.7	2.7	+
PC8-9	Sulfates and glucuronides	23.3-23.6	5.9	+
PC10 *	11-O-sulfate asenapine;	25.1	[7.4]	+
PC11 *	other sulfates and glucuronides of the N-oxide asenapine	25.6		
PC12 *	N+ glucuronide	26.8	[33.6]	+
PC13 *		27.2		
PC16 *	N-desmethylenapine N-carbamoyl glucuronide	28.7	[6.9]	+
PC19 *	N-desmethylenapine	29.7	[5.1]	+
PC20 *	Asenapine	30.2	[4.3]	+

Sum of plasma metabolites in brackets=57.3%

PEAKS IDENTIFIED BASED UPON CHROMATOGRAM IN FIGURE 2.

TABLE 3. Metabolites identified in plasma and urine. TABLE SUBMITTED BY THE FIRM IN SEPTEMBER 2008 TO MY REQUEST FOR INFORMATION HPLC SYSTEM 2

Peak	Name	% of total radioactivity
PC2/3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylenapine	5.1
PC4-6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylenapine; other conjugates (sulfates/glucuronides)	13.3
PC8-9	Sulfates and glucuronides	5.9
PC10	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide	7.4
PC11	asenapine	
PC12	N+ glucuronide	33.6
PC13		
PC16	N-desmethylenapine N-carbamoyl glucuronide	6.9
PC19	N-desmethylenapine	5.1
PC20	Asenapine	4.3
SUM		81.6

Note: "BOLDED" metabolites have been unequivocally identified.

Please note that the total for those bolded the PC10 and PC 11 have been excluded so the total now becomes 57.3%-7.4%=49.9%. Nonbolded metabolites have not been found in plasma.

FDA COMMENT ON Tables 2-3 and Figure 2. OCP agrees with Figure 2 for the chromatogram. However, the firm changes the metabolites which they believe they can identify between the July and September submissions. In July P10 and P11 were included whereas in September they were excluded. This is very inconsistent and not explained by the firm. Based upon the firms statements related to the performance of HPLC System2, the results are at best semi-quantitative. The total sum of identifiable material in plasma for AUC 1.5-12h is either 57.3% or 49.9%. Most notable is that neither the 57.3% or 49.9% values is defining a profile only a 1.5 to 12 AUC window for a drug with a half-life of 27 hrs.

Table 4. FRACTION OF TOTAL AUC(0-72h) REPRESENTED BY AUC 1.5-12 h FOR EACH SUBJECT.

SUBJECT	AUC(0-72h) ng/mlxh	AUC(1.5-12h) ng/mlxhr	$\frac{\text{AUC}(1.5-12\text{H})}{\text{AUC}(0-72\text{h})}$
1	1522.71	893.9	0.58
2	1282.06	716.22	0.55
3	1951.65	1113.67	0.57
4	1470.95	886.9	0.60
MEAN	1556.84	902.67	0.57

Table 5. OBSERVED METABOLITES IN THE 1.5-12 h POOLED PLASMA SAMPLE

OBSERVED METABOLITES	OBSERVED FRACTION IN POOLED 1.5-12h SAMPLE	OBSERVED FRACTION x MEAN RATIO OF $\frac{\text{AUC}(1.5-12\text{H})}{\text{AUC}(0-72\text{h})} = \mathbf{0.57}$	PER CENT OF OBSERVED FRACTION IN AUC(0-72h)
PC10	0.074	0.042	4.29
PC12	0.333	0.19	19.30
PC16	0.069	0.04	4.00
PC19	0.051	0.029	2.95
PC20	0.043	0.024	2.49
TOTAL PER CENT OF METABOLITES IN THE 1.5-12h POOLED SAMPLE RELATIVE TO THE TOTAL AMOUNT OF AUC (0-72 h)			33.04

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APPENDIX VIII-FIRM'S FINAL RESPONSE AND DATA SUMMARY



CONFIDENTIAL

September 23, 2008

Electronic Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA No. 22-117
Asenapine Sublingual Tablets
Serial No. 0038
**SUMMARY OF ASENAPINE METABOLITE PROFILE AS
DISCUSSED ON SEPTEMBER 19, 2008**

Dear Sir or Madam:

Reference is made to the New Drug Application No. 22-117 for Asenapine Sublingual Tablets received on August 31, 2007. References are also made to our submissions dated June 13, 2008 (Serial No. 0027), July 25, 2008 (Serial No. 0031), September 4, 2008 (Serial No. 0034), September 11, 2008 (Serial No. 0035), September 15, 2008 (Serial No. 0036), and September 18, 2008 (Serial No. 0037).

Lastly, reference is made to the teleconference that was held with the Division of Psychiatry Products on Friday, September 19, 2008, to discuss the asenapine metabolite profile. At the conclusion of the teleconference, Dr. Laughren asked that we submit a summary of the discussion. Our summary is enclosed. The key points are below.

The metabolism of asenapine was studied in healthy volunteers using state-of-the-art LC-MS, LC-MS/MS and liquid scintillation techniques.

- This is an extensively metabolized drug with well over 40 metabolites (most of which are polar conjugates) observed in plasma, urine and feces.
- The drug metabolism data presented in the NDA are typical of the state of the art for a drug with this extensive metabolite profile.
- The extensive metabolism of asenapine resulted in a complex metabolic profile with analytical challenges.
- Analytical limitations and extensive metabolism have precluded complete characterization of plasma samples beyond 12 hours.
- In terms of plasma metabolite profiling specifically, we have characterized ~ 80% of circulating drug-derived radioactivity in the 1.5 - 12 hour time period.

This submission is being provided in electronic format. The electronic files are supplied on one [1] CD-ROM and the submission has been checked for viruses during the creation using Symantec Netbackup Version 5.1 Windows Servers and found to be virus free.

Summary of Asenapine metabolism as discussed during September 19, 2008 teleconference:

The metabolism of asenapine was studied in healthy volunteers using state-of-the-art LC-MS, LC-MS/MS and liquid scintillation techniques.

- This is an extensively metabolized drug with well over 40 metabolites (most of which are polar conjugates) observed in plasma, urine and feces.
- The drug metabolism data presented in the NDA are typical of the state of the art for a drug with this extensive metabolite profile.
- The extensive metabolism of asenapine resulted in a complex metabolic profile with analytical challenges.
- Analytical limitations and extensive metabolism have precluded complete characterization of plasma samples beyond 12 hours.
- In terms of plasma metabolite profiling specifically, we have characterized ~ 80% of circulating drug-derived radioactivity in the 1.5 - 12 hour time period.

The 1.5-12 hr pooled plasma sample is the most representative profile of total exposure to plasma metabolites and asenapine.

Ideally, the metabolite profile would be obtained using pooled plasma samples from 0 to 72 hr. However, because mean plasma radioactivity concentrations at 24 hr were low (approximately 20 ng eq/mL) and decreased to approximately 8 ng eq/mL by 72 hr, metabolite profiling was not technically feasible after 12 hr and arguably not important to the overall metabolite profiles.

The most representative profile of total exposure to plasma metabolites and unchanged drug comes from a pooled (1.5-12 hr) plasma sample. The majority of the metabolites in this pooled sample remained above the detection limits for radioactivity which was necessary to provide quantitative estimates. Adding plasma from beyond 12 hr would have significantly diluted the sample and limited the ability to obtain a meaningful radiochromatographic profile. The 1.5 to 12 hr pooled plasma sample was obtained by combining the remaining, available plasma from all subjects at all time points and did not contain an equal contribution from each subject and necessarily every time point. This rigorous attempt to profile low levels of circulating metabolites was qualitatively successful; but only feasible for the 1.5-12 hr pooled sample.

By comparison, the 1 hr metabolite profile provided limited information presumably because sampling was too early and the plasma concentrations of some metabolites may not have reached the detection limits of the radioactivity profiling method.

Asenapine is extensively metabolized and its metabolites have been well characterized using LC-MS or by retention time comparisons.

Greater than 80% of the total chromatographic radioactivity in the 1.5-12 hr pooled plasma metabolite profile has been characterized. Metabolites representing about 50% of the profiled radioactivity were unequivocally (MS and NMR) identified and those representing another 31.7% of the chromatographic radioactivity were characterized by retention time comparisons. No one peak corresponds to more than 6% of the plasma radiocarbon profile in the remaining 18.3% of the radiochromatogram.

Referring to the radiochromatogram (Figure 1), it can be seen that asenapine (PC20) is extensively metabolized. The unequivocally identified peaks in the 1.5-12 hr radiochromatogram are shown in Table 1.

Table 1: Asenapine metabolites unequivocally identified in a pooled (1.5 – 12hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.

Metabolite Designation	% of radioactivity in chromatogram*	Unequivocally identified in plasma by**
PC12/13: Asenapine N+glucuronide	33.6	LC-ES-MS
PC16: N-desmethylenapine N-carbamoyl glucuronide	6.9	LC-ES-MS
PC19: N-desmethylenapine	5.1	LC-ES-MS
PC20: asenapine	4.3	LC-ES-MS
SUM of the total chromatographic radioactivity	49.9	

Most of the remaining chromatographic radioactivity which elutes between 13 and 25 min (Figure 1), corresponds to at least 15 different peaks (multiple metabolites coeluting within peaks observed within the radiochromatogram), none of which represents more than 6% of the plasma radioactivity profile. Most of these peaks have a discernible mass ion and have been, at a minimum, partially characterized by LC-MS. These peaks of interest are detailed in Table 2 and tabulated below:

Table 2: Asenapine metabolites characterized or partially characterized in a pooled (1.5 – 12hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.

Metabolite Designation	% of radioactivity in chromatogram*	Identified by retention time comparison **
PC2/3: Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylenapine	5.1	LC-ES-MS and deconjugation in urine fractions
PC4-6: Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylenapine; other conjugates (sulfates/glucuronides)	13.3	LC-ES-MS and deconjugation in urine fractions
PC8-9: Sulfates and glucuronides	5.9	LC-ES-MS in urine fractions
PC10/11: 11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	7.4	LC-ES-MS in urine fractions
SUM of the total chromatographic radioactivity	31.7	

*: data provided in Serial No. 0031

**: data provided in Report INT0003211

It was not possible to simultaneously obtain mass spectral data from the pooled 1.5 to 12 hr plasma sample. Nonetheless, by analyzing urine with the same LC-MS method as was used for plasma, retention time comparisons were made between known urine metabolites and plasma radioactivity peaks. Using these comparisons, it was determined that most of the radioactive peaks eluting before PC12/13 consisted of more than 3 metabolites. In total, this resulted in the characterization of more than 40 different asenapine metabolites in biological matrices.

In the 1-hr pooled plasma metabolite profile (Figure 2), approximately 32.1% of the circulating radioactivity has been identified unequivocally. The unequivocally identified peaks in the 1-hr radiochromatogram are shown in Table 3.

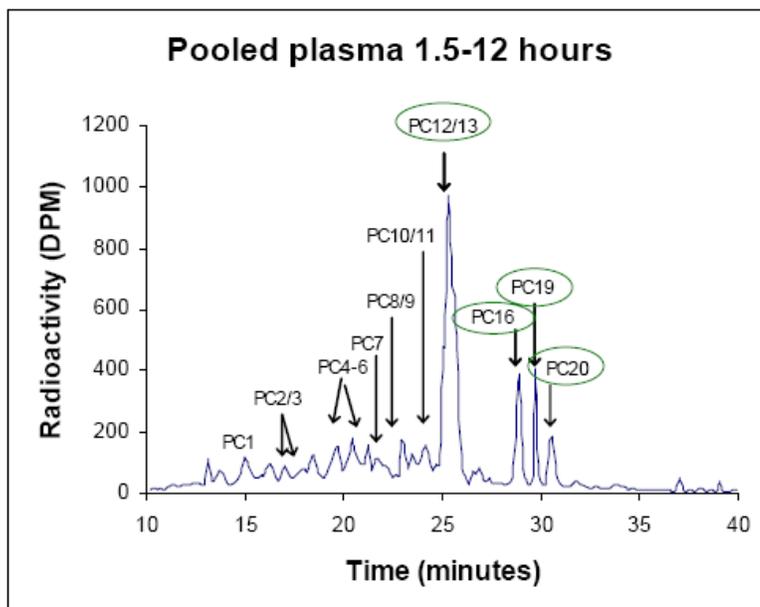
Table 3: Asenapine metabolites unequivocally identified in a pooled (1-hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.

Metabolite Designation	% of radioactivity in chromatogram*	Unequivocally identified in plasma by**
PC 12/13: Asenapine N+glucuronide	17.7	LC-ES-MS
PC16: N-desmethyiasenapine N-carbamoyl glucuronide	3.6	LC-ES-MS
PC20: asenapine	10.8	LC-ES-MS
SUM of the total radiochromatographic radioactivity	32.1	

PC10/11 (5.7%) has been partially identified with LC-ES-MS in this 1-hr pooled plasma sample. Also, three peaks were detected which could not be identified by mass spectrometry (at retention times 16.8, 20.1 and 23.8 min) and can only be quantified based upon their contribution to the total chromatographic radioactivity. These peaks were not obvious in the 1.5 to 12 hr pooled plasma sample (and hence were indicated as not present in Table 9-5, page 48/94 of Report INT00003211) possibly due to dilution, or alternatively, they may also represent rapidly cleared metabolites. It should also be noted that PC 19 (N-desmethyiasenapine) was not detected as a distinct peak in the 1-hr pooled plasma sample. Its presence was measured directly using a validated LC-MS/MS assay where Tmax ranged between 2 and 4 hours. It is probable that the plasma concentration of this metabolite at 1 hr post-dose was not yet above the detection limit for the radioactivity profiling method.

The metabolism data are described in Report INT00003211, except for quantification of the contribution of each peak to the overall radioactivity in the 1-hr and 1.5-12 hr pooled plasma samples, which was submitted to NDA 22-117 on September 18, 2008 (Serial No. 0037) and July 25, 2008 (Serial No. 0031), respectively.

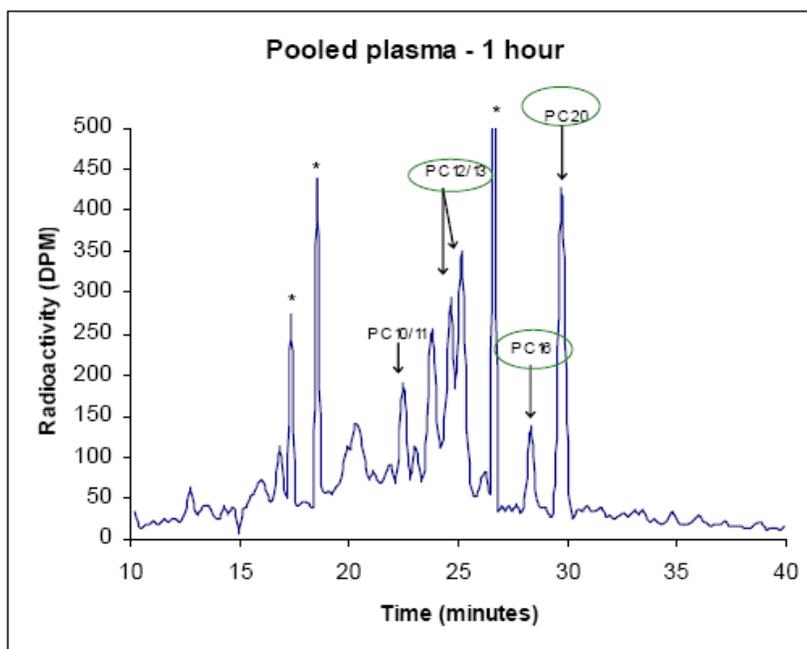
Figure 1. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.



Peak nr	Metabolite Designation	% of Total Chromatographic radioactivity
PC2/3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylenapine	5.1
PC4-6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylenapine; other conjugates (sulfates/glucuronides)	13.3
PC8-9	Sulfates and glucuronides	5.9
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	7.4
PC12 PC13	Asenapine N+ glucuronide	33.6
PC16	N-desmethylenapine N-carbamoyl glucuronide	6.9
PC19	N-desmethylenapine	5.1
PC20	Asenapine	4.3
SUM		81.6

- >80% of the radioactivity known: 50% unequivocally (○), 30% based on RT comparison with urinary compounds as analyzed using NMR and LCMSMS.

Figure 2. Radiochromatographic profile of a pooled (1 hr) plasma sample following administration of ¹⁴C-asenapine to 4 healthy male subjects.



Peak nr	Metabolite Designation	% of Total Chromatographic radioactivity
RT=16.8	Unknown	3.3
RT=20.1	Unknown	9.5
RT=23.8	Unknown	8.0
PC10	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	5.7
PC11		
PC12 PC13	Asenapine N+ glucuronide	17.7
PC16	N-desmethylenapine N-carbamoyl glucuronide	3.6
PC20	Asenapine	10.8
SUM		58.6

* = artifactual peak not related to asenapine based upon LC-MS analysis of the fraction
 RT = HPLC retention time in minutes

Asenapine is extensively metabolized and the metabolism has been well characterized using plasma, urine and feces samples.

A majority of the circulating drug-derived radioactivity has been characterized or at a minimum partially characterized. Most of the drug-derived material in human plasma following sublingual administration of asenapine is associated with polar, conjugated metabolites.

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

/s/

Andre Jackson
9/30/2008 10:18:44 AM
BIOPHARMACEUTICS

Raman Baweja
9/30/2008 01:37:33 PM
BIOPHARMACEUTICS

**NDA Review - Asenapine
OCP Review Amendment # 2
(Memo to File)**

NDA:	22-117				
Type of Submission:	Original NDA				
Submission Date:	August 30, 2007				
Associated INDs:	51,641	September 30, 1996	(Treatment of Psychosis)		
	70,329	August 3, 2004	(Treatment of Acute Mania in Bipolar I)		
Generic Name:	Asenapine Maleate				
Formulation:	Sublingual Tablets				
Strengths:	5 mg, 10 mg				
Route:	Sublingual (N.B. Route is mislabeled in Application Form 356h)				
Brand Name:	Sycrest®				
Sponsor:	Organon / Schering-Plough				
Additional Submissions and Dates since Original OCP Review Completed:	SN	Date	Code	Descriptor	Contents
	025	5-14-08	BM	Minor Amendment - Medical	Response to April 21 st Request for Neutropenia & Ganulocytopenia Cases
	026	5-21-08	BC	Minor Amendment - Labeling	Response to DMETS question (May 13, 2008)
	027	6-13-08	BB	Minor Amendment – OCP	Asenapine Metabolite Profile
	028	6-20-08	BL	Minor Amendment - Labeling	Response to June 16, 2008 Carton, Container, Blister and Label Comments
	029	6-20-08	BM	Minor Amendment - Medical	Response to June 17, 2008 Information Request
	030	6-23-08	BC	Minor Amendment – Chemistry	Response to Telephone Request from Office of New Drug Quality Assessment (June 19, 2008)
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.				

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2 Background

The original OCP review was essentially complete by April 30, 2008 and on that Wednesday and the following day May 1, 2008 the review was discussed with the OCP Team Leader Dr. Ray Baweja who apprised the DCP1 Division Director, Dr. Mehul Mehta, of the findings. During the following week slides for the briefing were prepared with a draft shown to Dr. Mehul Mehta on Wednesday May 7, 2008. On May 12, 2008 the OCP briefing was held and following research into requests from the Briefing the initial OCP review was placed in DFS on May 15, 2008. While working on labeling as requested post sign off of the OCP review this reviewer realized a) it was not possible to write labeling without adequate scientific data b) the CFR required nonapproval c) this reviewer had been laboring under a misconception based on previous and repeated instructions from management only to recommend acceptable or non-acceptable with regard to OCP recommendations. Consequently this reviewer wrote an e-mail on May 16, 2008 advising management of a pending change in recommendations and requested additional time in order to revise his review. After having begun writing an amended review, this reviewer discovered that OCP management was progressing with writing labeling recommendations. Consequently, on May 20, 2008 this reviewer placed a memo to the file in DFS regarding his change in recommendation. Over the next few weeks there were multiple attempts to force this reviewer to finalize a review prior to all the issues being flushed. These attempts and this reviewer's responses will not be discussed at this time. However, it is readily apparent from the sequence of events that attempts have been made to dismiss many of this reviewer's concerns without addressing the underlying scientific and clinical basis of these safety concerns.

This review amendment will briefly address many of these attempts to dismiss these concerns and will be placed in DFS prior to July 1, 2008 as a Memo to the File as specified by FDA policy and due both to time constraints and per FDA policy this memo to the file will be placed directly in DFS without secondary review by OCP management. Although this is allowed when a reviewer has a scientific dispute with FDA management this reviewer does not believe this extends to reviews by other disciplines that are in agreement with FDA management as has been done and is documented in this review. If this reviewer is in error with regards to policy this reviewer respectfully asks for the same courtesy as has already been shown to other reviewers who have not had their amended asenapine reviewers secondarily signed off.

3 New Amendments to the NDA

The following 6 amendments were made to the NDA after this reviewer completed his original review. All were made in response to communications from the FDA that do not appear to have been documented and that this reviewer was not informed of. The timing of each of them are such that this reviewer would not be able to appropriately respond to them prior to the PDUFA due date.

SN	Date	Code	Descriptor	Contents
025	5-14-08	BM	Minor Amendment - Medical	Response to April 21 st Request for Neutropenia & Ganulocytopenia Cases
026	5-21-08	BC	Minor Amendment - Labeling	Response to DMETS question (May 13, 2008)
027	6-13-08	BB	Minor Amendment – OCP	Asenapine Metabolite Profile
028	6-20-08	BL	Minor Amendment - Labeling	Response to June 16, 2008 Carton, Container, Blister and Label Comments
029	6-20-08	BM	Minor Amendment - Medical	Response to June 17, 2008 Information Request
030	6-23-08	BC	Minor Amendment – Chemistry	Response to Telephone Request from Office of New Drug Quality Assessment (June 19, 2008)

The first amendment requests cases of Neutropenia and Granulocytopenia, however this is different from the two cases of death this reviewer identified where neutropenia had not been achieved but the hematology values indicated that a trend was underway. Consequently this does not address the particular cases raised by this reviewer.

The asenapine metabolite profile amendment was serendipitously able to be addressed in the previous OCP review amendment.

The remaining amendments are addressed in the present amendment.

4 Discussion of Issues Raised by Other Reviews not Discussed Previously

4.1 Medical Reviews

4.1.1 Cross Disciplinary Team Leader's Review #1 – May 14, 2008

On May 14, 2008 the Cross Disciplinary Team Leader CDTL placed her review in DFS. Her remarks regarding the OCP review follow:

“The Clinical Pharmacology review to inform the regulatory processing of this application by the Division Director has not been completed as of 14 May 2008. Based on the review of the drug-drug interaction studies included in this efficacy supplement regarding adjunctive treatment, Dr. Kavanaugh and Baweja may recommend a number of hitherto unknown changes to asenapine labeling regarding drug-drug interactions with commonly used antidepressants evaluated in the double-blind, placebo-controlled trials. If, as Dr. Kavanaugh stated on 12 May 2008 that more than 99% of circulating radioactivity has not been identified, then an approval could not be considered. This statement requires verification by OCP. The full characteristics of drug-drug interaction require clarification for labeling.

At present, biopharmaceutics issues that would preclude an approvable action for this NDA remain undefined. After the Clinical Pharmacology review is signed off and filed with confirmed pharmacokinetic data and analyses, the review and labeling recommendations will taken into consideration for regulatory processing by Drs. Laughren and then by Dr. Temple.”

4.1.1.1 OCP Reviewer Comments and Recommendations

It's not known to this reviewer why the CDTL did not wait for the OCP review as she was aware that final changes were in progress and that the review needed to be finalized by OCP management first.

4.1.2 Medical Review Amendment #1 - May 15, 2008

The medical reviewer changed his conclusions from the original clinical review where he stated the acute schizophrenia study # 41004 was a failed study to a positive study with as asenapine differentiated from the negative control as the positive control did not.

4.1.2.1 OCP Reviewer Comments and Recommendations

The medical reviewer's statement is at variance with the regulatory history of the FDA going back many years. The FD&CA indicates that efficacy must be shown by 'adequate and well controlled studies'. It is common practice in science that experiments and studies need both positive and negative controls in order to be well controlled. This is especially important with treatment for certain psychiatric diseases due to the high and variable placebo response rate, which could differ between two different placebo arms.

It's also unknown why the medical reviewer did not obtain a secondary signature for this review amendment.

As with §4.1.4.1 an impartial outside medical review shall be requested as the points of contention are of such major importance to the public health.

4.1.3 OCP Reviewer Comment

This reviewer was attempting to complete the amended review by Friday June 13, 2008, the following documented amount and type of activity by other review disciplines is highly unusual and in fact has never been observed previously by this reviewer in his 10 years as a reviewer.

4.1.4 CDTL Review #2 – Recommendations – June 12, 2008

The points of contention between the CDTL and this reviewer in her review are too numerous to mention as they take up 13 pages in addition to CMC and Pharm/Tox issues.

The following note worthy statement is from this review regarding cases of possible asenapine toxicity that this reviewer would identify:

"Each case will be medically reviewed by Drs. Laughren, Mathis, Levin, and I for medical adjudication on 16 June 2008."

In addition this CDTL review included comments from the OCP TL regarding mass balance and metabolism that this reviewer was not aware of and which were communicated to the sponsor by Dr. Laughren around June 13, 2008¹.

4.1.4.1 OCP Reviewer Comments and Recommendations

This reviewer is unclear why the CDTL placed this review critiquing each point raised by this reviewer in DFS only 1 day prior to the expected completion of the amended OCP review. What is even more unclear is why this was placed in DFS before the expected completion of this reviewer's amended review why this reviewer was not notified.

As the points of contention between the CDTL and this reviewer in her review are too numerous to mention an impartial outside medical review shall be requested as the points of contention are of such major importance to the public health. However I will provide one illustration of the types of problems with the CDTL's analyses.

With regard to cardiac toxicity the CDTL makes the following statement:

"In the 15 May 2008 as well as in the 10 June 2008 OCP reviews, despite Dr. Stockbridge's conclusions in the DCRP review of 23 April 2008, OCP continued to conclude that the data supported a severe risk of cardiac toxicity associated with asenapine. On page 22 of the OCP review, in section 2.2.2, Summary of Major Conclusion), OCP opined that "There appears to be

¹ Verbal communication from OCP team leader on June 19, 2008

no margin of safety with regards to cardiac toxicity.” This contradicts the conclusions of Drs. Stockbridge’s and Balakrishnan’s interpretations of the data and conclusions in their review.

I defer to the expertise of DCRP in the evaluation of the clinical cardiological risk profile of asenapine.”

Yet the QT/IRT team in their consult of 4-23-08 clearly indicate that their assessment was based only on the sponsor’s summary of clinical safety which clearly contradicts the sponsor’s own earlier and more thorough analysis, and based on the thorough QT study which this reviewer has shown did not even provide all the information gathered and needed for a review. Nor did the QT/IRT team even examine any of the other clinical data that I put forward in my review. Normally I would also defer to experts in a field but when the experts admit that they haven’t even examined the data I have to reject their conclusions and recommend that additional review of this information be conducted by an impartial unbiased outside adjudicator.

Per the previous section there appears to have been a meeting to adjudicate the cases raised by this reviewer. Since only Dr. Levin appears to have signed the review from this meeting it is recommended that all notes from this meeting be preserved for the outside adjudicator.

This reviewer was attempting to have the amendment to the review completed by Friday June 13, 2008. The fact that the OCP team leader was requested to write comments to the file nearly a month after the original review, that they were communicated to the sponsor without any records being kept nor without notifying the reviewer, and that the communication of the response was to be made to this reviewer after he completed his review amendment, raises concerns as to the propriety of how this was handled. Since the Secretary is responsible for assuring that the review process is without bias, this will be taken up with the appropriate authorities as required by law.

For other recommendations see [XXXX](#).

4.1.5 Medical Review Amendment # 2 – June 27, 2008

4.1.5.1 OCP Reviewer Comments

4.1.5.1.1 Deaths

This review by the medical reviewer discusses specific safety items in more detail than discussed by him previously, although the discussion is still extremely superficial.

The medical reviewer gives a very brief description of each of the individual deaths reported and for almost every death of a patient receiving asenapine the medical reviewer indicates the death was either:

“probably unrelated to treatment with asenapine”

Or

“does not appear to be related to treatment with asenapine”

In one case where the medical reviewer does not deny the relationship is a case where the clinical investigator states that a suicide was possibly related to asenapine. For this case the medical reviewer states that “it is not clear what the (clinical investigator’s) rationale was”, thereby introducing doubt.

The neonatal case that this reviewer covered extensively was listed as by the medical reviewer as possibly related, and the reader is referred to the previous OCP review amendment.

In addressing suicidality the medical reviewer largely reiterates the sponsor's analysis which this review has already shown is flawed as there aren't placebo control groups in the long term studies consequently adjusting for total patient years biases the outcomes because suicides typically occur after 4-6 weeks in schizophrenics after they are discharged, and after 2-3 weeks in subjects with acute mania. In addition, this reviewer has already indicated that there is no clear increase in risk in schizophrenia.

For mania the medical reviewer inappropriately uses 12 week data which is not appropriately placebo controlled for the period beyond 3 weeks when the risk has likely largely already past.

“Mania Study (12-week)

An analysis of the ISST data was performed for the 12-week Bipolar Mania study. The results of the mean total score and change from baseline on Day 28, Day 63, and endpoint show a small increase in the mean total score across all treatment groups at endpoint (0.4 for asenapine 9- week, 0.1 for asenapine 12-week, and 0.2 for olanzapine 12-week). The results were similar between the olanzapine and asenapine groups.”

This reviewer referred back to the protocols to determine how ISST was utilized. For both the acute mania studies ISST was only included at baseline, it was then included at 3 weeks as part of the 3rd protocol amendments however, by this time the enrollment was largely over and 3 weeks ISST data was not obtained. In fact at the same amendment the sponsor added a Drug Safety Monitoring Committee to ensure patient safety. This indicates that the sponsor may have had a concern about increased suicidality with during the first 3 weeks. The sponsor also added a pharmacogenomic component to this study and this information should be obtained if the sponsor decides to pursue approval.

In addition the medical reviewer requested and obtained from the sponsor information on the following cases in SN 029 June 20, 2008 provided in response to a June 17th, 2008 information request from the medical reviewer.

Schizophrenia study P041513 Subject 368509

This subject completed suicide in (b) (6) a Suicide due to by ingestion of clozapine. The sponsor claims that the death was unlikely related to asenapine however the subject had been on asenapine 135 days, with a worsening of symptoms during July requiring coadministration of chlorpromazine. At the end of July this was discontinued, and 1 month later the patient committed suicide. This history suggests the possibility that asenapine was ineffective in this patient and thus suicide due to lack of efficacy should be considered possible in this case.

For SAEs the medical reviewer does not even appear to consider a differential diagnosis and appears to accept the sponsor's analysis at face value. Thus ven when an ECG is suggestive of an MI the medical officer still indicates that the even is reflex mediated bradycardia.

In this reviewer's opinion the medical officer's analyses are in direct contradiction to FDA guidance to reviewers in assessing safety signals observed premarketing.

4.1.5.2 Change in OCP Reviewer Recommendations

In OCP Review Amendment #1 it was recommended that the following comments to be forwarded only if asenapine is found approvable. It was thought that it was clear to FDA management hat the FD&CA required nonapproval due to the lack of this information. This can no longer be assumed by this reviewer. Consequently this reviewer now explicitly recommends that this information be required to be submitted prior to any determination of approvability and that per the FD&CA as outlined in previous reviews that the NDA not be approved as this information has not been provided.

1. Structures of all compounds with stereoisomerism and all information on receptor binding and potential pharmacologic activities of any and all metabolites and degradation products are needed including nomenclature. This will likely necessitate new mass balance studies. Please note this request is not limited to 'major' metabolites as this may eliminate clinically important species.
2. Complete drug substance and drug product information for any asenapine or asenapine derivative structure that has been used in any clinical or preclinical study is requested.
3. Complete data sets from any clinical study that has not been submitted so far is also needed. This includes data from the thorough QT study and includes pharmacokinetic, clinical laboratory, and AE data. As well as similar information that has not been submitted for early human studies or for any 'ongoing' studies should also be included. 'Ongoing' studies should be interpreted to include both studies that were ongoing at the time of the original NDA submission as well any subsequently conducted studies.

4.2 Chemistry Reviews

4.2.1 Chemistry Review Amendment #1 – May 21, 2008

On May 21, 2008 a chemistry review amendment made the following conclusions:

“I. Recommendations

A. Recommendation and Conclusion on Approvability

*The applicant provided acceptable responses for the CMC deficiencies stated in the review #1 dated 11-APR-08 (see evaluation in the Chemistry Assessment section in this review). However, from the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended **APPROVABLE** due to pending resolution of the following outstanding pharmtox issue regarding impurity (b)(4) which will have impact as the setting of acceptance limit for the drug substance specification:*

1. *The applicant proposed acceptance criteria for impurity, (b)(4), in asenapine drug substance at (b)(4) which is above the ICH Q3A(R) qualification limit of (b)(4). The pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) stated in her review dated 30-APR-08 (pp. 4) that the applicant should perform an embryofetal development study with (b)(4) in the rabbit to qualify this impurity during phase IV or reduce the specification of (b)(4) to the ICH Q3A(R) qualification limit of (b)(4).*

Release data for the drug substance batches used in clinical studies (20 batches) and batches used in to be marketed drug product batches (4 commercial batches) showed that process impurity (b)(4) is present at not more than (b)(4) level, which is well below ICH Q3A(R) qualification limit of (b)(4) indicating that the applicant may be able to reduce the specification of (b)(4) to the ICH Q3A(R) qualification limit of (b)(4).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review”

4.2.1.1 OCP Reviewer Comments

This amended review was signed by the chemistry reviewer and the Branch Chief without a counter signature by the CMC team leader. This reviewer has never observed this before. It's also strange that this came more than a month after this was mentioned at a meeting this reviewer was advised not to attend, plus this review makes this reviewer wonder why it wasn't included in the original NDA review.

The timing of this relative to the OCP review should also be noted.

4.2.2 Chemistry Review Amendment #2 – May 23, 2008

Approvable. At this time, CMC is unable to accept the release criterion for the impurity (b) (4) and thereby approve the drug substance specification.

4.2.2.1 OCP Reviewer Comments and Recommendations

This is a concurrence by the Director of DPA I/ONDQA Blair A. Fraser. This reviewer does not recall ever having seen something similar to this before. In addition this reviewer does not understand why this issue of an unqualified impurity was not raised with this reviewer previously yet the pharm/tox reviewer kept insisting on metabolite information from this reviewer, when this clinical assessments should be informed by the pharm/tox data and not go purely in the opposite direction.

The timing of this relative to the OCP review should also be noted.

4.2.3 Chemistry Review Amendment #3 – June 20, 2008

4.2.3.1 OCP Reviewer Comments and Recommendations

This review was performed based on a June 19, 2008 e-mail response to a June 19, 2008 telephone request from Dr. Chhagan Tele. Again there are no records of the request and the formal submission was not submitted until June 23, 2008 in submission number 030.

From the June 19th e-mail it appears that this request and submission is only with regards to particle size in primary stability batches. This also appears to be the case from the cover letter for SN 030.

However, there was no reason at this point to have detailed particle size data for each batch as it had already been determined that this was adequately addressed during the regular review period. What is very interesting is that Dr. Chhagan in his review also includes quite a bit about changes in the chemical manufacturing process of the active pharmaceutical ingredient (API) during the development of asenapine. This reviewer had previously asked Dr. Tele for this information as prior to the new FDA policies this reviewer would review this data for clinical importance, however previously Dr. Tele would not provide specifics. This data may or may not have clinical importance and there is insufficient time to OCP to review it prior to the PDUFA goal date. In addition, the information is not cross correlated with individual phase I – III clinical studies which is needed for an appropriate review. Consequently, this review may appear to technically address previous OCP recommendations however it does not address the use of this data in interpreting clinical pharmacology and safety data.

Again this review and submission raises questions as to the reason for the delay, the lack of appropriate documentation, and the lack of communication with OCP. It should be noted that OCP management has brought up these concerns with ONDQA regarding Dr. Tele in the past, as well as with other individuals in ONDQA.

4.3 Pharm/Tox Review Amendments

4.3.1 CAC Advisory Committee Review #2 - June 16, 2008

4.3.1.1 OCP Reviewer Comments

This was essentially a reiteration of the advice provided in the previous review from this committee and included in the Pharm/Tox review. The recommendations from this review follow:

“Executive CAC Recommendations and Conclusions:

The Committee concurred that the carcinogenicity studies filed to the NDA are considered "unacceptable" without completion of the full histopathological examination of the low and mid-dose dose male and female groups in the rat carcinogenicity study and the full histopathological examination of the low and mid-dose dose females in the mouse carcinogenicity study.

*David Jacobson-Kram, Ph.D.
Chair, Executive CAC”*

4.3.2 Pharm/Tox Review #3 - June 23, 2008

4.3.2.1 OCP Reviewer Comments

The following comments were made in this review by Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO. This reviewer cannot recall this ever occurring before. Based on these comments it seems to this reviewer that this reviewer's concerns regarding developmental and reproductive toxicities to a metabolite or impurities are being dismissed indirectly and inappropriately, while as is noncarcinogenic safety with long term usage.

“These studies were presented to the CDER executive carcinogenicity assessment committee. The committee could not fully evaluate the rat study because of the significant decrease in body weight and the lack of full histopathology examinations in all dose groups. Therefore, the committee recommended that the sponsor perform a full histopathology evaluation of the low and mid dose groups in the rat study. The committee could also not fully evaluate the mouse study because of the large variability in the lymphoma incidence in the groups evaluated. Therefore, the committee recommended that the sponsor perform a full histopathology evaluation of the low and mid dose female groups in the mouse study.

Developmental and reproductive toxicity:

The pharmacology/toxicology reviewer recommended pregnancy category C. Asenapine maleate was not teratogenic in studies in rat and rabbits although the maximum exposures tested did not greatly exceed the anticipated maximum human exposure (approximately 2 fold). Some fetal and neonatal toxicity was observed in a rat study at doses that did not exceed the human exposures. Pregnancy category C is appropriate in spite of these observed adverse effects because of the potential utility of the product in the proposed indication.

Impurities:

The sponsor proposed a (b) (4) specification for an impurity (b) (4) that exceeds the ICH threshold for qualification. The impurity was qualified in genotoxicity studies and 4 week studies in rats and dogs. A non-GLP pilot segment II study was conducted with the impurity in rabbits; however, the reviewer found this study to be inadequate for several reasons. The reviewer recommends that the sponsor conduct a rabbit embryofetal toxicity study with the impurity post-approval or reduce the impurity specification to (b) (4), which is the qualification threshold. I concur with these recommendations.

Conclusion:

Asenapine maleate could be used in a chronic manner in the intended indication; therefore, it is appropriate to have adequate carcinogenicity data prior to approval. I concur with the pharmacology/toxicology recommendation of the Division that this NDA not be approved until the complete information from the carcinogenicity studies is submitted, reviewed and found to support the approval."

**4.3.3 Pharm/Tox Team Leader's Comments on OCP
Amendment – June 24, 2008**

4.3.3.1 OCP Reviewer Comments and Recommendations

The pharm/tox leader made the following comments:

"Aside from the fact that data indicate that asenapine itself is a serotonergic antagonist (although of course it is possible that its metabolites are not), the range of adverse effects which Dr. Kavanagh is speculating to be due to serotonergic agonism (as well as the wide range of drug classes he implicates) is so broad as to be useless for informing the direction of any future clinical monitoring."

This is clearly inaccurate. Most of the problems I have described are the same as occur with Phen-Fen, and clinical monitoring with serial 2D echo cardiography is a known and accepted monitoring technique and will detect changes in a large percentage of patients receiving phen-fen within a few months. While I agree that the symptoms are broad, the first thing that a clinician needs is a **'high index of suspicion'** and that is why it is imperative that public communication should be rapid, vigorous, and repeated, especially as to mechanism and the range of possible drug classes that may be involved. In addition new methods of monitoring and communication are currently in development, e.g. perhaps pharmacogenomic screening may be helpful or even the serial CAT scans that have recently been in the news as to the propriety for Medicaid and Medicare to pay for them.

With regard to the embryofetal toxicity perhaps they were not alarming to Dr. Rosloff because he is used to looking at them without considering their cause or consequence. It would be expected that we would see them consistently with psych and other drugs that effect the same receptors, especially at high doses. For as noted many centuries ago by Paracelsus (1493-1541)

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison...."

Presently we know neither the metabolite exposures in animals or humans nor their receptor activities, so we cannot even guess at the relative risk in humans. Dr. Rosloff indicates that the effects are not a malformation but rather are due to maternal weight loss, however may not be a cause and effect as he implies but rather an associated finding, as some serotonin receptors mediate control of hunger. As for skeletal muscle and ossification the exact opposite effect at the very same skeletal sites are seen with the oxaxolidinone class of antibiotics giving strength to the hypothesis that this is mediated via a specific pharmacologic action (possibly mediated by 5HT, BMRP2, or sMAD). Finally he says that it's a transient reversible delay in development. Where is the evidence? Plus if we give this to children chronically, when does he expect the children's parents will stop giving them a chronically administered drug to control behavior to allow recovery, especially if he doesn't even warn them?

4.4 Drug Marketing Evaluation Team Nomenclature Reviews

4.4.1 DMET Review # 1 – May 7, 2008

4.4.1.1 OCP Reviewer Comments

The original DMETS consult regarding the name during the review cycle was sent on September 19, 2007 and is as follows:

“Organon has submitted new NDA 22-117 for asenapine maleate sublingual tablets for use in schizophrenic and bipolar patients. Please review the proposed tradename, Sycrest, and also there proposed packaging and provide feedback.”

The recommendation and signature timeline follow:

“FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

Felicia Duffy
5/6/2008 03:53:23 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
5/6/2008 04:34:47 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/7/2008 07:17:27 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/7/2008 03:21:50 PM
DRUG SAFETY OFFICE REVIEWER”

The review for the brandname was placed in DFS from May 6th – 7th 2008

However, on May 6, 2008 between the time of the placing into DFS of the review by the primary Drug Safety Office Reviewer and the second signatory, a new consult was sent to DMETS regarding a new Tradename, Saphris. This consult was sent by Dr. Laughren on May 6, 2008 at 4:24 PM.

This consult sent as a response to amendment number 021 from the sponsor submitted nearly a month before on April 10, 2008. The cover letter from this submission states:

“Reference is also made to electronic mail correspondence between Dr. Kiedrow (FDA) and Dr. Paporello, in which Dr. Kiedrow advised us to submit an additional trademark for review by the Division.

In addition

As per the Division’s recommendation, we are submitting the additional trademark Saphris as the proposed proprietary name for asenapine sublingual tablets. Sycrest will remain as our second choice.

We are requesting a review of the proposed proprietary name Saphris by the Division of Medication errors and Technical Support, (DMETS) for approval”

Considering that the submission was made on April 10th and was based on a request from the clinical division, this reviewer does not understand why the consult was not forwarded for nearly a month. Based on the language it seems that this new Tradename review should have been included in the original DMETS review rather than in a separate second review. This second review was signed off in DFS on June 2, 2008 and June 3, 2008.

4.4.2 DMET Review # 2 – June 3, 2008

4.4.2.1 OCP Reviewer Comments and Recommendations

The second DMETS review was placed in DFS on June 3, 2008 contained the following text (emphasis added):

“EXECUTIVE SUMMARY

At this time, the acceptability of the proprietary name, Saphris, is dependent upon which application is approved first. The results of the Proprietary Name Risk Assessment found that the proposed name, Saphris, is vulnerable to name confusion that could lead to medication errors with the name (b) (4) received an approvable letter in October 2006. If Saphris is approved first, we will recommend that the second product, (b) (4), seek an alternate name.

We also have concerns with the proposed product’s established name, asenapine, potential for confusion with olanzapine. Because established names are not regulated by FDA, we recommend the Applicant discuss this issue with USAN/INN (International Nonproprietary Name) and petition for a new established name, if they feel this is a significant safety concern with their product.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

In addition, this reviewer noticed the following selected recommendation from this DMET review:

“Furthermore, the established name (asenapine) of the proposed product may be prone to potential confusion because of its similarity to the currently marketed product, olanzapine. Thus, we recommend the Applicant discuss this issue with USAN/INN (International Nonproprietary Name) and petition for a new established name, if they feel this is a significant safety concern with their product.”

And the following was included as a comment to the sponsor:

“Olanzapine and asenapine share a similar orthographic prefix (‘olan-’ vs. ‘asen-’) see example below. Both names also the letter ‘a’ in the middle of the name, and they also share the same ending (‘-pine’). Adding to our concern regarding potential confusion between olanzapine and asenapine are overlapping product characteristics in addition to their orthographic similarities. These products share several overlapping product characteristics such as indication (schizophrenia and bipolar I disorder), strength (5 mg and 10 mg), dose (5 mg to 10 mg), dosage form (solid oral: sublingual tablet/tablet), and route of administration (oral)”

In addition this second review has the following disclaimer on the front of the review and on pages 3, 10, 11, 12, 13, 14, 16, and 26 indicating that it is not to be released under FOI.

*“** Note: This review contains proprietary and confidential information that should not be released to the public. **”*

The first review did not have this disclaimer.

Most of the pages with this disclaimer also contain information on the recommended change in the nonproprietary name from asenapine. However on other pages there are recommendations regarding labeling on what to do in case of swallowing and DMETS gives the reason for this as being based on a decrease in bioavailability and makes the following statement:

“The According to the Medical Officer’s review dated April 14, 2008, the bioavailability of asenapine is extremely low (2%) when swallowed, but yields a mean absolute bioavailability of 36% following sublingual administration.”

Where as the real reasons is due to the dose and time dependent hepatotoxicity observed with oral dosing. This reminds this reviewer of Dr. Zornberg’s question to OCP at the Scoping Meeting last fall.

This reviewer is quite concerned about the safety implications of DMETs recommendation regarding changing the nonproprietary name.

Asenapine’s International Nonproprietary Name (INN) was submitted to the World Health Organization in 2002 and it was granted in 2003.² This must then have later gone through the United States Adopted Name to obtain the same name in the US. If a new USAN is requested it will have to follow the present naming conventions which would likely mean a –sidone suffix as it’s an “antipsychotic with binding activity on serotonin (5HT_{2A}) and dopamine (D₂) receptors”. Resulting in a name that is similar to ziprasidone. However, these new naming conventions ignore the difference in chemical structure that these names also implied in the past and the associated toxicologic activities associated with those particular structure groups. By changing the name from asenapine we would be removing an extremely useful tool for

² RECOMMENDED International Nonproprietary Names (Rec. INN): List 49

recognizing that the toxic effects are similar to olanzapine and clozapine. A change in name would also make it extremely difficult for anyone to look up any research that has been published under asenapine in the past not to mention the typical clinician who would not be familiar with the history of the name of this compound. This would also completely frustrate the typical patient who would not know to use the search term asenapine when searching Clin Trials .gov.

In addition if the US adopted name (USAN) is changed and the International Nonproprietary Name is not then for immigrants or international travelers they might accidentally be prescribed an additional dose of the exact same medication, and considering the lack of margin of safety with asenapine this could be catastrophic.

Lastly DMETs indicated that the following was the criteria that they utilize in whether to recommend a proprietary name change (emphasis added):

“3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, **and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.**”

The nonproprietary name would not be used under the conditions of usual clinical practice for many many years and even then for a number of years the majority of prescribers will likely use the Tradename with the option that a generic may be dispense. Consequently, it appears that DMETs did not even apply or meet their own standards when marking this recommendation.

In conclusion it is strongly recommended for safety reasons that the nonproprietary name not be changed.

4.5 Comments and Recommendations regarding Warning of Imminent Danger to the Public Health

This reviewer would like to reiterate his previous recommendations that an immediate public health warning be issued regarding suicidality with olanzapine in bipolar disorder the use of antipsychotics in individuals with less severe episodes bipolar II, bipolar spectrum disorder, and in children, and the combined use of antipsychotics with a SSRI especially for longer than 8 weeks, and use in pregnancy and breast feeding as there are imminent dangers (hazards) to the public health and in making this recommendation this reviewer would like to highlight criteria afforded by 21 CFR §2.5.

Number of injuries anticipated

Schizophrenia is approximately 1% of the population
Bipolar I disorder is approximately 1% of the population
Bipolar II disorder is approximately 1% of the population
Bipolar Spectrum Disorder is approximately 2.5% of the population
Schizoaffective Disorder 0.5% - 0.8%
In addition there is misuse especially in children with ADHD (10% of the population) and autism, and the elderly demented (> 1% of the population)

Total ~ 7.5% of the population is at risk, and with chronic use, which is expected, and most if not all patients will probably experience the some 5HT2B mediated toxicity eventually, with some even experiencing sudden death.

Nature

Heart failure, MI, Cardiac Arrest, Pulmonary Hypertension

Duration of the anticipated injury.

Many of these may be permanent.

Finally, if we compare this with the recent warning regarding 'classical' antipsychotics then this surely meets the criteria for immediate dissemination without waiting for regularly scheduled dissemination of health information per the publicity section of the FD&CA.

4.6 Comments regarding Good Review Management Pilot Process

This will be addressed in more detail in subsequent documents,

This pilot process clearly indicates that the parallel review, the early communication to the sponsor, the inability of reviewers to collaborate due to distance, the commitment of opinions prior to being able to examine data, the ability of the sponsor to overload the application with excessive, convoluted, and missing data, the problems with the new electronic datasets including miscoding, and the reassignment of certain review responsibilities away from the scientifically appropriate review discipline as well as numerous other difficulties clearly demonstrates that the GRMP is excessively easy to manipulate to game the review process in order to place dangerous and ineffective drugs onto the market.

With the expected surge in dangerous drugs coming based on the 75% increase in IND from 2003 – 2006 and the lack of input OCP was allowed on INDs for Psych and Neuro drugs during this same time frame is likely to result in immense harm to the public health.

5 Signatures

Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.

June 29, 2008

CC list:

Robert Temple
Tom Laughren

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

/s/

Ron Kavanagh
6/30/2008 09:07:28 AM
BIOPHARMACEUTICS

**New Drug Application
Clinical Pharmacology Review – Amendment # 1**

NDA:	22-117
Type of Submission:	Original NDA
Submission Date:	August 30, 2007
Associated INDs:	51,641 September 30, 1996 (Treatment of Psychosis) 70,329 August 3, 2004 (Treatment of Acute Mania in Bipolar I)
Generic Name:	Asenapine Maleate
Formulation: Strengths:	Sublingual Tablets 5 mg, 10 mg
Route:	Sublingual (N.B. Route is mislabeled in Application Form 356h)
Brand Name:	Sycrest®
Sponsor:	Organon / Schering-Plough
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Acting Team Leader:¹	John Duan, Ph.D.

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¹ Usual Team Leader: Raman Baweja, Ph.D.

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2 Executive Summary

2.1 Introduction

Asenapine is a heterocyclic dibenzo-oxepino pyrrole antipsychotic, i.e. a tetracyclic D2 antagonist that includes a pyrrole as the fourth ring that is proposed for the treatment of schizophrenia or acute episodes of bipolar I disorder. Dosages are 5 – 10 mg BID SL for schizophrenia, and 10 mg BID SL for the acute treatment of mania.

After the completion of the original OCP review, it was realized that the clinical pharmacology program appeared to be designed to minimize the ability to detect and mitigate risks. Consequently this reviewer believed it was not possible to make appropriate labeling recommendations. Thus on May 16th 2007 the recommendation for NDA 22-117 was changed to not approvable as required by the Food Drug and Cosmetics Act, (sections 505 d) 1) b; d) 2) 5, and c) 7).

On June 13, 2008 the sponsor submitted an amendment to the NDA (amendment no. 27 modification type BB). The EDR notification was received just as this review was about to be finalized so this reviewer included a review of this amendment in the present amendment.

2.2 Summary of Major Conclusions

Amendment 027 submitted June 13, 2008 fails to address the concerns raised regarding metabolism and mass balance as outlined in the original NDA review and clearly cannot address concerns regarding metabolism raised in this amendment. A critique of this amendment may be found in § 4.6 Appendix 6 - Review of Amendment 027 Submitted June 13, 2008

Asenapine causes serious cardiovascular toxicities including death due to pulmonary arterial hypertension and both direct and indirect effects on the myocardium, and also likely via indirect effects on platelet aggregation. These toxicities may either manifest acutely or chronically.

Pharmacology / Toxicology data indicates that asenapine affects bone remodeling and ossification and this may be of concern during pregnancy, in growing children, and in other populations where bone remodeling is an issue, e.g. elderly women and renal failure patients.

Asenapine appears likely to cause pulmonary arterial hypertension in neonates, resulting in death and maiming of children, and may even cause death simply by breast feeding infants by exposed mothers to drug postnatally.

There is also a probability that asenapine causes other connective tissue disorders, such as hernias and rupture of tendons in addition to other problems.

Animal studies indicate that there may be an increase in motor activity. For a drug that may be used to treat bipolar disorder or 'off-label' for bipolar II, bipolar depression, or bipolar spectrum disorder in children increased motor activity could be mistaken for a symptom of the illness and not drug toxicity and could induce prescribers to inappropriately increase the dose, which would increase the risk of chronic cardiopulmonary toxicity.

Asenapine also appears to cause agranulocytosis and there is a possible risk of aplastic anemia.

Mechanistically effects on platelet aggregation and strokes are also expected.

Death from asenapine can come suddenly and without warning in otherwise young healthy individuals due to arrhythmias or strokes with symptoms easily misattributed to something else such as orthostatic hypotension. More likely most serious cardiovascular toxicities are cumulative resulting in a Phen-Fen

type toxicity especially when dosed for over a year, although symptoms which are likely to be misattributed to something else, (e.g. fatigue), may occur as soon as the first dose.

The entire development program appears designed to minimize detection and quantification of risks and thereby precludes the ability to write appropriate labeling. In fact it is this reviewer's opinion that in several instances the sponsors' actions clearly rise to the level of unlawful conduct and must be reported to the criminal investigators.

Preliminary review indicates that it is also less safe than competing agents and offers few if any advantages.

With respect to benefit there is insufficient data to presently support use in schizophrenia and as for bipolar disorder the data indicated that only the most severely ill (YMRS > 27) may benefit with a few weeks of treatment but possibly not beyond that. Thus even efficacy in bipolar disorder I needs to be confirmed.

After further review this reviewer believes that asenapine is unacceptably dangerous at this time, there was inadequate information submitted to assess safety and such information was expected. There is insufficient information to determine if it will have the effects it purports to as suggested in the labeling.

In conclusion the Food Drug and Cosmetics Act require that asenapine not be approved based on the following subsections and criteria:

505 d)

- 1) Investigations do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling
- 2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;
- 4) Upon the basis of the information submitted as part of the application, and upon other information with respect to asenapine, there is insufficient information to determine whether asenapine is safe for use under suggested conditions of use
- 5) On the basis of the information submitted as part of the application and based on other information, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling
- 7) Based on a fair evaluation of all material facts, such labeling is false and/or misleading in several particulars

In this reviewer's opinion the only way to potentially salvage this drug to redo the entire phase I and phase II programs with some additional phase III work including long term toxicity data. In addition, appropriate and complete preclinical pharmacology and toxicology data must be submitted that will allow a full vetting of the mechanistic bases of asenapine's toxicities and how they can be mitigated.

2.3 Recommendations

2.3.1 Recommendations re: Asenapine

It is recommended that asenapine N22-117 submitted on August 30, 2007 not be approved per the Federal Food Drug and Cosmetics Act under Sections 505 [21 USC 355] d) (1); (2); (3); (4); (5); and (7).

2.3.2 Recommendations re: Class Effects

As the toxicities also appear to be class effects for a variety of different classes of drugs re-evaluation of other drugs and drug classes should be undertaken and a communication to the public of an emerging public safety issue that is an imminent threat to the public health be communicated with maximum haste.

2.3.2.1 *Nonphenothiazine Antipsychotics*

Nonphenothiazine² antipsychotics that are at the top of the list with regards to the degree of concern regarding cumulative long term (> 1 year) cardiopulmonary toxicities include the following structurally similar compounds:

Olanzapine and in particular Symbyax®.
Clozapine
Pimozide (Orap®)
Quetiapine

These class effects are of particular concern in children as older antipsychotics are less likely to be approved and used in children and the toxicities identified may be especially clinically relevant in a population with forced compliance and that is otherwise at low risk for the type of cardiovascular toxicities expected, in addition due to less accumulated underlying cardiovascular disease it may take longer than in adults for adverse effects to become apparent or to be properly identified.

The elderly may also be at greater risk of long term toxicities (> 1 year) due to underlying physiologic changes. In general, the same age population that suffers from erectile dysfunction may also be at increased risk for cardiovascular toxicity.

2.3.2.2 *Other Therapeutic Classes and Specific Therapeutic Agents*

Many other drugs such as SSRIs, fluoroquinolones, steroids, avermectins, and food additives may also have similar effects but to various degrees. Information on an emerging public health issue on these and other compounds should be communicated in the next week with an Advisory Committee meeting scheduled as soon as possible.

2.3.3 Recommendations re: Criminal Investigations

Per instructions from OCP management (Dr. Mehta) any recommendations (or communications) regarding criminal investigations from this reviewer first obtain approval from the management chain of command. This constitutes a formal request to FDA management and recommends criminal investigation of individuals in various companies and organizations for failure to report deaths, attempting to mislead reviewers by various devices that are apparently intended to obfuscate and hide data required for review and that are needed to make safety assessments that would effect approval, and potentially sales and reimbursements. In fact the evidence suggests that there may have been an intentional design to harm, maim, and occasionally kill children so as to induce the need for purchasing other products from the sponsor or cosponsors.

² N.B. The term atypical antipsychotic has no clear definition and is typically used colloquially to denote more recently marketed drugs with differing effects at serotonergic receptors as compared to phenothiazines and less tardive dyskinesia as compared to the butyrophenone, haloperidol. Some of the older antipsychotics such as pimozide, molindone, and loxapine that are often included as 'typical' or 'classic' antipsychotics actually have much more in common with clozapine, and other 'atypical' antipsychotics.

Consequently this reviewer believes that the following section of federal law may have been potentially violated:

SEC. 301. [21 USC §331] Prohibited Acts.

(ii) The falsification of a report of a serious adverse event submitted to a responsible person (as defined under section 760 or 761) or the falsification of a serious adverse event report (as defined under section 760 or 761) submitted to the Secretary, (see §3.5.1.2 and §3.5.1.6).

There are more than instance which will require more time to cite appropriately and will be communicated only to the appropriate criminal investigators.

This reviewer believes the following laws may have also been violated; these include possible violations of law by FDA personnel. (N.B. This list does not encompass all potential violations). Per instructions from Dr. Mehta this reviewer requests that these concerns be referred to the appropriate criminal investigators.

18 USC § 201
18 USC § 286
18 USC § 371
18 USC § 372
18 USC § 1001
18 USC § 1002.
18 USC § 1018.
18 USC § 1111
18 USC § 1112
18 USC § 1117
18 USC § 1343
18 USC § 1347
18 USC § 1349
18 USC § 1505.
18 USC § 1512
18 USC § 1518

2.4 Comments and Requests

2.4.1 Comments to the Sponsor

2.4.1.1 Comments to be Forwarded Regardless of Approvability

With respect to the pregnancy that resulted in a premature delivery and death within 5 minutes of birth, it was noted that there is a history of a number of other pregnancies in this mother with poor outcomes.

This confounds interpretation however the timing of 2 of the spontaneous abortions indicate the either that these fetuses may have been malformed or that there may have been a hormonal issue. In addition other pregnancies in this patient resulted in a spontaneous abortion occurring at 20 weeks, and a caesarian section occurring at 34 weeks due to fetal distress. These other outcomes in combination with the premature birth with death occurring at 5 minutes post birth in the clinical trail raises questions as to the underlying cause(s). Specifically could there have been pre-eclampsia or vasoconstriction of blood flow to the placenta or to fetal tissues due to serotonergic effects of drugs, or a combination of the two. A medication history, fuller histories of the previous pregnancies including the postnatal history of the surviving infant, and an autopsy in the present case would be informative and as much of this information as possible should be obtained.

2.4.1.2 Comments to be Forwarded Only if Asenapine is found Approvable

Structures of all compounds with stereoisomerism and all information on receptor binding and potential pharmacologic activities of any and all metabolites and degradation products are needed including nomenclature. This will likely necessitate new mass balance studies. Please note this request is not limited to 'major' metabolites as this may eliminate clinically important species.

In addition, complete drug substance and drug product information for any asenapine or asenapine derivative structure that has been used in any clinical or preclinical study is requested.

Complete data sets from any clinical study that has not been submitted so far is also needed. This includes data from the thorough QT study and includes pharmacokinetic, clinical laboratory, and AE data. As well as similar information that has not been submitted for early human studies or for any 'ongoing' studies should also be included. 'Ongoing' studies should be interpreted to include both studies that were ongoing at the time of the original NDA submission as well any subsequently conducted studies.

2.4.2 Comments to the Medical Division

The sponsor has published several *in vitro* and preclinical articles implying that asenapine might be useful for impaired cognition and negative symptoms^{3,4}. With respect to cognition, asenapine impaired both short and long term memory in humans and would be expected to make certain features of dementia worse. OCP recommends that any final labeling include language that would mitigate ill-advised off-label use.

Please see:

- § 2.4.3 Comments to Pharmacology / Toxicology Review Team
- § 2.4.4 Comments Regarding Pilot Review Project
- § 2.4.5 Comments Regarding New FDA Regulations, Policies etc

In addition to the information available from this submission that indicates that the risk of all cause mortality increases over time; recent publications indicate that the risk of suicide is lower than previously thought and decreases over time and that a subpopulation at greatest risk may be identifiable. This suggests that the risk benefit ratio of antipsychotic medications changes over time and the chronic use of antipsychotic medications in schizophrenics is a public health issue that needs to be reexamined.

2.4.3 Comments to Pharmacology / Toxicology Review Team

Please consider the following comments with regards to your suggested labeling:

1. In the mechanism of action and pharmacodynamics section please include other receptors that have been excluded that are expected to contribute to pharmacologic actions, e.g. 5HT2B, D4 etc., including subtypes
2. With regard to pharmacodynamics, indicating whether compound activity is agonistic or antagonistic, and including effects by parent drug, metabolites, and degradation products as well their potencies is recommended as a minimum. In addition information on the expected clinical implication of effects at various receptors would be welcome if it's expected to be clinically important.

³ [Psychopharmacology \(Berl\)](#). 2008 Feb;196(3):417-29. Epub 2007 Oct 17

⁴ [Neuropsychopharmacology](#) advance online publication 16 April 2008; doi: 10.1038/npp.2008.20 <http://www.nature.com/npp/journal/vaop/ncurrent/full/npp200820a.html>

3. Please consider adding information addressing differences in efficacy and toxicity by stereoisomers that may be observed especially when they are produced by degradants, contaminants, physical drug interactions, and *in vivo* metabolism.
4. Please reconsider the wording of the pregnancy section. Although asenapine wasn't 'teratogenic' it did have dose dependent embryo-fetal toxicity in all species and strains, and in some studies some effects were observed at all dose levels. Some of these effects were consistent with known, likely mechanism based AEs, seen in humans with similar drugs and asenapine is expected to result in the same toxicities. Specifically, pulmonary arterial hypertension in newborns especially when coadministered with antidepressants. Plus asenapine may possibly increase pre-eclampsia in women.
5. Even in pups not exposed *in utero* there was an increase in the postnatal loss of pups exposed to asenapine only through breast milk.
6. Effects on skeletal muscle formation, and remodeling, including poor ossification, was seen in all animal species and appears to be a class effect. Consequently asenapine is expected to effect bone and connective tissue especially during development, growth, and in the elderly or other populations at risk, e.g. renal failure patients.

2.4.4 Comments Regarding Pilot Review Project

Please refer to the following appendices:

§ 4.7 Appendix 7 – Quality of the Submission

§ 4.8 Appendix 8 – Evaluation of Pilot NDA Review Process

2.4.5 Comments Regarding New FDA Regulations, Policies etc

Please see:

§ 4.9 Appendix 9 – Lessons Learned and Feedback on FDA Policies, Procedures and Regulations

2.5 Signatures

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Date

Senior Reviewer
Division of Clinical Pharmacology I

John Duan, Ph.D.

Date

Acting Team Leader
Division of Clinical Pharmacology I

3 Review

3.1 Background

3.1.1 Introduction

Asenapine and structurally related drugs (e.g. olanzapine and clozapine) exhibit a constellation of side effects that suggest agonist effects at serotonin 5HT_{2B} receptors and possibly related serotonin receptors.

5HT_{2B} receptor stimulation has been implicated in the valvular heart disease and pulmonary arterial hypertension associated with phen-fen.

3.1.2 Signs and Symptoms Associated 5HT_{2B} Agonism

The following is a list of symptoms from the National Heart Lung and Blood Institute at NIH that are associated with pulmonary arterial hypertension:

3.1.2.1 Pulmonary Arterial Hypertension

Difficulty breathing or shortness of breath (dyspnea) is the main symptom of pulmonary arterial hypertension (PAH). If you have PAH, you may feel that it is difficult to get enough air.

Other Common Signs and Symptoms

- Fatigue
- Dizziness
- Fainting spells (syncope)
- Swelling in the ankles or legs (edema)
- Bluish lips and skin (cyanosis)
- Chest pain
- Racing pulse
- Palpitations (a strong feeling of a fast heartbeat)

As the disease advances:

- The pumping action of your heart grows weaker.
- Your energy decreases.

In the more advanced stages, you:

- Are able to perform very little activity
- Have symptoms even when resting
- May become completely bedridden

It is clear from the list, that the symptoms are relatively nonspecific. Thus a high index of suspicion is needed for detection.

In addition to direct effects on the heart due to pharmacologic action at cardiac 5HT receptors, there may also be secondary effects due to the heart working against the resistance caused by pulmonary vasculature vasoconstriction that results in the increased pulmonary arterial pressure.

Acutely, this may include coughing up blood⁵. In addition there may be secondary effects on the heart that may show up either acutely or chronically depending upon the patient's underlying baseline physiology.

3.1.2.2 Cardiotoxicity

5HT2 agonism may also result in a variety of cardiac arrhythmias both acutely and chronically. For example Right Bundle Branch Block may be induced by a number of different illnesses that may be secondary to a variety of effects that can be secondary 5HT2B agonism as shown in Table 1.

Table 1 Differential Diagnosis of RBBB

Table 3. Differential Diagnosis of Right Bundle Branch Block.	
Congenital	- Isolated, idiopathic, and of no functional significance.
	- Atrial Septal Defect.
	-Other congenital heart disease resulting in systolic overload of the right ventricle.
Acquired.	- Idiopathic.
	- Ischaemic Heart Disease (IHD).
	- Myocardial Infarction (AMI).
	- Degenerative or destructive diseases of the conducting system (10).
	- Cor pulmonale.
	- Myocarditis (11).
	- Acute right ventricular strain (12).
	- Surgical ventriculotomy.
	- Trauma

Source: http://aeromedical.org/Articles/XAVM_714-9.html

A good example of the variety of cardiovascular symptoms that are seen with stimulation of serotonin receptors (e.g. 5HT2B) can be found simply by examining the side effect profile for dihydroergotamine as described in Micromedex:

"DHE Micromedex

Symptoms of ERGOTISM from high doses of dihydroergotamine (or prolonged use) include circulatory disturbances manifested by COLDNESS OF THE SKIN, severe MUSCLE PAINS, and vascular stasis, which can result in dry peripheral GANGRENE; symptoms are related to intense VASOCONSTRICTION and thrombus formation (AMA, 1990; Reynolds, 1982); ANGINA-LIKE PRECORDIAL PAIN, transient sinus tachycardia, and bradycardia may occur, along with either HYPOTENSION or HYPERTENSION (AMA, 1990; Reynolds, 1982). The incidence of vasoconstriction and gangrene appears to be less with dihydroergotamine than with ergotamine (AMA Department of Drugs, 1983).

Migraine drugs, including ergotamine, DIHYDROERGOTAMINE, methysergide, sumatriptan, avitriptan, and zolmitriptan, were found to cause coronary vasoconstriction to a degree that would not be hazardous in healthy subjects but could be harmful in patients with cardiovascular impairment, based on testing in isolated coronary artery segments. Coronary vasoconstriction was also significantly more prolonged with

⁵ <http://www.pph-net.org/pph-symptoms-pph-diagnosis.htm>

ergotamine and DIHYDROERGOTAMINE compared with sumatriptan and related 5-HT antimigraine agents (Maassen VanDenBrink et al, 1998a)."

3.1.2.3 *Connective Tissue Disorders*

Connective tissue disorders and alterations in skeletal formation may also be affected by drugs that stimulate certain serotonin receptors. Whether this is due to effects at alternative receptors that might also accept the drug, a common pathway, or both is not clear.

*According to the Merck Manual Primary Pulmonary Hypertension (PPH) "can be familial or sporadic; sporadic cases are about 10 times more common. Most familial cases have mutations in the gene for the bone morphogenetic protein receptor type 2 (BMPR2), part of the transforming growth factor (TGF)- β family of receptors. About 20% of sporadic cases also have BMPR2 mutations. Many people with PPH have increased levels of angiopoietin-1; angiopoietin-1 appears to down-regulate BMPR1A, a sister receptor to BMPR2, and may stimulate serotonin production and endothelial smooth muscle proliferation. Other possible contributing factors include abnormalities in serotonin transport and previous infection with human herpes virus."*⁶

PPH is also associated with scleroderma and other connective tissue disorders. As mentioned previously BMPR2 may have common final pathways with certain serotonin receptors, thus drugs that effect serotonin receptors should also be evaluated for effects on skeletal bone formation as well as effects on fibrosis of certain organs such as the heart and liver, and weakening of other connective tissues such as tendons and other tissues as evidenced by increases in congenital hernias.

Effects on skeletal bone formation and remodeling would be expected to be a more chronic toxicity and would be expected to show up in fetal skeletal formation, during growth when there is extensive bone remodeling, and in the elderly and especially in slightly built women or other populations where osteoporosis is an issue.

3.1.2.4 *Other Associated Toxicities*

A number of other adverse effects are also seen with the same drugs or conditions that cause PAH and include:

- Renal Failure
- Cirrhosis of the Liver (May be related to fibrotic tissue formation due to effects at serotonin receptors)
- Seizures⁷
- Psychosis and Suicidality

3.1.2.5 *Effects on Neonates*

When pulmonary arterial hypertension occurs in a fetus, death shortly after birth due to suffocation is a common complication. In those neonates who survive, 50% experience deafness and other neurologic deficits.

In fact the association of primary PAH and serotonin in neonates has been noted by FDA for selective serotonin reuptake inhibitors when used alone⁸.

⁶ <http://www.merck.com/mmpe/sec05/ch058/ch058a.html> accessed June 11, 2008

⁷ [Spencer DC, Hwang J, Morrell MJ.](#) Fenfluramine-Phentermine (Fen-Phen) and Seizures: Evidence for an Association. *Epilepsy Behav.* 2000 Dec;1(6):448-452.

⁸ <http://www.foxnews.com/story/0,2933,184396,00.html>

3.1.3 Time Course of Effect

With some patients with underlying pathophysiologic conditions that predispose them to serotonergic toxicities, cardiac effects such as asystole might be immediate, although as will be discussed later this can also vary with the specific agent involved, which serotonin receptors are affected, how they are effected and its potencies at various receptors as well as the effects of drug interactions.

With phen-fen, the prototypical 5HT2B clinical agonist, the effects may occur only after chronic use. This has been noted both by the FDA and others.^{9,10}

For example studies that have looked for evidence of phen-fen induced valvulopathy by echocardiography have found a 30% incidence after 3 months of use.

Other sources have claimed: *“A significant association exists between the use of the fen phen diet drug and PAH/PPH. Fen phen was taken off the market in the US in 1997. Studies have shown that it can be several years after having stopped taking diet drugs that patients develop the disease. Medical experts have testified that there is a potential latency of ten or more years between the last date on which a patient is exposed to diet drugs and the date at which the patient develops the first symptoms of what is ultimately diagnosed as PAH/PPH.”*

It should be noted that a high index of suspicion is required to see the signs of PAH with drugs, in fact the FDA website states: *“And even in symptomatic patients, the link between the symptoms and drug use may not be obvious because such a reaction is not common. These factors may explain why this problem was not discovered earlier.”*

Regardless of the time of onset, the duration may be in years resulting in significant morbidity even with treatment, if not mortality, and even if the effects are reversible the process may take years. For additional information the following articles may be of use.

[Fleming RM, Boyd LB](#). The longitudinal effects of fenfluramine-phentermine use. [Angiology](#). 2007 Jun-Jul;58(3):353-9. [Angiology](#). 2007 Dec-2008 Jan;58(6):772-3; author reply 774.

A number of other references regarding PAH and 5HT2B agonism are available and include the following:

Harrison W. Farber, M.D., and Joseph Loscalzo, M.D., Ph.D. Pulmonary Arterial Hypertension, [NEJM October 14, 2004](#) Volume 351:(16) 1655-1665

Robert J. Levy Serotonin Transporter Mechanisms and Cardiac Disease (Editorial) [Circulation](#) 2006;113:2-4 (<http://circ.ahajournals.org/cgi/content/full/113/1/2>)

Robert Naeije, M.D.a and Saadia Eddahibi, Ph.D. Serotonin in Pulmonary Arterial Hypertension (Editorial) [American Journal of Respiratory and Critical Care Medicine](#) Vol 170. pp. 209-210, (2004) (<http://ajrccm.atsjournals.org/cgi/content/full/170/3/209>)

3.1.4 Risk Factors

As shown by Fen-phen there is an even greater concern that a combination of a SSRI with an antipsychotic may increase risks substantially. Such a combination was approved in December 2003 for bipolar depression, (Fluoxetine/Olanzapine - Symbyax®; N21-250 - Lilly). The labeled indication is for “Depression associated with Bipolar Disorder”. In addition, such combinations are being proposed for more rapid onset in depression and may potentially be used off-label for bipolar spectrum disorder.

⁹ <http://www.fda.gov/cder/news/phen/fenphenqa2.htm> Diet Drugs - Fen Phen

¹⁰ <http://www.fda.gov/cder/news/mmwr.pdf>

Risk factors for PAH include smoking as hypoxia may contributory, and AIDS.¹¹, although it's claimed that the effect of cigarette smoking on PAH is due to hypoxia, an alternative or synergistic mechanism may be due to stimulation of 5HT receptors by cigarette additives, for example pyrroles such as found in asenapine are among the most common additives to cigarette tobacco.

Age may also be a risk factor not only due to decreased elimination of toxic substances, increased risk of drug-drug interactions, but also physiological changes due to aging such as atherosclerosis, and the loss of vascular elasticity and associated increased systolic hypertension in addition to the osteoporosis mentioned earlier.

3.1.5 Alternative Mechanisms for PAH

In addition to effects on serotonin receptors there are several other mechanisms that have been implicated in primary PAH. Foremost among them are due to effects on arachadonic acid and prostaglandins. Since, the clinical effects of acute cardiotoxicity with COX inhibitors such as rofecoxib (Vioxx® - Merck) are so similar, yet there is differing effects on survival by drug, e.g. sulindac and rofecoxib both cause effects on renal vasculature (rofecoxib in rabbits and sulindac (Clinoral® – Merck) in humans) yet rofecoxib has a high incidence of cardiac toxicity whereas sulindac doesn't. This may indicate species differences or unidentified COX-2 subtypes.

Some other mechanisms such as agonism of endothelin receptors may have similar final common pathways with stimulation of certain serotonin receptors.

¹¹ [Ngo MV, Gottdiener JS, Fletcher RD, Fericola DJ, Gersh BJ.](#) Smoking and obesity are associated with the progression of aortic stenosis. Am J Geriatr Cardiol. 2001 Mar-Apr;10(2):86-90.

3.1.6 Serotonin Receptors

Except for 5HT₃ all known 5HT receptors are G-coupled receptors with an inverse agonist effect. A receptor with an inverse agonist effect is essentially a 3 way switch. The baseline state without a ligand bound to the receptor produces no effect (i.e. it's neutral). Whereas some ligands when they bind cause an effect in one direction, for example up regulation of mitochondrial activity, and other ligands cause the opposite effect, for example down regulation of mitochondrial activity. Figure 1 is an example demonstrating the 3 possible responses seen with experiments that are typically performed with 5HT receptors.

Figure 1 Schematic of Potential Effects on Inverse Agonist Serotonin Receptors

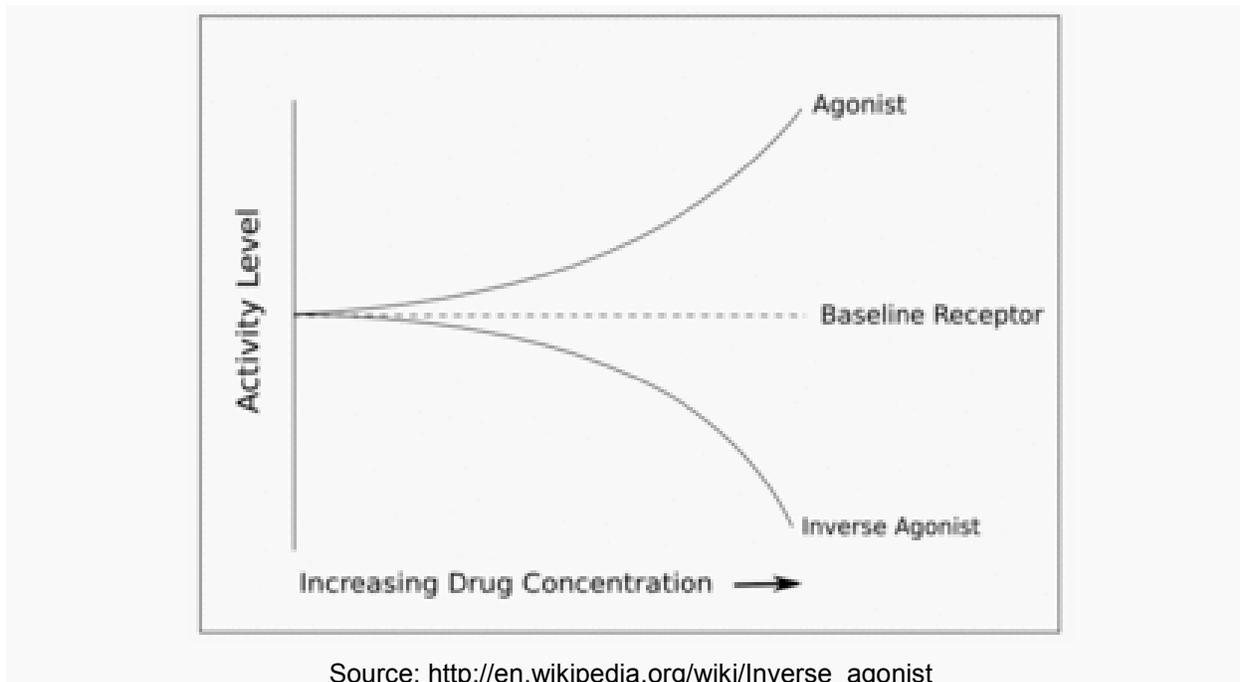


Table 2 is a summary of various 5HT receptors and their agonist and antagonist activities. This table was taken from a public website that is not peer reviewed and so may be in error. Consequently, this table is only included for conceptual purposes. Although this reviewer uses the term 5HT_{2B} for the effects of phen-fen the table indicates it's mediated via 5HT_{1B}. It's possible that this reviewer is using older nomenclature that has since been changed. However, it's also possible that effects are mediated at both receptors. As phen-fen cardiac valve effects are listed as an effect on 5HT_{2B} by the new NIMH Psychoactive Drug Screening Program.¹² Rather than spend time clarifying this issue this reviewer will simply ascribe the effects to 5HT_{2B} with the understanding that this might be an erroneous or incomplete designation.

Regardless of the nomenclature used it's clear that pulmonary vasoconstriction is a major problem with phen-fen and also occurs with ergots. It's noteworthy that the cardiac side effect profile noted with dihydroergotamine earlier is virtually identical to the side effects seen with asenapine.

A good review of 5-HT receptors has been written by scientists from Novartis, however as the article is 7 years old it is likely dated.¹³

A likely more reliable, although abbreviated description of serotonin receptors and functions may be found in section 4.1 in the appendix, and is from the website of the Lundbeck Institute, which is associated with Lundbeck Pharmaceuticals.

It's clear from this that simply reporting affinities for serotonin receptors without providing such plots is useless.

¹² <http://pdsp.med.unc.edu/> accessed June 2, 2008

¹³ Daniel Hoyer, Jason P. Hannon, Graeme R. Martin; Molecular, pharmacological and functional diversity of 5-HT receptors *Pharmacology, Biochemistry and Behavior* 71 (2002) 533–554

Table 2 Summary of characterized 5-HT receptors, with selected high affinity agonist and antagonist ligands

Receptor	Gene	Actions	Agonists	Antagonists
5-HT_{1A}	HTR1A	CNS: neuronal inhibition, behavioural effects (sleep, feeding, thermoregulation , aggression, anxiety)	buspirone psilocin LSD 8-OH-DPAT	spiperone methiothepin ergotamine yohimbine
5-HT_{1B}	HTR1B	CNS: presynaptic inhibition , behavioural effects vascular: pulmonary vasoconstriction	ergotamine sumatriptan	methiothepin yohimbine metergoline Risperidone
5-HT_{1D}	HTR1D	CNS: locomotion, anxiety; vascular: cerebral vasoconstriction	5-(Nonyloxy)tryptamine, ^[4] sumatriptan	methiothepin yohimbine metergoline ergotamine
5-HT_{1E}	HTR1E			
5-HT_{1F}	HTR1F			
5-HT_{2A}	HTR2A	CNS: neuronal excitation, behavioural effects, learning, anxiety smooth muscle: contraction, vasoconstriction / vasodilatation platelets: aggregation	α-methyl-5-HT LSD psilocin DOI	Nefazodone trazodone mirtazapine ketanserin cyproheptadine pizotifen atypical antipsychotics
5-HT_{2B}	HTR2B	stomach: contraction	α-methyl-5-HT LSD DOI Fenfluramine	yohimbine
5-HT_{2C}	HTR2C	CNS: anxiety, choroid plexus : cerebrospinal fluid (CSF) secretion	α-methyl-5-HT agomelatine LSD psilocin DOI	mesulergine agomelatine fluoxetine methysergide ^[5]
5-HT₃	HTR3A , HTR3B	CNS, PNS: neuronal excitation, anxiety, emesis	2-methyl-5-HT	metoclopramide (high doses) renzapride ondansetron alozetron mirtazapine memantine
5-HT₄	HTR4	GIT : gastrointestinal motility CNS: neuronal excitation, learning, memory	5-methoxytryptamine metoclopramide renzapride tegaserod RS 67333	GR113808 Piboserod
5-HT_{5A}	HTR5A	CNS (cortex , hippocampus , cerebellum): unknown	5-carboxytryptamine LSD ^[3]	unknown
5-HT₆	HTR6	CNS: unknown	LSD	SB271046 ^[6]
5-HT₇	HTR7	CNS, GIT, blood vessels: unknown	5-carboxytryptamine LSD	methiothepin risperidone

a Note that there is no 5-HT1C receptor since, after the receptor was cloned and further characterized, it was found to have more in common with the 5-HT2 family of receptors and was redesignated as the 5-HT2C receptor.

b Source: http://en.wikipedia.org/w ki/Serotonin_receptor Accessed June 2, 2008

A recent publication suggests that at least part of the efficacy of certain antipsychotics in schizophrenia may be mediated via antagonism of the 5-HT₆ receptor, which is a Galpha coupled receptor. Although antagonism by parents does not account for the effects of metabolites.¹⁴

In addition, it has been reported that agonism of the Endothelin-A receptor, Galpha subunit may induce cardiac hypertrophy.¹⁵

3.2 Receptor Activity

Table 3 shows the receptor affinities with asenapine and a number of other antipsychotics.

Every antipsychotic listed except for haloperidol and risperidone binds more potently to the 5HT_{2B} receptor than the dopamine D₂ receptors, however without information on whether there is agonist or antagonistic effects at the individual receptors predications of the potential clinical implications cannot be assessed.

Table 4 is from the original NDA and shows that in addition to asenapine various asenapine metabolites have similar or greater binding affinities to various serotonin receptors as compared to asenapine.

¹⁴ [Eur J Pharmacol.](http://www.ncbi.nlm.nih.gov/pubmed/18511034?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum) 2008 Jul 7;588(2-3):170-7. Epub 2008 Apr 20. http://www.ncbi.nlm.nih.gov/pubmed/18511034?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum Accessed June 17, 2008

¹⁵ [J Recept Signal Transduct Res.](http://www.ncbi.nlm.nih.gov/pubmed/15648448) 2004;24(4):297-317. <http://www.ncbi.nlm.nih.gov/pubmed/15648448> Accessed June 17, 2008

Table 3 Comparative Receptor Binding Affinities for Various Antipsychotics Expressed as IC50s (Moles/L)

	Function	Receptor	asenapine	aripiprazole	ziprasidone	quetiapine	olanzapine	risperidone	clozapine	haloperidol
G protein Coupled		5-HT1A	2.51E-09	2.69E-09	9.77E-10	1.66E-07	1.51E-06	1.78E-07	8.71E-08	5.13E-07
		5-HT1B	3.98E-09	2.82E-09	8.91E-10		2.51E-07	5.13E-08	2.69E-07	
		5-HT2A	7.08E-11	9.55E-09	3.09E-10	1.55E-07	1.32E-09	2.04E-10	4.07E-09	5.25E-08
		5-HT2B	1.78E-10	2.57E-10	8.32E-10	4.68E-08	3.89E-09	1.02E-08	1.62E-09	3.31E-07
		5-HT2C	3.47E-11	2.82E-08	9.77E-10	1.05E-06	3.89E-09	6.76E-09	2.75E-09	1.62E-06
Ligand gated cation channel		5HT3								
G protein Coupled	Fxn Unk	5-HT5A	1.45E-09	8.91E-07	1.12E-06	2.00E-06	1.00E-07	5.89E-08	2.51E-08	7.94E-07
	"	5-HT6	2.51E-10	2.29E-07	1.66E-07	2.29E-06	3.24E-09	2.19E-06	8.91E-09	3.63E-06
	"	5-HT7	1.15E-10	3.47E-08	2.51E-09	5.62E-08	3.72E-08	7.41E-10	6.46E-09	8.91E-08
	Excitatory	D1	1.41E-09		3.55E-09		1.17E-08	2.09E-08	2.29E-08	6.31E-09
G protein Coupled	Inhibitory presynaptic	D2A	1.26E-09	1.15E-09	8.13E-09	4.17E-07	2.14E-08	6.17E-09	1.35E-07	1.45E-09
		D2B	1.45E-09	1.23E-09	1.02E-08	4.79E-07	2.63E-08	8.51E-09	1.55E-07	1.74E-09
	postsynaptic	D3	4.17E-10	1.41E-09	4.47E-09	3.89E-07	3.47E-08	6.92E-09	2.19E-07	2.75E-09
4.7 assoc with ADHD		D4	1.12E-09	1.29E-07	4.68E-08	1.41E-06	1.78E-08	6.17E-09	4.68E-08	1.48E-09
		α1A	1.17E-09	3.24E-07	1.55E-08	6.46E-08	2.24E-08	5.13E-09	1.26E-08	2.51E-08
		α2A	1.15E-09	6.92E-08	2.57E-07	5.62E-07	1.48E-07	8.13E-09	2.88E-08	8.71E-07
G coupled	Ag dec BP	α2B	3.24E-10	1.91E-07	2.40E-07	8.32E-08	3.31E-07	9.55E-09	2.82E-08	5.62E-07
	Ag inc BP	α2C	1.23E-09	1.17E-08	4.17E-08	3.80E-08	4.07E-08	1.82E-09	1.58E-09	1.32E-07
	CNS integrative	H1	1.00E-09	2.04E-08		1.10E-08	3.39E-09	8.13E-08	1.74E-09	
		H2	6.17E-09							
		M1	8.13E-06	3.89E-06		2.82E-07	1.20E-08	2.69E-05	5.13E-09	5.62E-06
		M2	3.16E-05	1.20E-05		6.03E-07	3.98E-08	3.89E-05	7.08E-08	8.91E-06
		M3	2.14E-05	7.76E-06		5.13E-07	3.39E-08	2.51E-05	2.45E-08	1.35E-05
		M4	9.12E-06	5.89E-06		2.45E-07	2.24E-08	1.07E-05	2.09E-08	5.62E-06
		5HT2B/D2A Ratio	7.08	4.47	9.77	8.91	5.50	0.60	83.18	0.00

Table 4 Estimated IC50s (nMol/L) for Human Receptor Binding and Transporters Based on Reported pKis

Receptor	R&DRR INT00002643					Study 00003223				
	Asenapine	(-)asenapine	(+)asenapine	N-desmethyl	N-oxide	Org 191634-0 N-sulfated- N- Desmethyl	Org 213772-0 11-OH	Org 214025-0 11-O-sulfate	Org 216761-0 N-Gluc	Org 220473-0 7-OH
5-HT1A	2.5	9.1	2.7	6.2	1,071.5	10.0	4.0	31.6		25.1
5-HT1B	4.0	1.7	2.5	199.5	35.5					
5-HT2A	0.1	0.1	0.0	2.4	6.0	25.1	0.10	0.13		0.13
5-HT2B	0.2	0.4	0.9	2.5	38.0	10.0	0.10	0.40		0.32
5-HT2c	0.03	0.1	0.0	1.9	6.0	20.0	0.13	0.40		0.13
5-HT5A	1.4									
5-HT6	0.3	0.3	0.1	13.8	85.1	20.0	0.1	0.2		0.8
5-HT7	0.1	0.1	0.2	10.5	57.5	31.6	0.2	0.3		1.6
D1	1.4									
D2L	1.3	2.0	1.9	55.0	631.0					
D2S	1.4	1.4	1.1	47.9	478.6	100.0	4.0	15.8		4.0
D3	0.4	0.4	0.5	19.1	204.2	39.8	4.0	7.9		0.8
D4	1.1	1.0	2.5	97.7	446.7					
D4.7										
α1A	1.2	1.4	1.0	27.5	316.2	15.8	1.0	5.0		4.0
α2A	1.1	0.9	2.4	17.4	549.5	79.4	6.3	20.0		6.3
α2B	0.3	0.2	0.4	2.3	128.8					
α2c	1.2	1.1	4.9	37.2	616.6	63.1	10.0	15.8		10.0
H1	1.0					20.0	1.3	1.6		0.1
H2	6.17									
M1	8,128	7,244	10,233	8,318	60,256					
M2	31,623	38,905	33,113	36,308	64,565					
M3	21,380	15,488	21,878	25,704	67,608					
M4	9,120	7,244	6,166	9,333	37,154					
M5	2.5	9.1	2.7	6.2	1,071.5	10.0	4.0	31.6		25.1
SERT	4.0	1.7	2.5	199.5	35.5					
NET	0.1	0.1	0.0	2.4	6.0	25.1	0.10	0.13		0.13
DAT	0.2	0.4	0.9	2.5	38.0	10.0	0.10	0.40		0.32

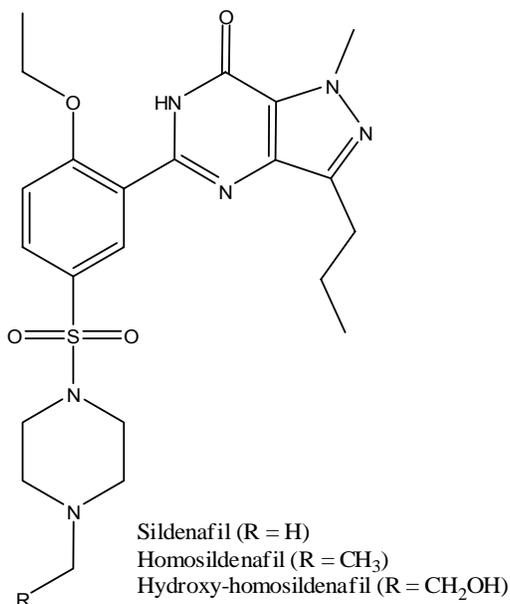
3.3 Potential Effect of Metabolism on Receptor Activity

Although it has been claimed by the sponsor in summary documents as well as in publications that asenapine itself is a 5HT_{2B} antagonist this does not mean that metabolites are also antagonistic.

3.3.1 Evidence from Other Pharmacologically Active Agents

A recent and relevant example of this possibility is the May 27, 2008 FDA announcement that Xiadafil™ contains hydroxy-homosildenafil a structural analog of sildenafil (Viagra® - Pfizer) that may be “potentially harmful” and “can interact in dangerous ways with drugs that a consumer is already taking”.^{16,17} The structures of sildenafil, homo-, and hydroxy-homo-sildenafil are shown in Figure 2.

Figure 2 Structures of Sildenafil and Selected Sildenafil Analogs



Sildenafil in addition to being used for erectile dysfunction, (Viagra® - Pfizer), is also approved to treat pulmonary arterial hypertension, (Ravatio® - Pfizer), which is one of the toxicities that Phen-fen was eventually recalled from the market for producing.

With regards to ‘herbal Viagra’, Dr. Todd Nippoldt of the Mayo Clinic has made a very interesting comment: *“Many herbal products marketed as sexual stimulants claim to be ‘natural versions’ of Viagra — but they aren’t the same as the prescription drug. Some contain substances (vasodilators) that improve blood flow by relaxing the walls of blood vessels. But no herbal products are as specific for blood vessels to the penis as Viagra and other similar prescription drugs are. As a result, these herbal remedies may cause generalized low blood pressure and restrict blood flow to vital organs.”*¹⁸

This raises questions as to which vital organs are blood flow diminished, and if a minor change in structure on the opposite end of the sildenafil molecule, which is the part that is similar to serotonin, alters the type of pharmacologic activity at certain serotonin receptor subtypes, then why wouldn’t metabolism of asenapine result in similar effects with respect to change a critical pharmacologic function.

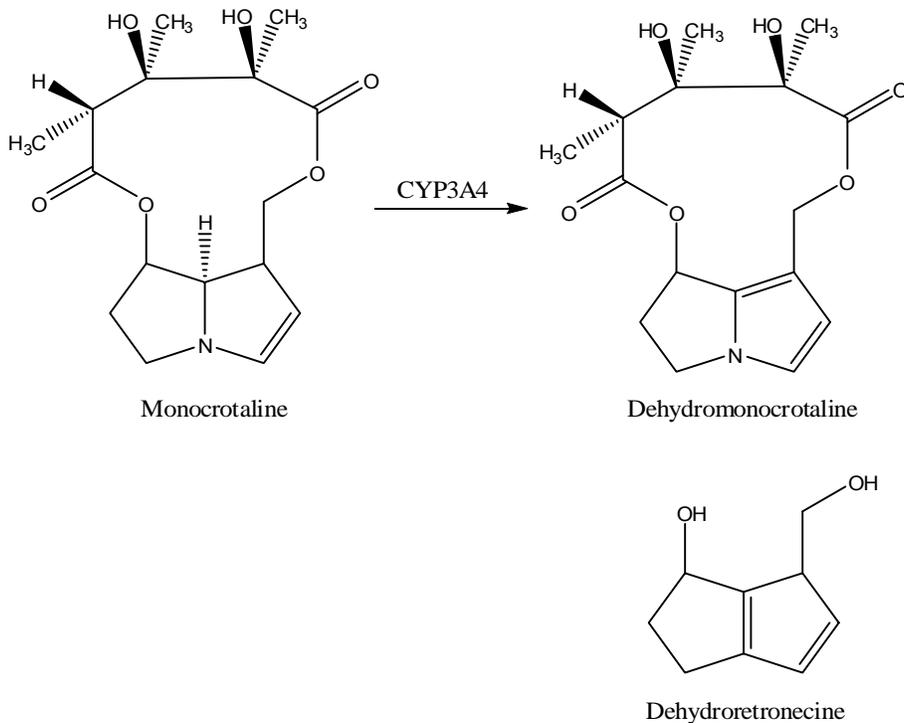
¹⁶ <http://www.fda.gov/medwatch/safety/2008/safety08.htm#Xiadafil> accessed June 2, 2008

¹⁷ <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01840.html> accessed June 2, 2008

¹⁸ <http://www.mayoclinic.com/health/herbal-viagra/AN00702> Accessed June 2, 2008

Even more noteworthy is the fact that the pulmonary arterial hypertension secondary to monocrotaline¹⁹, is mediated by its active metabolite monocrotaline pyrrole, (See Figure 3).

Figure 3 Structure and Metabolism of Monocrotaline



Ref: [Nucleic Acids Research Volume 26, Number 23 Pp. 5441-5447](http://nar.oxfordjournals.org/cgi/content/full/26/23/5441)
<http://nar.oxfordjournals.org/cgi/content/full/26/23/5441> accessed June 4, 2008

¹⁹ Monocrotaline is a plant pyrrolizidine alkaloid that has been used for decades to study mechanisms of pulmonary arterial hypertension.

3.4 *Cardiopulmonary Safety Signals Observed with Asenapine*

Near the end of the PDUFA review cycle this reviewer noticed a high incidence of cardiopulmonary SAEs and liver injury in healthy volunteers. In addition, there was a high rate of AEs when asenapine was given in a single low dose in combination with paroxetine or carbamazepine to healthy volunteers, thereby indicating serious pharmacodynamic and/or pharmacokinetic interactions.

While checking to see if any significant SAEs had been reported in the NDA that might be attributable to drug-drug interactions this reviewer found a death that appeared to be secondary to a developing aplastic anemia. Based upon known structure activity relationships, although 'unexpected' this was not totally surprising. Further analysis revealed that while all blood cell lines were decreasing, neutropenia and agranulocytosis and their complications would have likely ensued prior to full aplastic anemia developing, (see Figure 4 and Figure 5 in section 3.5.1.8). Therefore while death due to agranulocytosis is presumed by this reviewer and cannot be ruled out, presently due to the limited laboratory values available from prior to death only a moderate leucopenia can be presently documented and death would have likely ensued prior to full blown aplastic anemia developing. However, this reviewer believes that if the labeled actions indicated for similar events with the structurally and pharmacologically similar clozapine had been undertaken by the sponsor, the subject might still be alive. Instead documents in the IND and NDA indicate that the sponsor(s) were aware of what was occurring and simply did not take reasonable actions that might have prevented the patient's death. In addition, it's clear that this event was not reported to the IND as required, although it may have prompted the sponsor to institute a request to the IND for a drug safety monitoring board in order to break the study blind so as to fulfill reporting requirements for SAEs in Europe where the study was taking place.

This death and a second case of decreasing WBCs associated with death appear to be time dependent and due to a cumulative toxicity as they were associated with long term treatment, i.e. > 1 year. Examination of alternative mechanisms to explain other deaths that could not be attributed to the N-oxide revealed the potential for phen-fen type toxicities with asenapine or metabolites. This and requests for further clarification of subject identification by Dr. Temple along with serendipitous findings revealed numerous other cases of potentially life threatening toxicities. Some of which were known from the initial 30 day IND submission, (see §4.2 Appendix 2 – Safety Signal from Original IND Submission).

It should be noted that the signs and symptoms can appear contradictory as seen with dihydroergotamine. This variability in observed toxicities effect appears to be due to variability in effects at structurally related receptors, the complexity of opposing effects of parent drug as well as metabolites, and the variability in exposures and interindividual response potentially due to individual pharmacogenomic phenotypes, drug interactions, and underlying illnesses,. Thus potentially contradictory signs and symptoms should not be separated in assessing risk; rather they should be assessed cumulatively.

3.5 Listings of Adverse Events Potentially Related to Proposed Mechanism(s)

The following subsections include modifications of lists of potential cases previously provided to Dr. Temple on Tuesday, May 27, 2008.

Due to time constraints to provide this information, this reviewer has simply modified some tables provided by the sponsor. This is why the various tables are not 'pure'. For example suicide is included in the list of deaths in the phase II/III studies. This is clearly not a cardiopulmonary related death, although based on the acute bipolar studies and the known effects of certain serotonin receptor subtypes in the brain, suicide and suicidality should be considered a drug induced toxicity especially in patients with bipolar disorder.

In addition, cardiopulmonary effects, vasoconstriction and effects of serotonin and serotonergic receptors on platelet aggregation may also explain the increased risk of venous thromboembolism with antipsychotics.

This reviewer realizes that not all cardiac observations listed may be either due to asenapine or even similarly ascribed to asenapine by all people, however when the totality of the evidence including potential mechanisms are examined the data evinces to this reviewer that the toxicities and risks are likely associated with asenapine and cannot be easily dismissed as being unrelated.

Lastly this is only a limited listing of potential SAEs related to these underlying mechanisms, when going back to identify subject numbers for deaths per Dr. Temple's request this reviewer found numerous additional SAEs for cardiac arrhythmias in a single study. Since, SAEs in studies and in particular in chronic long term studies where they are most likely to occur due to cumulative toxicities were not examined, there is likely many more SAEs that are included the safety information that is available but that has not been identified as yet. Therefore the true risk of SAEs is likely under estimated even for the presently available data.

Many but not all potential SAEs of particular interest are highlighted in various ways. Highlighting was curtailed with §3.5.1.8 (Other SAEs Reported in Original OCP Review), due to a lack of time.

3.5.1.1 Subjects who Died in Primary Efficacy and Safety Phase 2/3 Studies

Table 61 Listing of subjects who died (combined Phase 2/3 studies, cohort E)
(N.B. additional subjects added found while examining details of deaths from Study P25517)^a

Study	Subject ID	Treatment	Preferred Term	Age/ Sex/ Race	AE Start / Stop Day	Action Taken	Related According to Sponsor	Intensity according to Sponsor
041013	28	asenapine 1.6 mg BID	epiglottitis laryngitis tinea pedis dystonia insomnia psychotic disorder dyspnea hematoma	49/Male/ Caucasian	5/5 5/5 4/5 5/5 4/5 3/5 5/5 3/5	NA NA None NA None Stopped NA None	No No No No No No No No	Severe Severe Mild Severe Severe Severe Moderate Moderate
			Pathologic examination showed erythema and severe edema of epiglottis and laryngo-pharynx and tracheitis consistent with acute laryngitis; stenosis of left anterior descending and first lateral branch of the left circumflex artery, mild stenosis of the right coronary artery and nephrosclerosis consistent with hypertensive atherosclerotic cardiovascular disease. The examiner's report also noted injuries to the left side of upper chest (CPR related), abrasions to the right elbow and confluent contusions of the lower extremities.					
041013	48	asenapine 1.6 mg BID	hyperthermia pulmonary embolism	57/Male/ Caucasian	47/47 47/47	None NA	No No	Severe Severe
			At screening, ECG showed right atrial enlargement purportedly due to the subject's history of COPD. The autopsy report indicated that the cause of death was pulmonary thromboembolism in the right pulmonary artery. Anorexia beginning 6 days after starting drug.					
25517	115024	asenapine 5-10 mg BID	completed suicide schizophrenia	25/Male/ Caucasian	18/18 18/18	None None	No No	Severe Severe
25517	127004	asenapine 5-10 mg BID	completed suicide	32/Male/ Caucasian	152/152	None	No	Severe
25517	130013	asenapine 5-10 mg BID	completed suicide	31/Male/ Caucasian	257/257	None	Unlikely	Severe
25517	131010	asenapine 5-10 mg BID	completed suicide	25/Male/ Caucasian	33/33	None	Unlikely	Severe
25517	186007	asenapine 5-10 mg BID	lobar pneumonia pneumonia	52/Male/	42/46 40/46	None None	Unlikely No	Moderate Severe
			On 4 August 2004 subject experienced productive cough. He was found to be pyrexia and had some shortness of breath on 6 August 2004. Subject was transferred to the casualty department and was diagnosed with pneumonia of left lower lobe (Lobar pneumonia). He was treated with ampicillin intravenously (and oxygen as needed) and improved. On (b) (6) subject returned to psychiatric hospital. There, subject collapsed; he coughed up brown sputum and then stopped breathing. Subject died on (b) (6). The reported cause of death was bronchopneumonia, no other medical problems or clinical signs could have played a role in subject's death, according to the investigator. No autopsy was performed. Cardiologist's report locally at screening said borderline left ventricular					

			hypertrophy but no evidence of left ventricular strain. Could be normal variant. In light of absence of any other cardiac features (signs or symptoms) taken to be normal variant. No cardiac or cardiovascular problems in the past or prior to the SAE					
25517	242020	asenapine 5-10 mg BID	coronary artery insufficiency	50/Male/ Caucasian	6/6	None	Unlikely	Severe
			<p>he was found dead lying near his bed at 03:10. The nurse had seen him sleeping in his bed at 02:00. Autopsy was performed on (b) (6). The preliminary report indicates acute coronary failure in the present of non-significant coronary sclerosis.</p> <p>The performed autopsy and microscopy have revealed the following abnormalities:</p> <ol style="list-style-type: none"> 1. Signs of severe hypoxia or anoxia in the cortex of the cerebral hemispheres evidenced by nerve cell changes following the so-called "ischaemic type". No such changes are observed in the rachidian bulb. 2. Small (40-100 um in diameter) fresh haemorrhages (most likely of diapedetic origin from micro vessels) in the cortex of the cerebral hemispheres. No haemorrhages are observed in the rachidian bulb. 3. Initial signs of arterosclerosis in the aorta and coronary artery. 4. Emphysema in the uppermost part of both lungs 5. Colloid nodular goiter None of the above factors can explain the sudden death. <p>It is most likely that due to some factors which cannot be detected at autopsy there was cerebral claudation of the cerebral hemispheres that caused severe hypoxia or anoxia of the cortex of the cerebral hemispheres. The hypoxia or anoxia, in its turn, resulted in disturbance of microvascular wall permeability in microvessels which led to small, microscopic haemorrhages in the cortex of the cerebral hemispheres. Further we can suppose that, as a result of some functional shifts, the changes in the cortex of the cerebral hemispheres caused acute reflex cardiac arrest (Cardiac failure acute) that was a direct cause of the sudden death. No relevant medical history. No relevant concomitant diseases were reported. No cardiac signs or symptoms present</p> <p>QTc 471</p>					
P25517	188002	Olanzapine 10 – 20 mg qd	On drug 364 days. Meds D/Ced 18Nov2004. On day of med d/c peripheral edema and joint stiffness reported.					
25517	248014	asenapine 5-10 mg BID	completed suicide schizophrenia, paranoid type	21/Male/ Caucasian	8/8 8/8	None None	Unlikely Unlikely	Severe Severe
A7501004/ A7501006		asenapine 5-10 mg BID	accidental overdose	32/Male/ Caucasian	53/53	NA	None	Missing
A7501004	40111002	asenapine 5-10 mg BID	completed suicide	49/Male/ Caucasian	12/12	NA	Possible	Severe
041021	125010	olanzapine 15 mg QD	overdose	33/Male/ Other	37/37	Stopped	Unlikely	Severe
25517	204011	olanzapine 10-20 mg QD	completed suicide	41/Male/ Caucasian	376/376	None	Unlikely	Severe
A7501004	41331009	olanzapine 5-20 mg QD	completed suicide	40/Female/ Asian	13/13	Missing	Unlikely	Missing
041023	363015	placebo	thymoma malignant	42/Male/ Caucasian	7/24	Stopped	No	Severe
P25517	192001	Asenapine 5 – 10 mg bid on meds 365	A 38 year old male subject, with a history of chest pain, started study medication on 20 November 2003. From 8 December 2003 to 10 December 2003 he experienced atypical chest pain. He was treated with paracetamol, acetylsalicylic					

		days.	acid and caffeine. An ECG done at week 3 visit was reported to be abnormal. Cardiology was consulted and a Troponin T test was found to be positive. Subject was hospitalized on (b) (6) for further investigation. Study medication was interrupted the same day. An angiogram was performed on (b) (6) for final diagnosis. Myocardial infarction (Myocardial infarction) (occlusion of right posterior inferior coronary artery) was confirmed. Study medication was continued and he was treated with isosorbide. He recovered with sequelae and was discharged (b) (6). Also Sinus rhythm 96 bpm. Mild left ventricle hypertrophy No murmur T wave inversion in AVF,I and II. No ST depression or pain on stress ECG.
P25517	194001	Asenapine 5 – 10 mg BID	19 yo BM Subject started taking study medication on 25 October 2003. On 1 (b) (6) subject was hospitalized for observation and for monitoring of his eating habits. He had experienced weight loss (Weight decreased), as he had no money to buy food. On 26 October 2004 study medication was discontinued according to protocol (not due to the adverse event). Subject recovered and was discharged on (b) (6).
P25517	194003	Asenapine 5 – 10 mg BID	19 yo BM On drug 310 days "Non-specific ST segment changes with ST elevation in the antero-septal leads as well as the infero-lateral leads. This is a normal early repolarization variant. Corrected QT interval is prolonged at 0.5. 22-DEC-04 Stress ECG subject only managed 5 minutes 14 seconds on a Bruce protocol achieving a maximum heart rate of 125/min with no evidence of arrhythmia or ischaemia."
P25517	22003	Asenapine 5 – 10 mg BID	50 yo WM on drug 281 days A subject using study medication was admitted to the hospital on (b) (6) due to breathlessness and thoracic compressing pain (5 hour duration). Subject was diagnosed with heart failure exacerbation (Cardiac failure). Study medication was continued and subject did not drop out of the trial. He was treated with metoprolol, polfilin, nitroglycerin, clexane, furosemide, enarenal and acetyl salicyclic acid. Subject recovered and was discharged on (b) (6).
P25517	221001	Asenapine 5- 10 mg bid	36 yo WM 63 days on drug. Also took ciprofloxacin and pefloxacin due to 2 degree burns Dec 7 – Dec 23 had Headaches.
P25517	221005	Asenapine 5- 10 mg bid	47 yo WF on drug 367 days. lowering of her hemoglobin level and hematocrit was noticed. She was hospitalized on (b) (6) and diagnosed with anaemia (Anemia). Study medication was continued. Subject was discharged on (b) (6). Anaemia had resolved on 20 April 2004.
P25517	174001	Asenapine 5 – 10 mg BID	ECG changes 19FEB2004 Moderate None Still present Probable
P25517	221010	Olanzapine 10- 20 mg qd	On olanzapine 22 days. diagnosed with an abnormal ECG: T wave abnormality, considered inferolateral ischemia, ST abnormality (decreased) (Myocardial ischaemia). Study medication was discontinued due to this adverse event. At the time of report subject had not recovered.

a Additional subjects were found by serendipitously while looked for information requested by Dr. Temple. A search of the case report forms for study P25517 was then performed using the search term ECG. Additional suspicious AEs are likely to have been found if additional search terms based on expected toxicities were to be performed and especially if all studies are examined.

Some of the deaths are particularly troubling as they could be due to an exacerbation of underlying conditions by asenapine including at doses that are considered to be subtherapeutic doses. If this is the case with a population that has been presumably carefully screened under conditions where the sponsor appears to have been aware of the risks *a priori* then it raises serious questions regarding the safety of asenapine in the studied population, which would be expected to be at lower risk than the population that would actually use the drug.

Another troubling aspect of this and other tables are the relative number of SAEs reported with asenapine as compared to active comparators which would be expected to have similar toxicities

Another concern is that subjects in these studies may have already been on similar drugs. Thus the degree of risk in treatment naïve patients is likely unknown as subjects who are likely to experience toxicities with asenapine acutely have already been screened out. This is likely to be less of a concern initially, however over time as older drugs come off patent and treatment naïve patients are more likely to be placed on asenapine first, the incidence of toxicities when patients are beginning treatment with asenapine is likely to rise as patients who may be genetically predisposed will not have been screened out as was the treatment population in the clinical trials.

3.5.1.2 Listings of Subjects who Died in Ongoing Studies

Table 5 Subjects Who Died in Ongoing Studies

Study	Subject ID	Treatment	Preferred Term	Age/Sex/Race	AE Start / Stop Day	Action Taken	Related According to Sponsor	Intensity According to Sponsor
041513/	315504	double-blind	respiratory failure	37/Male/Caucasian	204/204	NA	Unlikely	Severe
041513/	368509	double-blind	sudden death completed suicide	23/Male/Caucasian	96/96 96/96	NA Stopped	Unlikely Unlikely	Severe Severe
25543/	125005	double-blind	completed suicide not coded (suicide)	64/Male/Caucasian	31/31 30/30	NA Stopped	Possible None	Severe Severe
25543/	125006	double-blind	completed suicide schizophrenia, paranoid type	51/Male/Caucasian	191/191	NA	Possible	Severe
A7501007/	50281012	double-blind	bipolar I disorder completed suicide	24/Male/Caucasian	178/178 178/178	NA NA	Unlikely Unlikely	Severe Severe
A7501007/	51241008	double-blind	death neonatal drug exposure during pregnancy India died 5 min after birth	37/Female/Asian	385/385 385/385	NA NA	Possible Possible	Severe
P25520/	132017	double-blind	death	44/Female/Caucasian	491/521	None	None	Severe
P25520/	241041	double-blind	pulmonary embolism arteriosclerosis	57/Female/Caucasian	470/474 470/474	Stopped Stopped	Unlikely Unlikely	Severe
P25520/	246021	double-blind	cardiac failure	57/Male/Caucasian	430/430	None	None	Severe

3.5.1.3 Neonatal Risks

3.5.1.3.1 Human Data

The death of the neonate in the previous section is noteworthy as mechanistically it's expected that exposure to asenapine late in pregnancy might cause pulmonary arterial hypertension, (PAH). PAH in neonates frequently causes death within a few days of birth and of the infants who survive 50% experience deafness or other neurologic deficits.

Table 6 on the following page is a summary of the pregnancies reported in the NDA.

The studies are divided into completed and ongoing studies, which are essentially acute and chronic treatment studies. Since subjects are screened for pregnancies prior to enrollment and before starting drug any exposures in completed (acute) studies would occur early in pregnancy and would not be expected to show pulmonary arterial hypertension even if the pregnancy was allowed to proceed to birth. In addition, since exposure would be so early, if there were fetal damage and the the pregnancy were allowed to continue the most likely outcome would be a spontaneous abortion at around the end of the first trimester. Thus it is not surprising that the one pregnancy that proceeded to completion resulted in a healthy birth. This is not to say that there might not be more subtle effects but these 4 cases would not be expected to be informative unless there were a number of spontaneous abortions.

The ongoing studies (chronic) studies are potentially more informative. Table 6 was a first attempt by this reviewer to glean information, but work on this table was stopped at the end of the workday and the following day it was realized that a different approach was needed. This resulted in Table 7, which is a more detailed table for the pregnancies in the chronic studies and which was constructed that following day.

Treatments are still 'blinded' in the ongoing studies and although it would be possible to unblind them and even though study 25520 has already been unblinded even knowing the treatments would not be informative, as 3 of the pregnancies were terminated early and another appears to be a mistaken report.

With respect to the other 2 pregnancies treatments were stopped at around the end of the second trimester and since pulmonary arterial hypertension would only occur if exposure is later in pregnancy the healthy birth that is from this subset does not address this particular risk.

The last pregnancy is the case of the premature delivery and death. This is the same case which the sponsor listed as a possible death due to asenapine. The fact that the sponsor listed this death as potentially due to asenapine was the original flag that raised the concern of drug induced neonatal PAH to this reviewer.

This particular woman had a history of a number of other pregnancies with poor outcomes. This confounds interpretation, however the timing of 2 of the spontaneous abortions indicate either that these fetuses were malformed or that there may have been a hormonal issue. The third spontaneous abortion at 20 weeks, the caesarian section at 34 weeks due to fetal distress, and the premature birth in the present case, with death occurring at 5 minutes postnatal raise questions as to the causes. One wonders if there could there have been pre-eclampsia or vasoconstriction of blood flow to the placenta or to fetal tissues due to the patient's genetics or the serotonergic effects of antipsychotic drugs, or a combination of the two. A medication history, fuller histories of the previous pregnancies including the postnatal history of the surviving infant, and an autopsy in the present case would be informative and as much of this information as possible should be obtained and submitted to the NDA.

Table 6 Summary of Pregnancies Reported in Summary of Clinical Safety

Total Pregnancies Reported in NDA			9								
Completed Studies	# Pregnancies in Completed Studies		4								
	Treatments Associated with Pregnancies in Completed Studies	Asenapine	1								
		Olanzapine	3								
	Outcomes				Study	Subject	Country	Gestational Age at Exposure	Duration of Exposure	Comments	
			Asenapine	Pregnancy Ongoing							
				Healthy Births							
				Birth Defects							
				Neonatal Deaths							
				Therapeutic Abortions	1	A7501006	50341004	US	Not reported		4 weeks
			Lost to FU								
Olanzapine			Pregnancy Ongoing								
			Healthy Births	1	A7501004	41211007	US	Not reported	10 days		
			Birth Defects	0							
	Neonatal Deaths										
	Therapeutic Abortions	1	41021a	125023	US	Not reported	9 days				
Lost to FU	1	41021a	206003	US	Not reported	8 days					
Ongoing Studies	# Pregnancies in Ongoing Studies		5								
	Treatments Associated with Pregnancies in Ongoing Studies	Blinded	5								
		Outcomes	Blinded Treatments	Pregnancy Ongoing	0						
	Healthy Births			0							
	Birth Defects			1	A7501007	51231013		7 - 25 weeks?	24.5 weeks?		
	Neonatal Deaths			1	A7501007	51241008	India	Not Reported	26 weeks		
	Therapeutic Abortions			3	41513	376503	US	Not Reported	8 weeks		
					41513	361500	US	Not Reported	2 weeks		
		25520	242008	RU	Not Reported	?					
Lost to FU	0										

Study A7501006 9 week Extension Bipolar Maint Study Multinational PBO, Asenapine 5 – 10 mg BID, Olanzapine 5 – 20 mg Completed June 2006
 Study A7501004 3 week Acute Bipolar Study Multinational PBO, Asenapine 5 -1 0 mg BID vs. Olanzapine 5 – 20 mg Completed April 2006
 Study 41021 6 week Acute schizophrenia Study Multinational PBO, Asenapine 5 mg , Asenapine 10 mg, Olanzapine 15 mg QD, Completed May 2006
 Study A7501007 (Ext of A7501006) 40 week Extension Bipolar Maint Study Multinational, PBO, As 5 – 10 BID, Olanzapine 5 – 20 mg (Cut off for clinical database Jan 15, 2007) Study End May 2007 Planned
 Study 41513 (ext of 41023) 52 week total duration Extension Schizophrenia; PBO, As 5 mg, As 10 mg, Haldol 2 – 8 mg BID, Ongoing (Cut off for clinical database Jan 15, 2007) Study End Nov 2007 Planned
 Study 25520 52 week efficacy in Schizophrenia / Schizoaffective Disorder; PBO As 5 – 10 BID, Olanzapine 10 – 20 mg QD B Study End Sept 2006 (Terminated)

Table 7 Detailed Information on Pregnancies in Ongoing Studies

Study	Subject	Country	Drug Start Date	Drug Stop Date	Duration on Drug (weeks)	Date of Conception	Detection of Pregnancy	Duration of Exposure to Fetus	Outcome	Gestational Age at Pregnancy Termination (weeks)	Comments
41513	376503	Romania	7-Jan-2006	11-Jun-2006	22.1	(b) (6)		8 weeks	Pregnancy Terminated (b) (6)	10	
41513	315507	US	19-Jan-2006	12-Jul-2006	24.9			3 months	Not Applicable	NA	Nov 8, 2006 Reported that Pregnancy Test was false + - needs clarification
41513	361500	Russia	10-Nov-2005	26-Dec-2005	6.6			16 days	Pregnancy Terminated (b) (6)	6	
25520	242008	Russia	14-Sept-2004	24-Jul-2006				3 weeks	Pregnancy Terminated (b) (6)	3	It was claimed that subject did not inform investigator of pregnancy
A7501007	51241008	India	30-Jul-2005	27-Jul-2007	103.9			26 weeks	Preterm Delivery (b) (6)	29 - 31.5	Positive pregnancy test when tested at end of trial. The mother has a history of four pregnancies. One live birth per Caesarean section, due to fetal distress, performed at the gestational age of 34 weeks and three spontaneous abortions: the first at the gestational age of 14 weeks, the second at the gestational age of 12 weeks and the third at the gestational age of 20 weeks.
A7501007	51231013	India	5-May-2006	14-Dec-2006	32			24.5 weeks	Healthy Baby - Estimated Delivery Date (b) (6)		

3.5.1.3.2 Animal Data

The pharmacology / toxicology review was referred to in order to see if preclinical data might shed light on the risk of pulmonary arterial hypertension with asenapine.

Table 8 shows a summary of fertility and early embryonic development studies from the April 30, 2008 Pharm/Tox Review. It is divided into 4 sections:

- Pilot Mating and Fertility Studies
- Mating, Fertility, and Teratogenicity Studies
- Embryo-fetal Development and Teratogenicity Studies
- Pre- and Post-Natal Development Studies

The table is largely self-explanatory. Comments include comments taken directly from the pharmacology and toxicology review and are shown in italics. Those comments that this reviewer believes are interest are highlighted in red or blue text. Where additional data or information elucidate the results they are also referred to in the comments section, and these tables immediately follow Table 8.

Pilot Mating and Fertility Studies

There was little effect of asenapine.

Mating, Fertility, and Teratogenicity (Early Embryonic Development) Studies

This study was considered inadequate however it's noteworthy that there's a congenital heart defect in one rat. It's noteworthy that there's a dose dependent post-natal mortality that occurs primarily in the first few days post partum and there's a high degree of cannibalism in the high dose group. This indicates potential issues with both late stage fetal development and possibly with breast feeding. These results are consistent with the suspected toxicities. It should be noted that in this study Wistar Rats were used, however with monocrotaline the risk of PAH is greatest with Sprague-Dawley Rats and might be due to differences in metabolic activation due to metabolism.

Embryo-fetal Development and Teratogenicity

There were 6 embryo-fetal development and teratogenicity studies where rats or rabbits were exposed to asenapine during the period of fetal development that corresponds to implantation to closure of the hard palette in rats or the period of organogenesis in rabbits.

What's striking is that in every one of these six studies there are indications of effects on bone formation and in some there are also indications of effects on connective tissue. Specifically there are dose dependent effects on bone ossification, including increases in poorly ossified and nonossified bone.

As has been seen with other drugs when a particular litter is effected the data is excluded from the analysis, even that this may indicate that is a borderline dose for the toxic effect and there may be increased exposure to parent drug or metabolite in that particular dam.

These studies were initially conducted in Sprague-Dawley and Wistar/HAN rats with PO administration and later in 2005 in Sprague-Dawley Rats with IV administration. In addition 3 different rabbit strains were used. The fact that effects were seen in two different species and all strains, were dose dependent and were even seen when conditions would be expected to minimize finding effects, significantly raises the level of concern that these effects are based on a mechanism that is common across a variety of species and will be seen in humans. In addition the suspected mechanism indicates that connective tissue effects will be seen not only in neonates but also in older individuals where bone remodeling is ongoing, such as growing children whose skeletons are constantly reforming as they grow.

A high incidence of bone malformations were seen in rabbits at doses of 30 mg/kg/day (see Table 8 and Section 0 (Appendix 3 – Skeletal Exams in Chinchilla Rabbits - Study SDG RR 2914) however even at low doses likely to produce exposures only a few fold higher than in humans effects on bone ossification were seen.

Other findings include brain malformation and an umbilical hernia and repeated findings include effects on the eye, and hydronephrotic kidneys in both rabbits and rats. Particularly worrisome is the evidence of pulmonary effects in rabbits and that for several experiments the examinations appear designed to avoid detecting certain problems, i.e. visceral and soft tissue findings, in spite of the fact that the sponsor appears to be looking specifically for skeletal problems.

Based on these studies there is no margin of safety relative to the human dose in Sprague-Dawley Rats. Plus in Chinchilla and New Zealand White Rabbits there is a 2 – 3 fold increased risk for major visceral malformations at asenapine exposures only double those in humans.

Pre- and Post-Natal Development Studies

There were 5 pre- and post-natal development studies in Sprague-Dawley Rats.

Two of these, including one conducted in 1992, were fostering studies where pups either exposed or not exposed in utero were fostered by dams either exposed or not exposed to asenapine. This is highly unusual unless the sponsor is looking for a specific effect such as toxicity due to breast feeding. Also troubling is that all but one of these studies utilized IV dosing which would minimize the formation of any toxic metabolites. The IV pilot studies that appear to be primarily for dose selection purposes for the second fostering study clearly show that there is an increase in mortality due to exposure in utero late in pregnancy, as would be expected with a drug causing PAH. Having both an IV and PO fostering allow comparisons and although the IV dose was 1/10 the PO dose the pup mortality was still increased in the first 4 days post-partum, (20% - 25%), as compared to 3% in the control group, but what is amazing is that this increased mortality was seen even when the pups were only exposed by breast feeding.

Although 2 of these studies noted that pups were bluish and this was explained as hypothermia, the fact that this also occurred on the heads and snouts and is consistent with the mechanism suggests that it may actually be due to cyanosis.

Table 8 Summary of Fertility and Early Embryonic Development Studies from the April 30, 2008 Pharm/Tox Review

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (Comments in <i>Italics from Pharm/Tox Review</i>)
Pilot Mating and Fertility	SDG 2315	1981	NO	Rat Sprague-Dawley	PO	30 mg/kg/day		Males: No Effect of asenapine Females: Decrease in Pregnancy Rate
Mating, Fertility, and Teratogenicity (Early Embryonic Development)	SDG RR 3115	1990	YES	Rat Wistar	PO	0, 0.5, 2.5, 15 mg/kg bid	Up to day 21 (i.e. parturition) or 21 days post partum	<p><i>“There were no teratogenic effects observed in this study. However, it is unclear whether the external and visceral malformations were properly examined. Visceral examination demonstrated one MD fetus with a heart defect. Two abnormal fetuses were reported at the LD upon external examination. Therefore, only 3 malformed fetuses were reported upon external or visceral examinations. It appears extremely unlikely that no spontaneous external or visceral findings were detected in any fetus in all other groups. Therefore, evaluation of teratogenic effects in this study is considered inadequate.”</i></p> <p>See Table 9. There was a dose response in both fecundity and with post-natal survival. Most of the postnatal deaths occurred by day 4. <i>“The incidence of cannibalism in Group 4 (the high dose group) was high.”</i></p>
Embryo-fetal Development and Teratogenicity	SDG RR 2316	1988	NO	Rat Sprague-Dawley	PO	30 mg/kg/day	Days 6 to 17	<i>“The abnormal litter ratio was 13.3% and 40.0% in the control and asenapine treated group, respectively. Malformations were detected in 2/213 control fetuses in 2 litters and 4/107 treated fetuses in 4 litters (hydronephrotic kidney in 2 control and 2 asenapine-treated fetuses, and bilateral anophthalmia in 2 additional asenapine-treated fetuses). The degree of ossification of various skeletal elements (e.g. sternebrae 5, 5th proximal phalange) was slightly less in fetuses of asenapine treated group.”</i>
	SDG RR 2961	1990	YES	Rat Wistar/HAN	PO	0, 0.5, 2.5, 15 mg/kg bid	Days 7 - 17	<p><i>“Asenapine was not teratogenic in this study. The NOAEL for maternal toxicity was considered to be below the LD. The NOAEL for the reproduction and F1 parameters was the MD. However, it is unclear whether the external and visceral malformations were properly examined. Only one malformed fetus was reported upon external or visceral examinations in the LD group. It appears extremely unlikely that no spontaneous external or visceral findings were detected in any fetus in all other groups. Therefore, evaluation of the external and visceral teratogenic effects in this study is considered inadequate.”</i></p> <p><i>“This study was also reviewed by Dr. Lois Freed under the IND 51,641. She concluded that “the lack of specific findings suggests reduced sensitivity to detect soft tissue abnormalities, variants, etc. Unless data can be provided that adequately document the sensitivity of the methods used to assess fetal effects, the studies may need to be repeated”.</i></p> <p><i>“On visceral examinations, no abnormal findings” was reported for all groups, including control. Drug-related effects on skeletal parameters were noted, including both increases and decreases in ossification. The incidence of incomplete ossification and non-ossified skeletal elements (sternebra, vertebra, and limbs) was slightly increased in the asenapine-treated groups. These findings were generally not statistically significant, except non-ossified metatarsalia 1 (hind limb) at the HD and decreases in non-ossified digit 5 distal phalanx (forelimb) at all doses.”</i></p> <p><i>“Wavy ribs were observed in the control, LD and MD, but not in the HD fetuses. There were no increases in skeletal malformations in dosed groups.”</i></p>
	INT00002826	2005	YES	Rat Sprague-Dawley	IV	0, 0.3, 0.9, 1.5 mg/kg body weight/day Rate not specified	Days 6 to 17 from implantation to hard palate	<p><i>“within short time after application animals show short-lasting ataxia and then persist in a motionless condition. Muscle tone was increased. Animals remain conscious, but high-grade reduced in motoric activity.”</i></p> <p><i>“There were no external or visceral findings related to the test article. Skeletal abnormal findings (malformations and variations) were noted in 4 fetuses in 3 litters (14% of all litters) of the control group, 3</i></p>

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (Comments in <i>Italics</i> from Pharm/Tox Review)
								<p><i>fetuses in 3 litters (14% of all litters) at the LD, 4 fetuses in 3 litters (14% of all litters) at the MD, and 10 fetuses in 5 litters (24% of all litters) at the HD. The percentage of all fetuses affected was 2.6% (4/152), 1.9% (3/154), 2.7% (4/148), and 6.6% (10/151). Abnormal findings at the HD included zygomatic arch fusion, rudimentary cervical rib, misshapen scapula, fused thoracic vertebral arch, dumbbell-shaped or bipartite lumbar or thoracic vertebral body, misshapen cervical vertebral arch, and fused rib. These findings were of low incidence and restricted to one to three litters. The majority of findings occurred in several fetuses of one single litter delivered by dam no. 85. Dam no. 85 was more sensitive than other animals since its body weight development was lower than that of all other animals in this group on days 6-10 of pregnancy. Macroscopic observations indicated a mass in the chest wall region (d=20 mm) of dam no. 85, which was considered an incidental occurrence by the Sponsor. Excluding the litter delivered by the dam no. 85, malformations were observed in 6 fetuses in 4 litters (20% of all litters; 3.9% of all fetuses) at the HD."</i></p> <p><i>"There were no test article-related external or visceral findings in fetuses at any dose level. Skeletal examinations demonstrated minimally increased incidence of a variety of abnormal findings in 5 HD litters. However, the majority of the findings occurred in one individual litter from the HD dam no. 85. Macroscopic observations indicated a mass in the chest wall region of this dam, which was considered an incidental occurrence. Therefore, findings in the litter from the dam no. 85 can be excluded from the assessment of teratogenic effects. In conclusion, findings at the HD are not considered drug-related. The NOAEL for maternal toxicity and for fetal and skeletal abnormalities is the HD of 1.5 mg/kg/day AE (2.11 mg/kg/day expressed as the maleate). This dose is equal the MRHD of 10 mg b.i.d. on mg/m2 basis."</i></p>
	SDG RR 2328	1982	NO	Rabbit Dutch	PO	30 mg/kg/day	<p>Day 6 to 18 of Pregnancy</p> <p>Period of organogenesis</p>	<p><i>"Fetal examinations included external malformations, sectioning for brain and eye defects, and trunks examined only for skeletal malformations (alizarin red stain) (Individual animal data for malformations were not submitted). One control and two drug treated females were not pregnant, resulting in a slight decrease in pregnancy rate (91.7% and 83.3%, respectively). There were no other drug-related effects on any other parameters, except malformed brain in one fetus in group administered asenapine."</i></p> <p>N.B. the trunks were not examined for visceral malformations.</p>
	SDG RR 2914	1990	YES	Rabbit/Chinchilla	PO	0.5, 2.5, and 15.0 mg/kg b.i.d at an interval of 5 hours	<p>Day 6 to 18 of Pregnancy</p>	<p>Mortality (dams): Two HD females (No. 62 and No. 52) died about 5 minutes after the second daily administration: No. 62 (day 10 of gestation, day 5 of dosing) and No. 52 (day 15 of gestation, day 10 of dosing). In female No. 62 dyspnea and ventral recumbency were observed prior to death. These symptoms started about 20 minutes after the first daily administration in the morning. No clinical signs were observed in female No. 52. At necropsy, reddened and incompletely collapsed lungs were noted in female No. 52. The Sponsor considered both deaths to be drug related.</p> <p>Clinical signs (dams): Animals were observed twice daily. Dyspnea and ventral recumbency were observed in HD female No. 54 on days 18 and 19 of pregnancy. These signs were similar to the observations in HD female No. 62 that died as described above.</p> <p><i>"There were dose-related (all doses) increases in non-ossification or incomplete ossification of the number of skeletal elements when expressed as affected fetuses. When expressed as the number of affected litters, drug-related increases were noted primarily at the HD. These developmental delay effects may be related to the decreased maternal body weight and food consumption at the HD. There were certain skeletal elements in which the incidence of non- or delayed ossification was reduced in dosed groups when data are expressed as number of affected fetuses, e.g., non-ossified rib 13 (left, right), decreases in incomplete ossification of digit 5 medial phalanx (right forelimb), toe 4 medial phalanx (left and right) were associated with increases</i></p>

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (Comments in <i>Italics from Pharm/Tox Review</i>)
								<p><i>in the incidence of nonossification of these same sites. There was also an increase in shortened rib and flying rib at the HD.</i></p> <p>(See §0 Appendix 3 – Skeletal Exams in Chinchilla Rabbits - Study SDG RR 2914)</p>
	SDG RR 4428	1995	YES	Rabbit NZ White	PO	0.025 0.125 0.625 mg/kg/day	Day 6 to 18 of Pregnancy with Toxicokinetics AUC 2 x Hum Exam for visceral AUC 179 Pulm red Foci	<p><i>“Mortality (dams): There were 7 unscheduled deaths. According to the Sponsor, 5 animals were sacrificed after being accidentally paralyzed; these animals were replaced. One MD female died on day 24 of gestation. Subcutaneous hematoma on the abdominal wall was noted in this animal at necropsy. One HD female died on day 9 of gestation. Polypnea and ptosis were observed between 5 min and 2 h after dosing in this animal. At necropsy, many red foci on the surface of all lobes of the lungs were noted. The reason of death was not further explained by the Sponsor</i></p> <p><i>Clinical signs (dams): Animals were observed daily for clinical signs. Polypnea (all animals), occasional motor incoordination (18/26 animals), occasional ptosis (all animals), and occasional hyperactivity (8/26 animals) were observed at HD usually from 5 to 30 minutes after dosing and lasted up to 2 hours after dosing</i></p> <p><i>Toxicokinetics: The exposure achieved at the HD in this study (AUC0-24: 179.02 ng-h/mL) was 2-fold higher than that achieved at steady state following sublingual administration of asenapine at the MRHD of 10 mg b.i.d. (AUC0-24: 86.8 ng-h/mL). (See Table 10)</i></p> <p><i>Offspring (malformations, variations, etc.): Visceral malformations (major defects) were observed in 1/177, 2/111, 1/97, and 4/164 control, LD, MD, and HD females, respectively. In the HD group, 1 fetus had 2 major defects; the other fetuses had each one malformation. The abnormal litter ratio was 0.5%, 1.4%, 1.0% and 3.9% in the control, LD, MD, and HD females, respectively. Malformations noted only in the HD fetuses consisted of the following: exencephaly (1), misformed pons cerebelli (1), and umbilical hernia (1). Hydronephrotic kidney was detected in 1 control, 1 LD, and 2 HD fetuses. Major skeletal malformation (flexure of the forelimb) was observed only in one fetus in the MD group. Minor skeletal and visceral anomalies were also observed. However, the LD and MD groups were not examined.</i></p> <p>There is a 2 – 3 fold increased risk for major visceral malformations at asenapine exposures double those in humans (See Table 11)</p> <p><i>This study was also reviewed by Dr. Lois Freed under the IND 51,641. She concluded in her review of January 9, 1998 that “Due to technical problems, data from a number fetuses could not be used (11 C, 5 LD, 6 MD, 13 HD fetuses). Unfortunately, individual line listings were provided only for those fetuses that could not be used. Due to the lack of adequate fetal examination, the data from this study cannot be considered to have adequately assessed the teratogenic potential of Org 5222”. Therefore, the individual line listings for all fetuses included in the final analysis, with each fetus identified by number and litter, were requested from the Sponsor at that time. The requested data were submitted to the NDA 22-117. Although 6.2% and 7.9% of the total number of fetuses were not available for skeletal examinations in this study, the overall number of fetuses examined is sufficient for an adequate study”</i></p>
Pre- and Post-Natal Development	SDG RR 4299	1992	YES	Rat Sprague-Dawley	PO	0, 15 mg/kg bid at an interval of 5 hours	Days 17 – 21	<p>During lactation, when dosing stopped, the decrease in body weight gain in parental animals was not observed anymore. In the group administered 3 mg/kg/day one female delivered dead fetuses only, one female had no live fetuses left on day 1 of lactation and one female had no live fetuses left on day 4 of lactation.</p>

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (Comments in <i>Italics</i> from Pharm/Tox Review)
								<p><i>“asenapine caused severe clinical signs of lethargy in the parent animals leading to adverse effects on nursing behavior. No signs of fetal mortality were observed in asenapine-treated animals terminated on day 21 of pregnancy. Body weight of pups delivered by asenapine-treated animals was transiently lower than that of the controls. Neonatal mortality was high (up to 85.7%) in all asenapine-treated groups at 24 hours after delivery. The neonatal mortality in the group of non cross-fostered animals was higher than the neonatal mortality in the group of cross-fostered animals. (see Table 12)</i></p> <p><i>These data indicated that the increased neonatal mortality was most likely caused not only by changes in nursing/lactation process due to lethargy of parental animals or effect on lactation but also by the effects of asenapine on offspring development during pregnancy. The results of this study in comparison with the data indicating neonatal mortality in the Segment I rat study (No. SDG RR 3115) with treatment extended to the lactation period and no increase in neonatal mortality in the Segment II rat studies (No. SDG RR 2961) with treatment up to day 17 of pregnancy demonstrated that the neonatal mortality is caused by disturbances induced during the last part of pregnancy. In addition, this study demonstrated that the selected HD (15 mg/kg b.i.d.) exceeded the MTD for segment III oral study in rats.”</i></p>
	NL0012545	1998	NO	Rat Sprague-Dawley	IV	0, 0.3, 3 mg/kg/day	Day 6 to Day of Delivery (Day 21)	<p><i>“The Sponsor concluded that the dosage of 3 mg/kg/day can be regarded as too high in the subsequent pivotal study because clinical signs observed at this dose are not desirable in the period of nursing. This conclusion appears to be reasonable based on the data obtained in this study.”</i></p> <p>(See Table 13)</p>
	NL0048584	2003	NO	Rat Sprague-Dawley	IV	0.5, 1, 2 mg/kg/day	Day 6 to Day of Delivery (Day 21)	<p><i>“At the first check after parturition, 6 pups in each MD and HD groups and 1 pup in the control group were found dead with or without milk in their stomach, partly cannibalized or missing, and with bluish discolorations of the skin indicating hypothermia. Based on these findings, the HD was considered too high for the subsequent pivotal study NL0052638.”</i></p> <p>(See Table 14)</p>
	NL0052638	2003	YES	Rat Sprague-Dawley	IV	0, 0.3, 0.9, 1.5 mg/kg/day	Day 6 to Day 20 post partum (weaning)	<p><i>“Dams were terminated and necropsy was conducted on day 21 post partum. Developmental and behavioral parameters of F1 generation (randomly selected 4 males and 4 females per litter) were assessed on days 4 and 21 post partum. Water maze test was conducted on day 35 post partum. Selected F1 animals (1 male/1 female per litter) were paired on day 70 post partum. C-section on these animals was performed on day 14 of pregnancy.</i></p> <p><i>F0 in-life: There were no test article-related deaths. After having lost all pups in their litters, 1 MD female and 4 HD females were sacrificed for humane reasons.</i></p> <p><i>The duration of pregnancy was extended by one day in some animals administered asenapine. The number of animals affected was 1, 4, 7 and 3 in control, LD, MD and HD females, respectively. Post implantation loss (i.e. number of implantation sites relative to the number of pups counted at the first litter check) was significantly increased in all groups administered asenapine (9.9, 15.5, and 10.9% at LD, MD and HD, respectively, compared to 2.1% in the control group). However, a more detailed analysis demonstrated evidence of undetected postnatal loss between parturition and performance of the first litter check. These findings indicate that post implantation loss values reflect to a great part postnatal pup loss. Postnatal loss was significantly increased from day 0 to day 4 post partum in the MD group (24 cases; 9% of pups in 10 litters) and in the HD group (72 cases; 25% of pups in 16 litters). Total litter loss occurred in 1 MD female</i></p>

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (Comments in <i>Italics</i> from Pharm/Tox Review)
								<p><i>and 4 HD females.</i></p> <p><i>According to the additional analysis conducted by the Sponsor, post implantation loss likely reflected undetected loss of pups during or after parturition i.e. before the first check could have been performed. Although the mean pup weights were initially similar for all groups, body weight gain was minimally to slightly decreased during lactation period in dosed animals compared to controls.”</i></p> <p>(See Table 15)</p>
	INT00000051	2005	Yes	Rat Sprague-Dawley Fostering Study	IV	0, 1.5 mg/kg/day	Day 6 to Day 10 post partum	<p><i>“This study was designed to assess effects of asenapine on the pregnant and lactating female and on the development of the conceptuses and the offspring until day 10 of lactation. Female rats were treated intravenously with vehicle (group 1) or asenapine (group 2) from implantation (day 6 of pregnancy) through to day 10 of lactation. Cross-fostering (10 litters/group) was performed after littering (at first litter check) as indicated in the table below (see Table 16). At day 11 of lactation, the necropsy of dams and pups was conducted. (See Table 16)</i></p> <p><i>Post implantation loss (i.e. number of implantation sites minus number of pups counted at the first litter check) was slightly increased in animals administered asenapine (group 2; 17%; 79 out of 24 litters) compared to the control group 1 (9%; 45 out of 22 litters).</i></p> <p><i><u>F₁ physical development:</u> At first litter check after parturition, 23 dead pups were noted in the group 2 administered asenapine compared to one dead pup in the control group 1. An increased incidence of missing pups (considered to be cannibalized by the dam or nursing female) was noted in group V/HD (23 pups from 7 litters), HD/HD (10 pups from 5 litters) and in HD Control (11 pups from 4 litters). There was no increase in other groups. 3 pups in 3 litters of asenapine treated females had no milk in the stomach and two pups were bluish discolored in the head or snout area. Postnatal pup loss was increased up to 19%-26% in the cross-foster group V/HD group, HD/HD group and HD Control group up to day 4 of lactation.”</i></p> <p>(See Table 17)</p> <p>During lactation days 1 to 10, suckling of individual pups had not occurred at all (or was low) in the HD/HD and HD Control groups as shown below: (See Table 18)</p>

Table 9 Results of Fertility and Early Embryonic Development in Wistar Rats - Study SDG RR 3115

Group	Control	Low Dose	Mid Dose	High Dose
Dose mg/kg bid (Maleate salt)	0	0.5	2.5	15
Number of Births	122	106	65	32
# Pups found dead at first litter check	0	0	2	1
# Pups found alive at first litter check (Survival)	122	106	63	31
# Pups Alive at Day 4	122	102	58	24
# Pups Alive at Day 21	120	102	56	23
% Survival at:	First Litter Check Day 1 Post Partum	100%	100%	96.9%
	Day 4 Post Partum	100%	96.2%	89.2%
	Day 21 Post Partum	98.4%	96.2%	86.2%

Table 10 Asenapine Toxicokinetics in New Zealand White Rabbits – Study SDG RR 4428

Dose (mg/kg/day)	t½ (min)	AUC (0-24) (ng.h/ml)	Normalized AUC (0-24) (ng.h/ml) / (mg/kg)	CL (ml/min/kg)	V.central (l/kg)
0.025	46.60	4.88*	192.56*	115.05	2.73
0.125	52.35	41.53	327.51	51.07	1.93
0.625	58.90	179.02	285.43	59.02	2.25

n = 5 rabbits per dosing group.

* As the AUC could not be calculated up to 24 h for the 0.025 mg/kg/day group, it was calculated up to and including the last measurable concentration (AUC 0-t).

Table 11 Rate of Major Visceral Defects with Asenapine in New Zealand White Rabbits – Study SDG RR 4428

Dose mg/kg/day	0.0	0.025	0.125	0.625
N	177	111	97	164
Visceral Major Defects	1	2	1	4
%	0.6	1.8	1.0	2.4

N.B. There's approximately a 2 – 3 fold increased risk at exposures twice human exposures.

Table 12 Design and Results of PO Asenapine Fostering in Sprague-Dawley Rats - Study SDG RR 4299

		Group		
		1	2	3
Dose mg/kg BID PO	Dose Prenatal	0	0	15
	Dose Postnatal	0	15	15
Fostered Post-natally		No	Yes	No
Comments			Delivered by C-section	
Survival 1st 24 hrs (%) ^a		100.0%	70.7%	14.3%
Survival on Day 7 (%)		92.7%	28.3%	7.15%
% Change in Survival from end of Day 1 to Day 7		7.3%	42.4%	50%

^a Largely died by cannibalization within 4 hours of birth

Table 13 Design and Results of Pilot Lactation Study in Sprague-Dawley Rats - Study NL0012545

		Group		
Dose mg/kg/day IV	Dose Prenatal	0	0.3	3
	Dose Postnatal	0	0	0
Survival 1st 24 hrs (%)		99.2%	96.7	57.3%
Survival at End of Lactation (%)		98.3%	94.6%	37.2%

Table 14 Design and Results of Pilot Lactation Study in Sprague-Dawley Rats - Study NL0048584

Dosage Group	LD	MD	HD
Dose mg/kg/day IV	0.5	1	2
Live Births	100%	100%	100%
Survival at Day 4	98%	88%	71% ⁰
Survival at End of Lactation (%)	98.3%	94.6%	37.2%

Table 15 Survival in Pre-and Postnatal in Sprague-Dawley Rats - Study NL0052638

Group		Control	LD	MD	HD
Dose mg/kg /day IV		0	0.3	0.9	1.5
Implantations (Births)		292	293	310	321
Post Implantation Losses		6	29	48	35
Total Number Pups at First Litter Check		286	264	262	286
# Dead Pups at First Litter Check		0	0	1	1
# Living Pups	First Litter Check	286	264	262	285
	Day 1 Post Partum	286	259	254	271
	Day 2 Post Partum	276	254	240	225
	Day 3 Post Partum	275	253	239	219
	Day 4 Post Partum			238	215
	Day 5 Post Partum				216
	Day 6 Post Partum	274			217
	Day 7 Post Partum		251		
	Day 13 Post Partum			237	
Day 26 Post Partum	273				
% Loss Birth to First Litter Check		2.1%	9.9%	15.8%	11.2%
% Survival	Birth to First Litter Check	97.9%	90.1%	84.5%	88.8%
	Day 1 Post Partum	97.9%	88.4%	81.9%	84.4%
	Day 2 Post Partum	94.5%	86.7%	77.4%	70.1%
	Day 3 Post Partum	94.2%	86.3%	77.1%	68.2%
	Day 4 Post Partum			76.8%	67.0%
	Day 5 Post Partum				67.3%
	Day 6 Post Partum	93.8%			67.6%
	Day 7 Post Partum		85.7%		
	Day 13 Post Partum			76.5%	
Day 26 Post Partum	93.5%				

Table 16 Study Design in IV Asenapine Sprague-Dawley Rat Fostering Study – Study INT0000051

Cross foster groups	Exchange of litters (dam/litter)	Dam from	Litter from
Vehicle/vehicle	V/V (exchange of litter from vehicle treated dams)	Group 1	Group 1
Vehicle/high dose	V/HD (vehicle treated dam with litter from test-item-treated dam)	Group 1	Group 2
High dose/vehicle	HD/V (test item-treated dam with litter from vehicle-treated dam)	Group 2	Group 1
High dose/high dose	HD/HD (exchange of litters from vehicle-treated dam)	Group 2	Group 2
Control groups	No exchange of litters		
Vehicle control	V Control		
High dose control	HD Control		

Table 17 Postnatal Mortality in IV Asenapine Sprague-Dawley Rat Fostering Study – Study INT0000051

Period Post Partum	Statistics	V/V	V/HD	HD/V	HD/HD	V Control	HD Control
Days 1-4	Pup loss (%)	2.8	19.4	3.3	25.8	0.7	20.2
	No. of litters affected	3	7	2	9	1	6
Day 5-10	Pup loss (%)	0	0	2.8	0.9	2.1	6.0
	No. of litters affected	0	0	3	1	3	1

Table 18 Lack of Postnatal Suckling in IV Asenapine Sprague-Dawley Rat Fostering Study – Study INT0000051

No Milk in Stomach	V/V	V/HD	HD/V	HD/HD	V Control	HD Control
No. of pups affected	0	2	0	28	1	34
No. of litters affected	0	1	0	5	1	8

3.5.1.3.3 Neonatal Effects (b) (4)

Even more problematic is the Pharm/Tox review conclusions regarding a single oral dose embryo-fetal development study of (b) (4)

“Moreover, a 9-fold increase in the incidence of malformations, and signs of embryotoxicity demonstrated as a 2-fold increase in post-implantation loss, were observed in fetuses of female rabbits dosed with (b) (4) at 80 mg/kg/day during the period of organogenesis in this non-GLP pilot study.”

It should be noted that although (b) (4) is dosed at 80 mg/kg/day in these animal toxicology studies which is likely much greater than any human doses it is possible that this study could be used as a surrogate toxicology study for other species with higher exposures in humans. Table 19 shows an example of how it could hypothetically be done, so that this data could be used to more fully inform us of the human toxicity of other circulating species. However, presently this can not be done without the receptor binding and metabolism information requested.

Table 19 Example of How Requested Mass Balance, Receptor Binding and Toxicology Data could Hypothetically be used to Evaluate Potential Safety Issues with Asenapine

Chemical Species of Interest	Relative 5HT2B Binding		Agonist or Antagonist	Dosage (mg/kg/day)		Relative Toxicologic Exposures	
	Humans	Rabbits		Humans	Rabbits	Humans	Rabbits
(b) (4)	1	0.01	Agonist	0.0004	80	0.0004	0.8
Hypothetical Toxic Asenapine Metabolite	0.8		Agonist	1		0.8	

3.5.1.3.4 Conclusions Regarding Neonatal Effects

What's troublesome with asenapine is that a neonatal death was seen in the present NDA, and in animal reproductive studies a number of pups died within 1 – 4 days of birth. In this one neonatal death the mother had potentially confounding factors that makes interpretation problematic every other pregnancy I've found during the clinical trials resulted in a therapeutic abortion whereas in another NDA I've reviewed for a drug with clear teratogenic effects in animal studies therapeutic abortions were limited to 25% of pregnancies

Although the extrapolation of dose response from animals to humans is especially with regards to breast feeding, the fact that human infants, but generally not adults, produce CYP3A7 that may also increase exposures to toxic metabolites raises additional reasons for caution for toxicity to breast feeding infants in humans.

The totality of the data suggests that asenapine causes pulmonary arterial hypertension and death when there's exposure in utero and even potentially when exposure is only via breast feeding.

In addition to asenapine, mechanistically the observed toxicities are also expected with certain other atypical antipsychotics and certain toxicities such as PAH may have a more than additive risk in the presence of a concurrently administered selective serotonin reuptake inhibitor.

3.5.1.4 Potential Developmental Risks

Since the pharmacology / toxicology developmental studies indicate a risk of problems with bone remodeling during childhood and since the pharm/tox review of the juvenile development study immediately followed the pregnancy and lactation studies, I have included a summary here for convenience, (see Table 20).

In addition to Table 20, the following is from the pharm/tox review:

“Neurobehavioral assessment: Motor activity was significantly increased in all treated groups (up to 2.2-fold and 1.8-fold in males and females at the HD, respectively) when tested within a week of the end of treatment. Increased activity was also observed in males a week later and again at 30 days after the end of treatment. However, a recovery was noted in males. No recovery was noted in females following the completion of treatment as late as on day 30 (last testing).”

Two things are noteworthy, one is that only organ weights are reported and more detailed examinations were not performed that could point to connective tissue, bone, or other chronic toxicities, and second the fact that there is an increase in motor activity, which was also reported in adult animals. For a drug that may be used to treat bipolar or off-label' for bipolar spectrum disorder in children increased motor activity could be mistaken for a symptom of the illness and not drug toxicity and could induce prescribers to inappropriately increase the dose.

Note see footnote b, as the vehicle pH can effect solubility, bioavailability, and the degree of toxicity observed.

Table 20 Summary of Juvenile Development Studies from April 30, 2008 Pharm/Tox Review

Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments
INT00033485	2004	Yes ^a	Rats SD	SQ	0, 0.4, 1.2, 3.2 mg/kg/day ^b	Days 14 – 60 post partum	<p><i>“A group of sibling rats (22/sex) administered the vehicle served as a control group. An additional set of animals (18/sex/group) served as a satellite group for the assessment of toxicokinetic parameters on the first day of treatment. Three dosing sites were used: the central scapular region and the flanks by the left and right hind limbs.</i></p> <p><i>Motor activity was reassessed at 2 and 4 weeks after the end of treatment. The animals were paired at 14 weeks of age for the assessment of their reproductive performance (sexual maturation, estrus cycle, fertility and precoital interval), with the females killed and examined on day 14 after mating. At necropsy, a full macroscopic examination of the tissues was performed. Brain, pituitary, and reproductive organs were weighed. Brains of selected animals from the control and HD groups (N=10) were examined microscopically.</i></p> <p><i><u>Mortality:</u> One HD male was killed for humane reasons on day 15 of age after showing clinical signs of under reactivity, irregular respiration, and reduced body temperature. This death may be drug-related. This animal was replaced.</i></p> <p><i>Minimal, dose-related reduction in activity and ptosis were noted at all dose levels until weaning on day 21 of age (mainly on days 1 and 2 of dosing). Towards the end of the treatment period, these effects were more obvious and were observed within 15 minutes of dosing and lasted for over 4 hours.</i></p> <p><i>A slight decrease in food consumption was observed in males in all treated groups from day 35 of age until the end of treatment. In females, food consumption was minimally higher from day 42 of age and remained higher in the MD and HD groups until the end of the study.”</i></p> <p><i><u>Microscopic evaluation of the brain:</u> There were no toxicologically significant differences in brains from the control and HD group animals at the end of the recovery period.”</i></p>

a Except for toxicokinetics

b vehicle: solution of sodium citrate · 2H₂O (9.414 mg/mL) + Na₂HPO₄ (14.48 mg/mL) + NaCl (0.5 mg/mL) + NaOH to pH 5. N.B. pH can effect stability and potentially binding affinities of asenapine and could effect study results

3.5.1.5 Comments on Other Preclinical Data

Although not reviewed here, as this reviewer cannot remember if the following was pointed out in the original OCP review, the following is included so as not to inadvertently have this overlooked.

It was noticed that a few months ago the sponsor published a study in animals suggesting that asenapine might be useful in dementia. However human phase I studies showed that asenapine actually impaired both short and potentially long term memory. This should be included in any labeling as off-label use in the elderly is likely to result in a substantial increase in cardiovascular deaths.

3.5.1.6 Deaths in Clinical Pharmacology Trials

The following is from the sponsor's summary of clinical safety and from the Clinical Study Report for Study A7501018.

“There were no deaths that occurred within 30 days of the last dose or that were related to treatment in the clinical pharmacology trials. There was one subject (55 year old Caucasian male) in study A7501018 (Phase 1 study in subjects with hepatic impairment) who developed complications following surgery for an umbilical hernia and died from the complications. The surgery was performed 10 days after the subject completed the study (received 1 dose of asenapine 5 mg) and the death occurred two months later (more than 30 days after the last dose) and is not counted in the integrated database analysis.”

“Subject 10021006 (severe impairment, Child-Pugh C) died on Day 57 (46 days after completing the study) due to a severe umbilical hernia that was not considered related to study treatment. There were no other deaths and no withdrawals due to AEs. Two additional subjects had serious, non-fatal AEs (severe syncope and severe hepatic cirrhosis); both subjects recovered. Two AEs were considered severe, 23 were mild, and 58 were moderate. No AEs were reported for subjects receiving SL placebo tablets on Day -1. The most frequent AEs were somnolence, dizziness, dysgeusia, and oral hypoesthesia; all but 1 occurrence of somnolence were considered treatment related. Additional AEs related to the mouth occurred in 1 subject each, including dry mouth, dysphagia, glossodynia, lip hemorrhage, and oral discomfort. There was no clear pattern in the incidence of AEs across treatment groups.

Changes in clinical laboratory values in subjects with hepatic impairment were consistent with their diagnosis. Other laboratory deviations were sporadic and not considered clinically significant. Five subjects had decreases of >20 mm Hg in systolic blood pressure and/or >10 mm Hg in diastolic blood pressure. Three were associated with AEs (2 dizziness and the severe syncopal episode). Heart rates generally remained within normal limits, with the exception of the severe syncope. None of the findings from physical examinations or ECGs was considered clinically significant.

Conclusion(s): These results indicate that:

- *Subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment had similar total and unbound asenapine exposure to that of healthy subjects. The asenapine total and unbound exposure was increased 5- and 7-fold, respectively, in subjects with severe (Child-Pugh C) hepatic impairment.*
- *Desmethyl-asenapine exposure was reduced 33% in subjects with mild or moderate hepatic impairment and 70% in patients with severe hepatic impairment.*
- *Subjects with mild or moderate hepatic impairment had similar asenapine-glucuronide exposure to that of healthy subjects. Asenapine-glucuronide exposure was increased 1.9-fold in subjects with severe hepatic impairment.*
- *Single, 5-mg doses of asenapine are generally safe and well tolerated when administered SL to healthy subjects and subjects with varying degrees of hepatic impairment.”*

This reviewer did not previously highlight the hernia or death that occurred, however the timing and to report it in the section of SAEs is suspicious. 5HT, BMRP2 and Smad may be involved in fibrosis of the liver and in weakening of connective tissue. In addition, there were several cases of umbilical issues in animal teratogenicity studies. Although this was only single dose study, adding an additional insult that might be expected to aggravate a chronic underlying process, when there may be prolonged exposures to asenapine and metabolites raises concerns with chronic use in both patients with cirrhosis, those who may tend to drink, e.g. patients with PTSD if it's used in them, or even otherwise healthy individuals who may take the drug chronically.

In addition, the sponsor's conclusions and sponsor's labeling proposals appear to be intentionally misleading especially with respect to subjects with mild hepatic impairment and this conclusion is supported by analyses in the original OCP NDA review.

The sponsor's signatory for this study is Larry Alphs, MD from Pfizer. Dr. Alphs was also one of the signatories to the request for the Drug Safety Monitoring Board that is contemporaneous with the SAE in the woman who may have died from agranulocytosis, but was not reported.

The information available leads this reviewer to believe that one or more individuals at Pfizer and Organon as well as others at other companies intentionally mislead the FDA as to important information regarding the safety of asenapine that would have been needed to make a decision regarding this NDA. Based on this and Chapter 18 of the United States Code this reviewer believes that the Inspector General or another criminal investigative unit must be informed.

As this reviewer was instructed by Dr. Mehta that any such requests must obtain prior approval by FDA management, this request will be included in the recommendations.

3.5.1.7 Suspicious SAEs from 120 day Safety Update

Table 21 Subjects with Suspicious SAEs from 120 day Safety Update

Study	Subject	Date	Demo	Drug	Days on Drug	SAE	Comment
25543	118012	5-7-07	41 yo WM 78.1 kg	Asenapine 5 – 10 BID	179	Ultrasound 4mm dissection of pericardial lamellas above of the anterior wall RV and 4,5mm. Dissection above the ventricle. Ultrasound 2 days later: Comparing to the previous examination, the pericardial lamellas LV 3,8 mm.	Unclear from description if this is related to stab wound or not.
25543	143006	3-13-07	67 yo WF 57 kg	Asenapine 5 – 10 BID	92	In the beginning of March control lung X-Rays were performed and this time a radiologist determined a progression of changes and assessed them as a suspicion of carcinoma metastases to the lungs (Lung cancer metastatic). mild sinus tachycardia (Sinus tachycardia), mild poor R wave progression (Electrocardiogram poor R wave progression), mild left anterior hemiblock (Bundle branch block left) and mild left axis deviation (QRS axis abnormal) since 13 March 2007. Cardiac and respiratory insufficiency was determined as a direct cause of death. As a primary death cause atherosclerosis was registered.	
25543	194004	4-6-07	36 yo WM 95 kg	Asenapine 5 – 10 mg BID	150	Suicide attempt	
25544	121503	7-20-07 ?	59 yo M 71.8 kg Australian.	Org 5222	364 days Day 444 (80 days after drug stopped)	Epigastric pain radiating to the throat accompanied by collapse. Subj noted to have low BP, Haematemesis (small volumes) was noted twice at admission. Interim Dx MI,, anterior ischaemia, hypotension. No cause found for haematemesis by endoscopy. 5 days after presentation Abd pain with cough inc. respiratory rate, tachypneic, poor peripheral circ. No CP. Developed severe metabolic acidosis, inc ST in inferior and antereolateral leads. Poss further MI with ischaemic bowel or PE. Cardiac arrest with asystole. Pxt expired.	Olanzapine for 9 months prior to trial. Aug 05 – May 4, 06 Also may have been on ranitidine. Smoker 1 PPD. Scr 4-7-06 Day Scr 1.6 11-3-06 Day Scr 1.8 Clcrest 48 ml/min
25543/ 25544	176509	5-22-07	69 yo F (germany)	Asenapine		76 days after starting asenapine subject experienced disorientation, with progressive disorientation, memory impairment and disturbance in executive functioning. 8 months after initial complaint dx by local psychiatrist with dementia, PI disagreed and attributed cognitive dysfunction to meds for EPS, after 10 months on drug subject dropped out and switched to mirtazapine.	
41512	224505	5-25-06	55 yo BF 77,6 kg	Asenapine 5 – 10 mg BID	196	Potentially Malignant hypertension. 230/130 mmHg. Headache. Also had ST & T wave abnormaliites with possible antereolateral ischchemia, Short QT interval. LVH with repolarization abnormalitiy. QT prolongagrion. Sinus bradycardia.	
	224506	4-9-06	47 yo WM	Asenapine	144	Exacerbation of Schizophrenia and Suicidal ideations. Incomplete RBBB at screening.	

7501008	10461049	8-13-06	112 kg 47 yo WM 128 kg	5 – 10 mg Asenapine 10 mg	3	Progress to RBBB, Cannot rule out lateral infarct. Poss inferior infarct. Age undetermined. Exacerbation of Depressive Sxs.	
7501009	11121003	2-21-07	65 yo M Russian	Asenapine and Li	282	Weakness, Difficulties swallowing, disarticulate speech, involuntary movements of left arm. Stroke vs. EPS?	
	11291003	9-22-06	37 yo Thai Male	Asenapine and Li	31 days.	9 previous hospitalizations for Bipolar I 4 for mania or mixed episodes. No previous hx of suicidality. Smokes heavily. Attempted suicide by jumping from overpass. 6 weeks after d/c of asenapine completed suicide by ingestion of "bathroom washing liquid".	Presumably an akali
7501013	10751010	1-24-07	33 yo F			Szrs	
A7501021	10661002	1-22-07	74 yo F	?		Subj fell on day 15, study med stopped on day 41. Subject fell again on day 49, on day 55 subject was found on the floor and dx with fractured left hip.	6 week Elderly S/T study.
	10161002	5-22-06	76 yo F			Subject took asenapine for 41 days on day 69 subject suddenly slumped forward in chair and pulse was barely palpable. CPR was unsuccessful. Dx - Cardiopulmonary arrest.	
	10231002	9-30-06	75 yo M		4	Faintness attrib to orthostatic hypotension on day 2 however ECG showed sinus bradycardia, with marked sinus arrhythmia and RBBB and left anterior fascicular block. Day 4 dx'ed with Uremia with acute mental status changes. Subj has hx of CAD, CHF, PAD, Pulm HTN, Aortic valve calcification, DJD, Patent foramen ovale.	

3.5.1.8 Other SAEs Reported in Original OCP Review

Table 22 Summary of Selected Cardiac AEs per Original OCP Review

Study	Objective	Subject	Dose	Time	AE	Comment
25506	IV study	1/2	0.7 mg IV over 30 min	15 min after end of infusion	Repeated Asystole with AV block responsive to Atropine Not vasovagal	Young healthy male. No cardiac illness found
25501	SD	1/6	30 mg PO SD	2.5 hrs	Asystole 8.7 sec with junctional escape rhythm	Young healthy male. No cardiac illness found
A7501015	Pivotal BE study		5 mg		2 subjects with "hypotension"	
A7501016	Pivotal BE study		5 mg	Telemetry monitoring	10 bradycardia 8 tachycardia 7 sinus pause 3 junctional rhythm 1 bradycardia with junctional rhythm	
41026	Pivotal BE Study		5 mg		At least 4 subjects effected Claimed that it's vasovagal orthostatic hypotension in 3 but 1 subject clearly not orthostatic in nature, and no description of another. Thus only 1 conceivably orthostatic.	
25525	Paroxetine DDI Study		5 mg SL BID		Afib requiring cardioversion with sotalol MI's (possibly 2) Hepatotoxicity Hypertension and inc HR	
25526	Imipramine DDI				Collapse and LOC of Unknown origin. Questionable relationship to asenapine, but possible.	
TQT Review					One subject died of cardiac failure in an ongoing trial	
25517						

Table 23 Selected Cardiac AEs with Additional Details per Original OCP Review

Study	Subject	Comments
A7501016		The following is from the clinical study report: <p><i>“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).”</i></p>
41026	20	<p><i>“One subject (Subject 20) had a neurally mediated reflex bradycardia (without loss of consciousness) in supine position after treatment with the ^{(b) (4)} tablet.”</i></p>
25525	101029	<p>Subject 29. At Day 13 (07 November 2005) during Sequence A (Day 8 asenapine day after DM) atrial fibrillation was reported. The subject was dosed at 08:38 hr with 20 mg paroxetine and at 09:08 hr with 5 mg asenapine. Atrial fibrillation started 1 hr and 22 minutes after administration of 5 mg asenapine and was ended after chemical cardioversion with sotalol at 09:27 the next day. The investigator judged the SAE of mild intensity and probable related to either asenapine or paroxetine or the combination of both trial medications. After the trial, the subject visited the cardiologist of the CWZ for several assessments.</p> <p>The cardiologist concluded that the subject had no structural heart disease (see for more details Appendix A, narratives). In this period (lasting until March 2006) the subject was diagnosed with presumably diabetic ketoacidosis due to new-onset of diabetes mellitus at 02 March 2006. The outcome of the SAE was recovered with sequelae (diabetes). The investigator judged this SAE of severe intensity and unlikely related to asenapine, unlikely related to paroxetine and not related to dextromethorphan administered at Day 11.</p>
	09	<p>dropped out due to ECG changes (negative T in II, III and AVF, main reason), “non-cardiac” chest pain, pain between scapulae and shortness of breath at Day 7. (Day 2 of asenapine)</p>
	08	<p>dropped out at Day 15 due to persistent moderate headache (main reason), drowsiness and intermittent nightmares. (Day 10 of asenapine 1 day after paroxetine day 4 after DM)</p>
	14	<p>dropped out due to hypertension (154/88 mmHg with a PR of 93 bpm, main reason), mental restlessness, insomnia, intermittent night sweating, emotional lability, fatigue, nightmares, myalgia shoulders and neck and headache at Day 9. (Day 4 of Asenapine)</p>
25526	37	<p>In this subject there was a subject who was found unconscious 1.3 days after dosing with imipramine 75 and 10 days after dosing with asenapine. Although it was not ascribed to asenapine the timing is similar to that seen in subject 37 in study 25525 and a drug interaction with one or more other drugs a week or two after a single dose of asenapine cannot be ruled out.</p>

Table 24 Selected Adverse Events by Treatment – Study 25528^a

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

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

Table 25 Sponsor's Table 55 Summary of adverse events by system organ class and high level group term occurring in 10% of subjects (clinical pharmacology – healthy subjects studies, cohort F)

Adverse Event Category	Placebo	Asenapine				
		<5 mg BID	5 mg BID	10 mg BID	15 mg BID	All
n (%)	(N=96)	(N=657)	(N=64)	(N=18)	(N=6)	(N=745)
Any adverse event	39 (40.6)	562 (85.5)	63 (98.4)	18 (100)	6 (100)	649 (87.1)
Cardiac disorders	0	68 (10.4)	2 (3.1)	1 (5.6)	1 (16.7)	72 (9.7)
Cardiac arrhythmias	0	61 (9.3)	1 (1.6)	1 (5.6)	0	63 (8.5)
Gastrointestinal disorders	9 (9.4)	435 (66.2)	58 (90.6)	14 (77.8)	5 (83.3)	512 (68.7)
GI signs and symptoms	7 (7.3)	94 (14.3)	15 (23.4)	3 (16.7)	4 (66.7)	116 (15.6)
Oral soft tissue conditions	2 (2.1)	390 (59.4)	54 (84.4)	12 (66.7)	3 (50.0)	459 (61.6)
General disorders and administration site conditions	7 (7.3)	145 (22.1)	40 (62.5)	5 (27.8)	3 (50.0)	193 (25.9)
General system disorders	4 (4.2)	114 (17.4)	38 (59.4)	4 (22.2)	2 (33.3)	158 (21.2)
Nervous system disorders	21 (21.9)	452 (68.8)	52 (81.3)	15 (83.3)	6 (100.0)	525 (70.5)
Headaches	8 (8.3)	100 (15.2)	20 (31.3)	5 (27.8)	3 (50.0)	128 (17.2)
Neurological disorders	16 (16.7)	437 (66.5)	48 (75.0)	13 (72.2)	6 (100.0)	504 (67.7)
Psychiatric disorders	2 (2.1)	84 (12.8)	39 (60.9)	8 (44.4)	3 (50.0)	134 (18.0)

Source: 2.7.4 Appendix Table 2.2.FW

Table 56 Adverse events by preferred term incidence greater than or equal to 2.0% (clinical pharmacology – healthy subjects studies, cohort F)

Adverse Event Category n (%)	Placebo (N=96)	Asenapine				
		<5 mg BID (N=657)	5 mg BID (N=64)	10 mg BID (N=18)	15 mg BID (N=6)	All (N=745)
Any adverse event	39 (40.6)	562 (85.5)	63 (98.4)	18 (100)	6 (100)	649 (87.1)
Somnolence	6 (6.3)	358 (54.5)	29 (45.3)	9 (50.0)	6 (100.0)	402 (54.0)
Paraesthesia oral	1 (1.0)	245 (37.3)	38 (59.4)	9 (50.0)	3 (50.0)	295 (39.6)
Hypoaesthesia oral	1 (1.0)	205 (31.2)	22 (34.4)	12 (66.7)	0	239 (32.1)
Dizziness	6 (6.3)	140 (21.3)	12 (18.8)	3 (16.7)	3 (50.0)	158 (21.2)
Dysgeusia	0	127 (19.3)	5 (7.8)	1 (5.6)	0	133 (17.9)
Fatigue	1 (1.0)	93 (14.2)	34 (53.1)	2 (11.1)	0	129 (17.3)
Headache	8 (8.3)	99 (15.1)	20 (31.3)	5 (27.8)	3 (50.0)	127 (17.0)
Restless legs syndrome	0	72 (11.0)	5 (7.8)	0	0	77 (10.3)
Nausea	4 (4.2)	61 (9.3)	10 (15.6)	2 (11.1)	0	73 (9.8)
Dizziness postural	2 (2.1)	52 (7.9)	5 (7.8)	5 (27.8)	1 (16.7)	63 (8.5)
Dry mouth	0	60 (9.1)	2 (3.1)	0	0	62 (8.3)
Restlessness	1 (1.0)	42 (6.4)	11 (17.2)	4 (22.2)	0	57 (7.7)
Insomnia	1 (1.0)	16 (2.4)	31 (48.4)	3 (16.7)	1 (16.7)	51 (6.8)
Paraesthesia	0	26 (4.0)	6 (9.4)	3 (16.7)	2 (33.3)	37 (5.0)
Diarrhoea	0	24 (3.7)	12 (18.8)	0	0	36 (4.8)
Akathisia	0	31 (4.7)	3 (4.7)	0	0	34 (4.6)
Oral discomfort	0	34 (5.2)	0	0	0	34 (4.6)
Hypotension	0	30 (4.6)	0	1 (5.6)	0	31 (4.2)
Bradycardia	0	27 (4.1)	0	0	0	27 (3.6)
Miosis	0	21 (3.2)	0	0	0	21 (2.8)
Tachycardia	0	21 (3.2)	0	0	0	21 (2.8)
Glossodynia	0	21 (3.2)	0	0	0	21 (2.8)
Abdominal pain	2 (2.1)	17 (2.6)	2 (3.1)	1 (5.6)	0	20 (2.7)
ALT increased	0	8 (1.2)	9 (14.1)	0	1 (16.7)	18 (2.4)
Dysarthria	0	10 (1.5)	7 (10.9)	0	0	17 (2.3)
Dyspnoea	0	6 (0.9)	7 (10.9)	3 (16.7)	0	16 (2.1)
Nasopharyngitis	0	13 (2.0)	2 (3.1)	0	0	15 (2.0)

Figure 4 Hematology Values Prior to Death for Subject 132017 -Study P25520

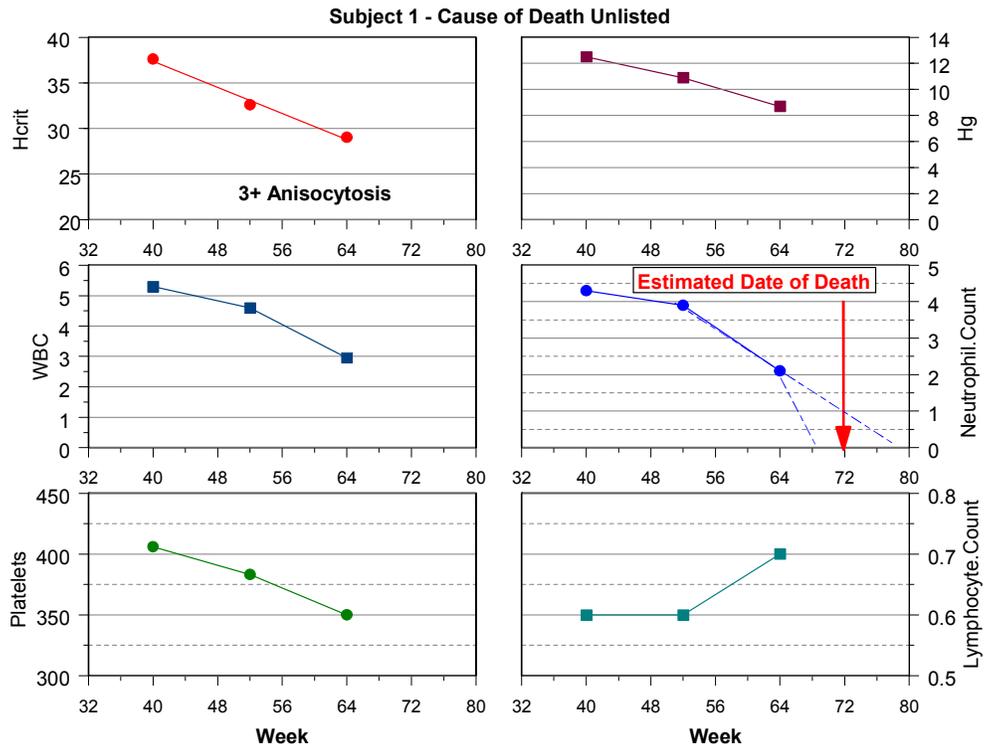
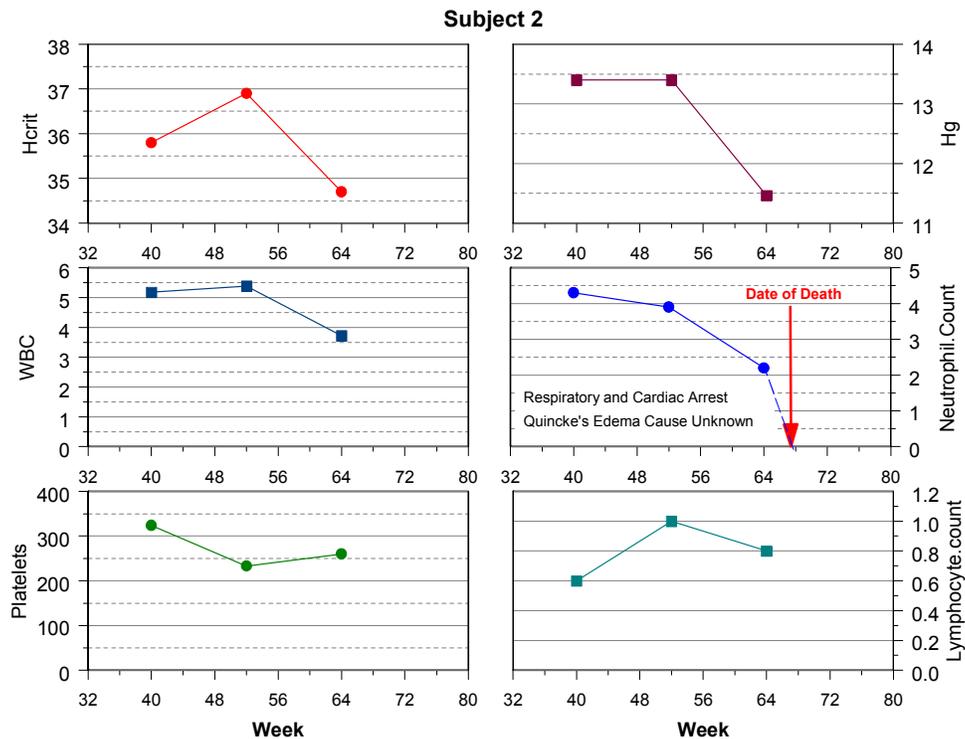


Figure 5 Hematology Values Prior to Death for Subject 241041 -Study P25520



3.5.1.9 *Relative Rates of Cardiovascular and Pulmonary SAEs from Ongoing Studies*

Although a preliminary assessment, Table 26 appears to indicate that the risks with asenapine are greater than the risk of similar toxicities with olanzapine. A similar pattern was noted in §3.5.1.1, Subjects who Died in Primary Efficacy and Safety Phase 2/3 Studies.

Table 26 Relative Rates of Cardiovascular and Pulmonary SAEs from Ongoing Studies

Study	# SAEs	Total N	Treatment	Relative Risk for Asenapine
41512	5	207	As/Olanz/PBO	2.4
25520	5	534 Rand 3:1	As/Olanz	0.9
41513	3	187	As/Hal/PBO	1.6
25543 ? / (25544)	2	124	As/Olanz	1.6
A7501012 Comparison of Suicidality	5	576	As/PBO	0.9
A7501013 & A7501014 Predominant and Neg Sxs	2+6	104	As/Olanz	7.7
A7501021	Elderly			
A7501007	3	218	As/Olanz/PBO	1.4
A7501008* Li VPA	3	326	As/PBO	0.9
A7501009 Li VPA	1	77	As/PBO	1.3

3.5.1.10 SAEs Reported in IND Reviews

The hypotension and syncope in the subject in study 25504 is noteworthy as structurally similar compounds also from Organon appear to result in extreme CNS depression when taken in combination with alcohol and may in whole or part be the basis for the class labeling on antidepressants and other CNS depressant medications even though the degree of the interaction may vary by drug.

Pulmonary emboli, DVTs, and strokes are commonly seen with antipsychotics and may be mechanistically related to either vasoconstriction or effects on platelet serotonin receptors that effect aggregation.

Table 27 Subjects with SAEs in Phase I/ II Studies reported in IND Reviews per Dr. Roberta Glass

Study	Subject	Available Description
25501	?	
15501	?	Treatment emergent RBBB
25504	?	Hypotension syncope vomiting after 14 days. Sponsor questioned if this might be due to EtOH and diazepam
25505	?	New onset Sinus tachycardia Baseline incomplete RBBB
25506	?	
25511	9	
41013	28	
	48	<i>"Patient Died. Possible obstruction of pulmonary arteries, thrombus in lungs and/or questionable pneumonia are possible contributing factors."</i>
25517	186007	
41513	315504	
A7591007	50281012	
P25520	132017	
	241041	
	246021	

3.5.1.11 Other Potentially Mechanistically Related AEs

3.5.1.11.1 Connective Tissue Disorders and Fibrotic Effects

Another side effect that has been reported with asenapine is ruptured tendons. Based upon the similar cardiac effects on ECG seen with the fluoroquinolone antibiotics and the increased rupturing of tendons mentioned by Dr. Woodcock in the announcement of the Sentinel program.²⁰ This might be due to effects on the BMP2 gene product,²¹ and this might somehow also be related to schizophrenia and Parkinsonism, as well as development of brain tumors.^{22, 23} Pharmacodynamic interactions of effects on sleeping have also been described for fluoroquinolone antibiotics and herbal Viagra.

Potential dose and time dependent hepatotoxicity was seen with asenapine, also as mentioned previously some cases of cirrhosis of the liver appear mediated through 5HT receptors.

3.5.1.11.2 Neuropsychiatric Side Effects

Effects on cognition, wakefulness, suicidality, vivid dreams, seizures, hostility and violence, and worsening psychosis have been reported to be common to a number of drugs including asenapine and other atypical antipsychotics and suggest a common mechanism. Based on effects on specific parts of the brain associated with the atypical antipsychotics, the known association of these areas with some of these functions, as well as the distribution of certain types of serotonin receptors in these areas, there may be a common underlying mechanism(s) via serotonin or other receptors.

3.5.1.11.3 Other Observations

Recently FDA issued a warning against Xiadafil 'herbal viagra' which may have a connection with effects on serotonin receptors, and similar warnings by FDA with respect to ephedra preceded the announcement of the risks of phen-fen in 1997. More recent FDA warnings with respect to cardiotoxicity with OTC cough and cold medicines in children raise concerns regarding a possible mechanistic link between these otherwise seemingly disparate observations.

²⁰ <http://www.nytimes.com/2008/05/23/washington/23fda.html>

²¹ <http://ghr.nlm.nih.gov/condition=pulmonaryarterialhypertension>

²² <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1571542>

²³ Am J Physiol Lung Cell Mol Physiol. 2005 Feb ;288 (2):L370-8 15516492 ([P](#),[S](#),[E](#),[B](#))

3.6 **Metabolites and Other Species Potentially Responsible for Asenapine's Non-Hematologic Toxicities**

When the totality of clinical pharmacology information is examined it suggests that asenapine's toxicity primarily resides in the hydroxylated metabolites, including a mono-hydroxy, a catechol, and/or one or more conjugative metabolites.²⁴ This includes the increased risks observed with structurally similar compounds when given in combination with MAOIs and the increased toxicities when given with carbamazepine.

This reviewer found in the pharmacology literature that for monocrotaline that toxicities in Sprague-Dawley rats are increased when given intravenously as compared to orally or by other routes of administration and that this could not be explained by differences in metabolism. This has been proposed to potentially be due to a degradation product formed in aqueous solutions however when aqueous solutions were examined none were found. Although increased toxicities have been observed when IV solutions in DMSO have been administered. It has also been noted in the literature that monocrotaline has stereoisomers that they may have different toxicities.

On Thursday June 5, 2008 at around 2:30 PM this reviewer spoke to the chemistry reviewer about the possibility of degradation products in the drug product used in the IV study with the case of cardiac asystole and requested that he obtain information on the drug substance and the diluents used in this study. The chemistry reviewer suggested that this reviewer look at his review, which this reviewer had already done for the IV drug product. Due to the lack of time, this reviewer requested that the chemistry reviewer research and provide this information.

A short time later while looking for the pharm/tox review to check some information, this reviewer serendipitously found that the day after the original OCP review was signed off, the chemistry review team, (minus the usual chemistry team leader), amended their review to request a lowering of the limit for the impurity (b) (4) which based on the molar dose of asenapine is a low absolute amount. The recommendation from the amended chemistry review follows:

“I. Recommendations

A. Recommendation and Conclusion on Approvability

*The applicant provided acceptable responses for the CMC deficiencies stated in the review #1 dated 11-APR-08 (see evaluation in the Chemistry Assessment section in this review). However, from the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended **APPROVABLE** due to pending resolution of the following outstanding pharmtox issue regarding impurity (b) (4) which will have impact as the setting of acceptance limit for the drug substance specification:*

- 1. The applicant proposed acceptance criteria for impurity, (b) (4), in asenapine drug substance at 0.3% which is above the ICH Q3A(R) qualification limit of (b) (4). The pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) stated in her review dated 30-APR-08 (pp. 4) that the applicant should perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity during phase IV or reduce the specification of (b) (4) to the ICH Q3A(R) qualification limit of (b) (4).*

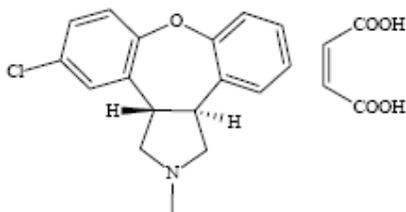
²⁴ Although this reviewer previous indicated that no more than approximately 4% of circulating species had been accounted for when estimates of relative exposures from asenapine glucuronide from the carbamazepine drug-drug interaction study, (3X, 7.5%), desmethyl-asenapine from the valproate interaction study, (1/3, 1%), and the 11-O-Sulfate from the fluvoxamine interaction study, (<1/3, <1%) are considered the amount of circulating species identified is still less than 15% of the total circulating radioactivity.

Release data for the drug substance batches used in clinical studies (20 batches) and batches used in to be marketed drug product batches (4 commercial batches) showed that process impurity (b) (4) is present at not more than (b) (4) level, which is well below ICH Q3A(R) qualification limit of (b) (4) indicating that the applicant may be able to reduce the specification of (b) (4) to the ICH Q3A(R) qualification limit of (b) (4).”

Upon checking the original OCP review for the structure of (b) (4), this reviewer found that (b) (4) should be separable and identifiable by the sponsor in any mass balance or metabolism studies.

As this reviewer was reading the amended chemistry review this reviewer noticed the following figure, Figure 6.

Figure 6 Structure of Asenapine from Chemistry Review



Asenapine maleate (Org 5222) contains two chiral centers. Asenapine maleate is a racemate.

It then struck this reviewer that although asenapine has 2 chiral centers and although the easy way to manufacture it is to have 4 diastereomers, it is a racemic compound and thus the sponsor is specifically controlling manufacture to avoid 1 set of stereoisomers. This is highly unusual unless there is a toxicity concern. Since, N-desmethyl asenapine may be secondarily metabolized by 11-hydroxylation and since the sponsor is avoiding looking at these metabolites, and as metabolites can be active with differing activity this suggests that the toxicity with the original IV formulation might have been due to either a stereoisomer and/or a metabolite of the stereoisomer, or a contaminant or degradation product if it were dissolved in DMSO prior to secondary dilution²⁵.

The recommendations from the original chemistry review dated April 11, 2008 follow:

“I. Recommendations

A. Recommendation and Conclusion on Approvability

*From the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended **APPROVABLE**. The outstanding issue is pending acceptable responses to the following CMC deficiencies.*

- 1. The acceptable limits for impurities should not be based on strength. Reduce the acceptance criteria for both strengths for the degradation product (b) (4) and total degradation products to the levels that are more consistent with your data.*
- 2. Revise unspecified each individual impurity limit for both strengths to no more than (b) (4) based on maximum daily dose of 20 mg/day.*

²⁵ One or more of these hypothesis can be supported if information on the drug substance and drug product used in this study is obtained.

Note: In e-mail (dated 26-MAR-08) and in the NDA WRAP-UP meeting (dated 07-APR-2008), the pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) indicated that the data supporting qualification of impurity (b) (4) at the level (b) (4) was not acceptable and that additional information will be requested. However, in the WRAP-UP meeting, Dr. Barry Rosloff (Pharmtox Team Leader) stated that the limit for impurity (b) (4) is acceptable; unless the "requested" phase 4 studies (when done correctly) show a problem. If a problem is seen, then the limit for this impurity will need to be lowered."

This reviewer did not attend the wrap-up meeting as an external contractor was supposed to attend and this reviewer did not believe it was necessary to reveal trade secrets to a contractor for evaluating business processes and thus believed that participating might be unlawful. The OCP team leader agreed that this reviewer could skip the meeting as OCP had no new information and thus the time would be better spent completing the review. The OCP TL participated by conference call from Arizona, and per this reviewer's recall reported to this reviewer something about Dr. Rosloff and an impurity with a (b) (4) level. Upon checking this reviewer cannot find / identify the management consultant on the list of participants in the Outlook calendar. This is not surprising as this reviewer does not believe the contractor had an FDA e-mail account.

Subsequent to reading the above chemistry recommendations this reviewer checked the Pharm/Tox review dated April 30, 2008 and found the following:

"2. Qualification of impurity (b) (4): Drug substance impurity (b) (4) has been present in the drug substance commercial size clinical/stability batches at (b) (4). However, the Sponsor proposed to set a specification limit for this impurity in asenapine drug substance at (b) (4), thus above the ICH Q3A(R) qualification limit of (b) (4). The content of (b) (4) in relevant asenapine batches used in the preclinical program was below the limit of detection. A non-GLP pilot segment II study in rabbits was performed with this impurity; however, this study is considered inadequate for several reasons, including the following: (1) only a single dose of (b) (4) was employed which did not result in any maternal toxicity; (2) the number of animals per group was less than the recommended 16 per group, with only 34 fetuses examined in the (b) (4) group; (3) relatively high post-implantation loss was observed in the control group; (4) no information on drug analysis was provided; (5) no toxicokinetic data were obtained; (6) (b) (4) was administered orally, although asenapine is being administered by the sublingual route; and (7) unclear terminology was used to describe fetal findings. Moreover, a 9-fold increase in the incidence of malformations, and signs of embryotoxicity demonstrated as a 2-fold increase in post-implantation loss, were observed in fetuses of female rabbits dosed with (b) (4) at 80 mg/kg/day during the period of organogenesis in this non-GLP pilot study. The NOAEL has not been identified for these effects. Therefore, the Sponsor should perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity during phase IV or reduce the specification of (b) (4) to the ICH Q3A(R) qualification limit of (b) (4)."

It should be noted that April 30th is after the OCP reviewer was supposed to have the review completed. Due to timelines and the amount of material this reviewer was required to review this reviewer was unable to check the reviews of other disciplines prior to sign off of the original OCP review.

It should also be noted that the ICH limits will allow amounts of this contaminant in commercial batches higher than the amount of this contaminant that has been used to define the safety profile of asenapine.

Finally on June 13, 2008 this reviewer found the information in the pharmacology /toxicology study noted in § 3.5.1.3.3, Neonatal Effects of (b) (4).

To aid in understanding the differences in the 3-dimensional changes that could result in minor alterations that could effect binding site interactions this reviewer constructed molecular models of asenapine and (b) (4) and these are shown in Figure 7 and Figure 8.

Figure 7 shows that the trans- isomer results in a twist in the pyrroles ring that results in one carbon of the pyrroles ring standing up away from the plane of the table on which it's resting and pushes the nitrogen into the table. Whereas Figure 8 shows that in (b) (4) the pyrroles ring and the nitrogen lie flat.

Unfortunately molecular models are constrained by the physical limits of the connecting pieces, however conceptually hydroxylation of the non-halogenated benzene on the side as the carbon in the pyrrole ring of asenapine in Figure 7 that is being pressed into the table might result in a flattening out of the pyrroles ring so the 3-D conformation is more similar to that seen with (b) (4) in Figure 8.

To examine this and not have the physical constraints of a molecular model a 3-D chemical drawing program was used to show possible physical conformations of asenapine, (b) (4), and selected metabolites, (see Figure 9 to Figure 13).

Comparison of (trans-) asenapine in Figure 9 and dihydroxy-asenapine (the catechol) in Figure 11 clearly shows that the position of the pyrroles group changes, and that the position of the pyrroles group is more similar to that in (b) (4) in Figure 12. In addition, the 3-dimensional shape of desmethyl-asenapine in Figure 10 is similar to the shape of asenapine in Figure 9. Plus addition of sulfate conjugates to the catechol, (see Figure 13), also results in a 3-dimensional shape intermediate to asenapine and the catechol.

While this reviewer realizes that this program may not be truly accurate with regards to these changes in conformation, as possibly evidenced by the change in the halogenated benzene from a planar to a boat conformation, it does help to provide some insight and does tend to support this reviewer's hypothesis for the toxic species.

Figure 7 Molecular Model of Asenapine

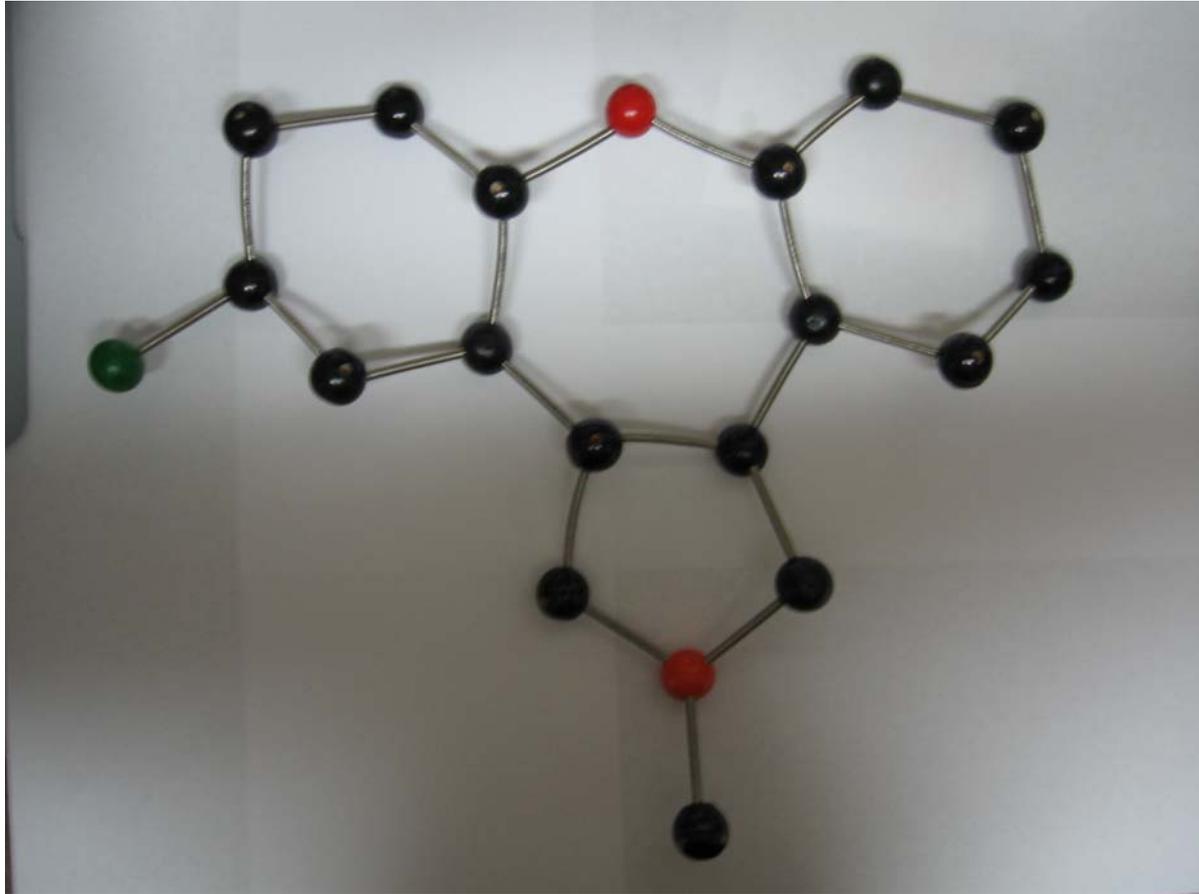


Figure 8

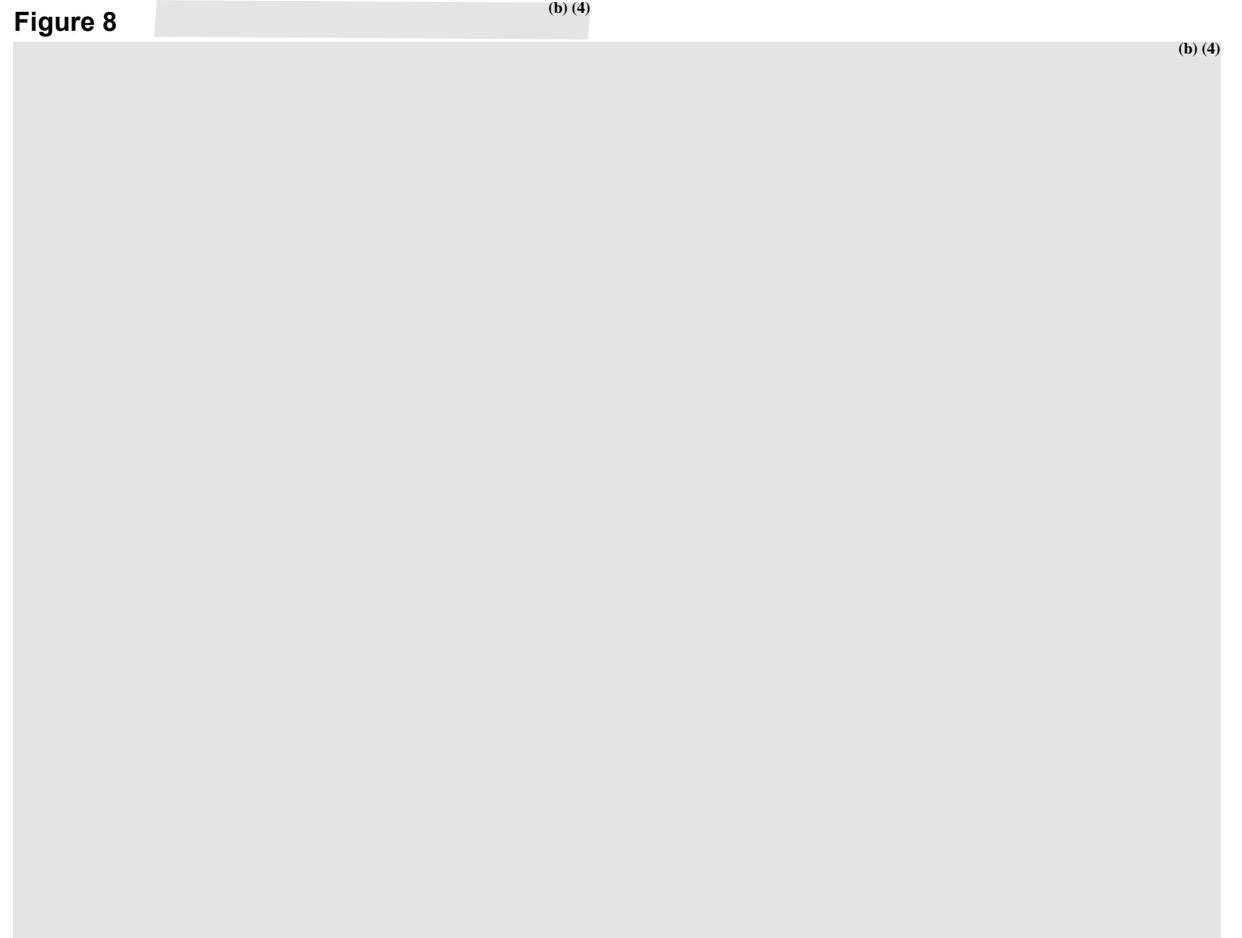


Figure 9 Asenapine

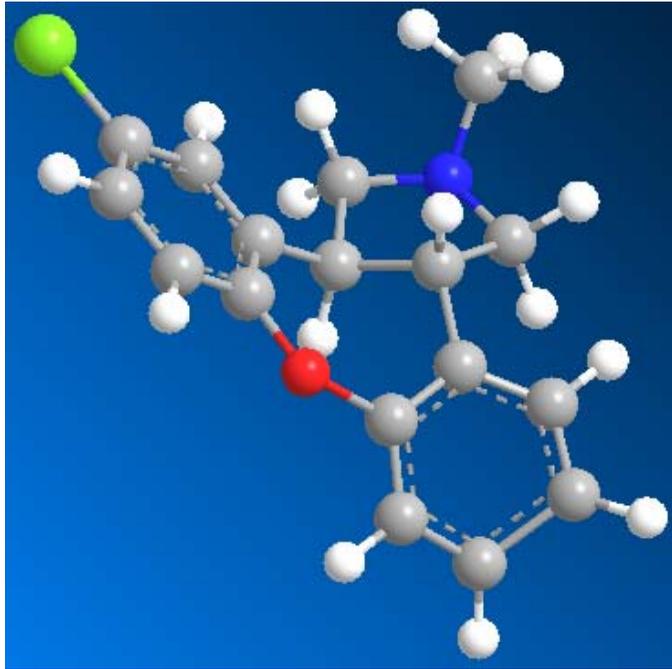


Figure 11 Asenapine Catechol

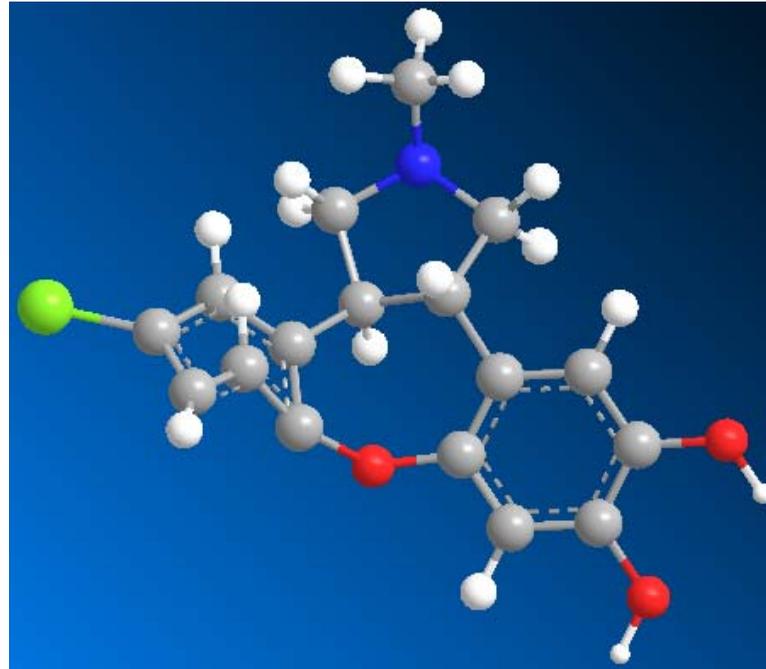


Figure 13 Desmethyl-Asenapine- DiSulfate

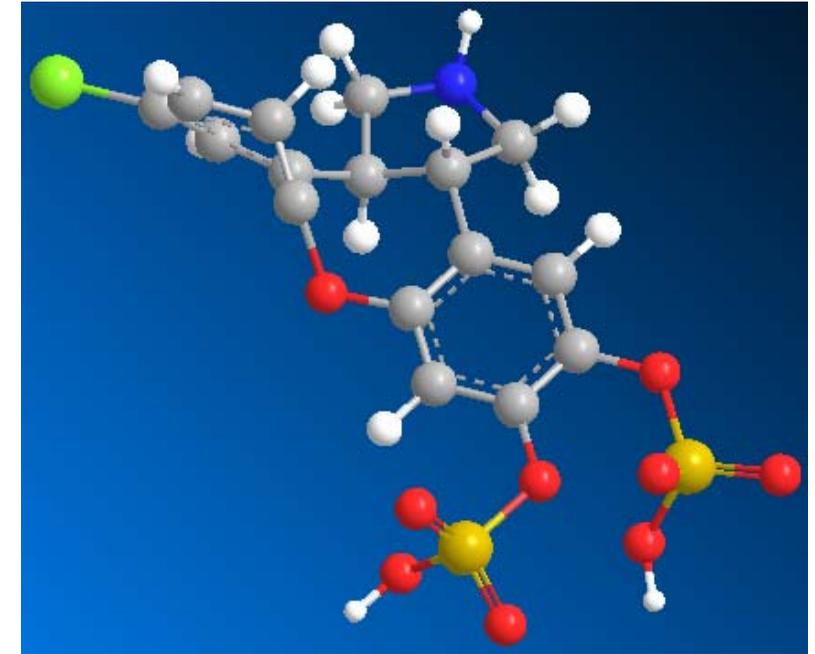
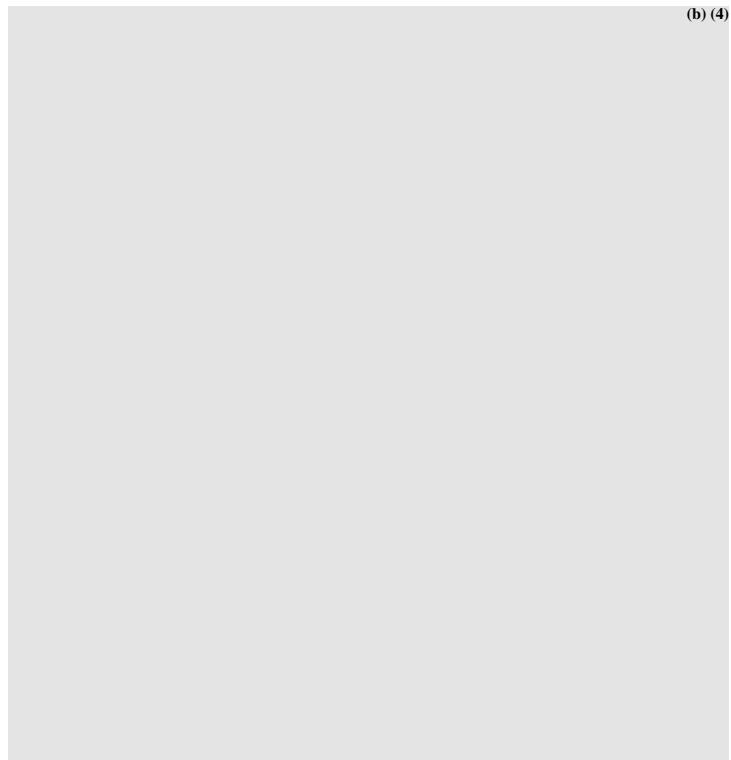
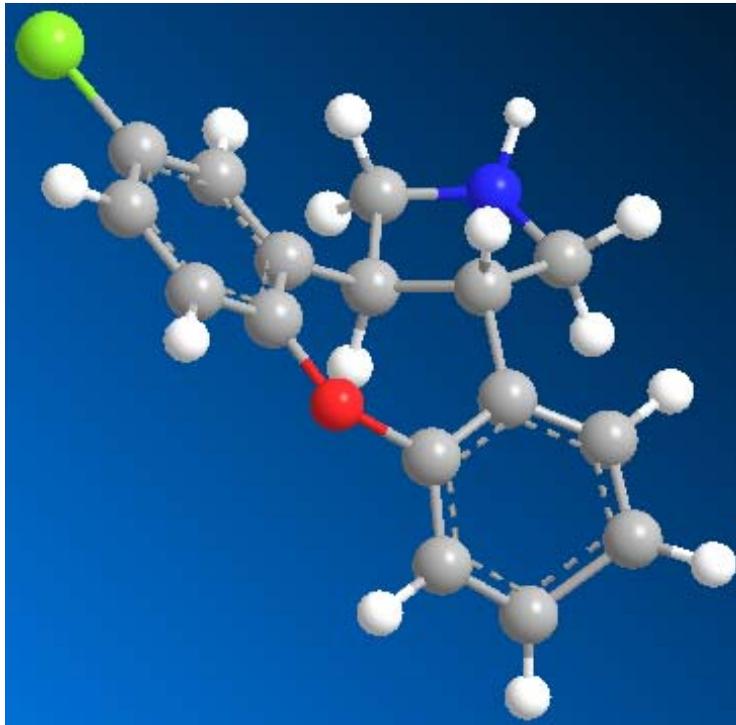


Figure 10 Desmethyl-asenapine



3.7 Major Deficiencies in NDA 21-117 and Reassessment of Approvability

Based upon the information presented so far in this amendment it is clear that there are numerous deficiencies in NDA 21-117 that appear to be intentional so as to hide critical information needed to make an informed determination of the safety of asenapine and in order to mislead the FDA. A brief description of a limited number of selected deficiencies follows. More detailed discussions may be found in the original OCP review, however conclusions regarding the clinical relevance with respect to the safety conclusions some the original OCP review including a lack of any margin of safety have now become of even great concern based on additional review.

Basic Pharmacology

The sponsor failed to provide information on the receptor activities of various metabolites and contaminants that are needed to understand the effects of both intrinsic and extrinsic factors on both safety and efficacy.

Mass Balance Phenotyping

The sponsor has not identified over 85% of the circulating species and in particular has avoided evaluation of those metabolites and pathways most likely involved with the potentially lethal toxicities of asenapine. For example even though multiple enzymes may be involved in a particular metabolic pathway without the relative contributions for all pathways and the distributions evaluation and mitigating risk is virtually impossible. This also includes prevention of the identification of pharmacogenomic factors that are expected to have an impact on safety. In addition, the sponsor clearly obfuscated the information available and in spite of a direct request for clarification of the available information that was needed for safety review the sponsor avoided providing the information.

Basic Pharmacokinetics

Based on the detected accumulation of the potentially hematologically toxic N-oxide in the thorough QT study and the long half-lives of total radioactivity observed it appears that the sponsor has likely not adequately characterized pharmacokinetic characteristics of metabolites that might affect time dependent toxicities. The enantiomeric selective metabolism and kinetics discussed in the original submission now appears to have much greater overtones regarding potential toxicity and needs to be more fully addressed.

Subject Selection and Assessment of Chronic Toxicities

The sponsor's subject selection criteria for safety and efficacy studies, including a history of acute tolerance to similar compounds, lack of risk factors such as prior viral hepatitis, the limited number of subjects treated chronically, and the lack of long term data and placebo controls all have the effect of minimizing the detection of risks and skewing the risk benefit assessment.

Effects of Race and Ethnicity

There were few blacks included in studies and virtually none in pharmacokinetic studies except for the pediatric adolescent study. Eighty percent of African Americans express CYP3A5 as compared with 20% of white Americans. Although substrate specificity and intrinsic clearance may vary between CYP3A4 and 3A5, we must be concerned a priori that the similarity in substrate specificity between the two enzymes might result in increased formation of toxic metabolites in the African American population and thus the risk benefit profile could not have been adequately assessed in this population which is expected to be at higher risk than Caucasians. This is especially problematic as individuals in prison or children in foster care are more likely to be persons of color and individuals in prison and foster care are also more likely to be inappropriately prescribed antipsychotic medications.

Other populations that may also be at higher risks for hematologic toxicities include Finns, Ashkenazi Jews, and Thai (or possibly the 60% of the population of Bangkok that are of Han Chinese ethnicity). Finns and Ashkenazi Jews have higher risks of agranulocytosis, and Thai have higher risks of aplastic anemia with clozapine.

Effects of Gender

The effect of gender was not formally examined. Although there was some data that was found at the end of the review cycle that could have been extracted, but by the time it was realized that such data was available there was insufficient time for reanalysis and review. Unfortunately although the sponsor could have easily included this analysis in the NDA they did not do so.

Both increased CYP1A2 activity that might result in increased formation of toxic metabolites as well as smaller body mass in women would be expected to increase exposures to toxic metabolites. In addition, there could be interactions with various sex hormones including oral contraceptives. Thus any safety analyses would need to take account of these factors.

Effects of Age

There was limited information on pharmacokinetic and pharmacodynamic effects with age. The same concerns with gender are also of concern in the elderly. In addition, underlying chronic conditions such as atherosclerosis, and cardiovascular disease would be expected to increase toxicity. Increased toxicity in older adults (non-elderly) was noted in the original review for olanzapine but was not highlighted in the labeling. This subsequently resulted in a black box warning. In addition, it's possible that the cardiovascular toxicity with asenapine might be worse than with olanzapine. The elderly PK study was reported in an incomplete form and submitted to the NDA in a manner that appears designed to avoid its detection.

The original olanzapine review included studies for psychosis in dementia but it was not approved for this indication. In spite of this apparently the sponsor later pushed prescribing for this off-label indication with the known consequences of increased mortality and a black box warning for a class effect.

Pediatric Pharmacokinetics

The pediatric pharmacokinetic study only included mean and not individual data. Subjects ranged in age from 12 – 17 years of age but the weight over the entire range was at the 80th percentile and thus would underpredict the exposures expected in practice. The most obvious example was the inclusion of a 200 lb. 12 year old. There were also very few subjects. Both of these demographic characteristics are common and tend to let inappropriate adult doses be used in children with the associated greater risk in toxicity. The subjects were also primarily African American. Therefore this short term study may give the sponsor some insight into potentially greater risks with African Americans but the short duration and underdosing would be likely result in an under appreciation by most readers of the study report of the risks identified. This under appreciation of the risks in the actual population that would use the drug would then likely result in mislabeling of the drug.

Effects of Smoking

The effect of induction of CYP1A2 by smoking was conducted in chronic smokers so that no increase in formation of the likely toxic metabolites would be found.

Effects of Renal Impairment

Both due to the short duration and by not examining the likely toxic species, the study was biased against elucidating the both the cardiovascular and other risks from asenapine in this population, including both effects on bone, as well as platelet aggregation, and possibly salt and water balance.

Effects of Hepatic Impairment

Without examination of the likely toxic species, this study was also biased against finding any problems. In spite of this there are indications of increased risk in even mildly impaired subjects. This hints that patients with cirrhosis or fibrotic processes may be at increased risk due to increased genetic susceptibility in addition to any increased risk due to altered pharmacokinetics.

Drug Interaction Studies

Some of the drug interaction studies appear to be designed to give some idea of the potential increased risks via surrogate examination of the effects on pharmacokinetics while at the same time minimizing the possibility of finding adverse effects by using low single doses. After identification of the risks with asenapine, the likely toxic species, and the timing of events it appears that the sponsor intentionally designed these studies in such a manner so as to allow labeling that would protect the sponsor from liability if preemption should pass the US Supreme Court. At the same time the sponsor appears to have tried to obfuscate or avoid monitoring the most pertinent information needed to mitigate risks so as to avoid detection by the FDA.

Paroxetine – An increase in pharmacodynamic adverse effects with a SSRI as expected. In fact several subjects having severe AEs with even a single dose of asenapine added to paroxetine, yet the study is ostensibly primarily a pharmacokinetic interaction study.

Cimetidine – Inhibition of multiple pathways may increase hematologic toxicities over time.

Valproate – Without examination of the likely toxic species, this study was biased against elucidating the risk of problems in this population.

Carbamazepine – Expected to induce the formation of the toxic metabolites responsible for cardiopulmonary toxicities, yet an extremely low dose was used much below what would be expected to be used clinically. In spite of this there was a several fold increase in signs and symptoms of cardiopulmonary toxicity with even a single dose of asenapine whereas toxicity is expected to be cumulative over time. In addition to a pharmacokinetic interaction a pharmacodynamic interaction is also possible.

In the second End-of-Phase II meeting held on April 27, 2004 the sponsor specifically requested whether approval would be granted for asenapine as adjunctive therapy in bipolar I disorder based only on data with lithium and valproate, (see Figure 14).

Figure 14 Minutes from April 27, 2004 EOP2 Meeting Regarding Adjunctive Therapy in BP I

Question Related to Bipolar Indication: Adjunctive Therapy

Question 1.3.1: Does the Agency agree that a study comparing asenapine treatment with placebo as adjunctive treatment to lithium or valproic acid in bipolar I disorder patients experiencing acute manic episodes is adequate for an additional labeling claim for adjunctive therapy for asenapine?

Discussion: The Agency stated that the proposal appears acceptable.

What's disturbing about these meeting minutes is by this time the sponsors appear to have already long known that there was likely an increased risk of severe and lethal toxicity with this combination and they were trying to avoid detection of this by the FDA while also getting approval for a lethal drug combination. What's even more disturbing is that one of the co-sponsors in attendance at this meeting was

simultaneously preparing to submit an NDA to treat the very same expected toxicity that would result in an increase in sales for one of their most profitable drug products, (see N21-845 submitted Dec 2, 2004, Approved June 3, 2005).

In later discussions at the pre-NDA meetings held July 18, 2006 and February 22, 2007 the sponsors appear to be trying to limit submission of longer duration safety data, especially nonserious safety data that might point to a developing chronic toxicity that might be detected prior to an initial approval. In contrast detection post approval could result in a significant increase in overall sales that might offset decreased sales from this single product.

This effect could hypothetically even be multiplied via extension of marketing exclusivity and via marketing to the pediatric population.

MAOIs - No drug interaction studies with monoamine oxidase inhibitors, yet this would be expected to result in severe toxicity, even more so if used in combination with an SSRI in a patient with refractory depression. Base on recent trends in labeling to avoid using the term contraindication, there is a good likelihood that the clinical significance of this type of interaction would be underappreciated.

Other Major Deficiencies

Thorough QT Study – Both safety and pharmacokinetic data from the TQT study was not submitted and as the highest and longer duration of study with intensive pharmacokinetics this would have been extremely useful information. Instead the lack of submitting the information, some of which was not submitted even after requested by OCP, simply in itself represents a major deficiency that according to the FD&CA must result in nonapproval.

Cumulative Toxicities – cardiopulmonary, hematologic, and connective tissue toxicities appear to be cumulative with greater risks the longer patients are on medication. In spite of this the sponsor curtailed the only study of greater than 1 year total exposure ostensibly as the study was un-interpretable without a placebo arm. In addition, the sponsor may have limited the amount of safety information provided that was available from long term studies.

Suicidality – Increased risk of suicide and suicidality in adults with bipolar disorder I treated with asenapine or olanzapine for 2 to 3 weeks. This is compared to no risk seen in patients on placebo. (Please refer to original OCP review.)

Lack of Substantial Evidence of Efficacy – Please refer to original OCP review.

3.8 Assessment of Risks Relative to Currently Approved Compounds

3.8.1 Other Antipsychotics

The following compounds are presently marketed in the US. Dr. Temple has indicated that any assessment of risk benefit will likely include a comparison to the following presently marketed compounds.

- Clozapine (Clozaril®)
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Paliperidone
- Ziprasidone (Geodon®)
- Aripiprazole (Abilify®)

Of the ones that are currently approved the first 3 are structurally most similar to asenapine. In the OCP briefing this reviewer pointed out that the side effect profile for asenapine is remarkably similar to the labeled side effect profile for both clozapine and olanzapine. Figure 15 and Figure 16 on the following page are slides from the original OCP briefing and provide an overview of the particular toxicities and structure activity relationships associated these compound. However it should be noted that asenapine is the only pyrrole and thus may have both qualitatively and quantitatively more severe AEs.

Even if asenapine is compared to clozapine which is available on a restricted basis it needs to be remembered that there is data to show that clozapine does work in some individuals with schizophrenia who did not respond to classical antipsychotics, whereas there is no such data for asenapine. Plus in this reviewer's opinion there is a lack of substantive data to support the efficacy of asenapine in schizophrenia. In addition it should be remembered that due to the variety of serotonin receptors and their various effects just because a patient will respond to clozapine when they don't respond to a classical antipsychotic does not mean that the same is true for asenapine.

Thus the most relevant compound to assess the safety of asenapine against is olanzapine.

The sponsor reported their position as to the safety of asenapine relative to olanzapine American Psychiatric Association Meeting held in Washington DC in May as described in a press release from the sponsor shown in §4.4 Appendix 4 – Schering-Plough May 8, 2008 Press Release for Asenapine. These statistics are also put forward by the sponsor in the common technical document summary sections of the NDA. While on face asenapine seems no more dangerous than olanzapine, these statistics only cover total statistics and do not address the safety data referred to in this review amendment. Specifically they do not include sufficient long term safety data and the numbers do not adequately reflect the relative incidence of serious AEs and death. When serious AEs and deaths are compared asenapine appears to be significantly less safe than olanzapine. In addition, the signal for serious long term safety problems rather than arguing for the approval of asenapine actually argues for an immediate reevaluation of the safety of olanzapine. In addition it might be more appropriate to compare the safety of olanzapine to the safety profile of other antipsychotics.

Recently published articles have raised significant concern about the **long term** safety of antipsychotics and in particular that the more recently introduced antipsychotics increase all cause mortality and decrease life expectancy to a greater extent than older antipsychotics²⁶. This is significant as the

²⁶ [Saha S, Chant D, McGrath J](#). A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007 Oct;64(10):1123-31.

schizophrenic population is already at an increased risk of death from all causes compared to the non-schizophrenic population²⁷. Most recently there has been a publication that seems to argue for an acceptable risk benefit for the use of antipsychotics in schizophrenics²⁸. However even a cursory examination of the article reveals that the benefit may be only for a subset of the schizophrenic population. For example patients who are already suicidal, who are young, who are early in the course of their illness (< 4 years) and have had only 1 or 2 psychotic episodes. In addition to the fact that the risk of suicide is lower than previously thought and decreases with the duration of illness²⁹, whereas the risk of death from the drugs appears to increase with time argues for as limited treatment duration as possible to simply get a psychotic episode under control with subsequent switching to non-antipsychotic disease management if possible. In addition, other publications suggest that the risk benefit may be different in different populations or with disease severity.³⁰

²⁷ [Auquier P, Lançon C, Rouillon F, Lader M, Holmes C](#). Mortality in schizophrenia. *Pharmacoepidemiol Drug Saf*. 2006 Dec;15(12):873-9. Review. PMID: 17058327 [PubMed - indexed for MEDLINE]

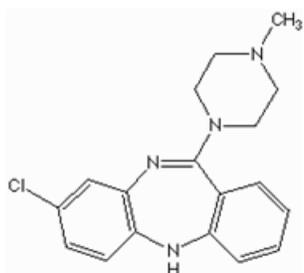
²⁸ [Haukka J, Tiihonen J, Härkänen T, Lönnqvist J](#). Association between medication and risk of suicide, attempted suicide and death in nationwide cohort of suicidal patients with schizophrenia. *Pharmacoepidemiol Drug Saf*. 2008 Mar 10

²⁹ [Palmer BA, Pankratz VS, Bostwick JM](#). The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry*. 2005 Mar;62(3):247-53.

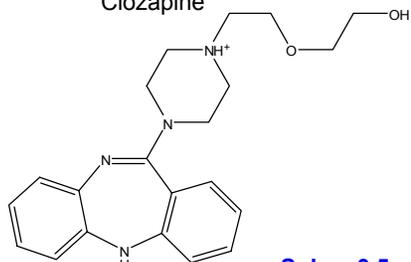
³⁰ [Thirthalli J, Jain S](#). Better Outcome of Schizophrenia in India: A Natural Selection Against Severe Forms? *Schizophr Bull*. 2008 Mar 13. [Epub ahead of print] PMID: 18339655 [PubMed - as supplied by publisher]

Figure 15 Structure Slide # 1 from OCP Briefing

Dibenzopyrriidine / Benzofuranopyrriidine
Dibenzopyrrole

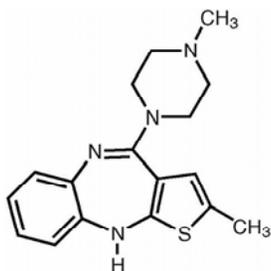


Clozapine

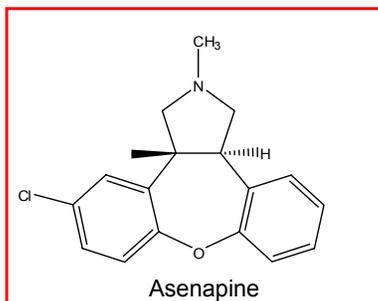


Quetiapine

Soly ~ 3.5 mg/ml

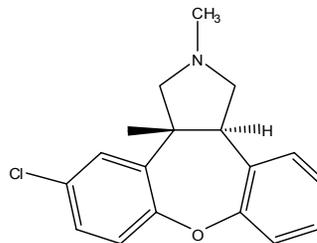


Olanzapine

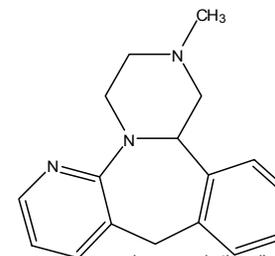


Asenapine

Figure 16 Structure Slide # 2 from OCP Briefing



Asenapine



Mirtazapine

(Remeron – Organon 1994)

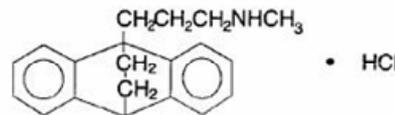
Antidepressant
excessive sedation with alcohol
or [benzodiazepines](#)
Agranulocytosis
DDI – MAOIs
CL dec 40% in elderly males
10% in elderly Females

In pre-marketing clinical trials of mirtazapine, 2 out of 2796 patients developed AGRANULOCYTOSIS (absolute neutrophil count (ANC) less than 500 cells/cubic millimeters with symptoms) and 1 patient developed severe NEUTROPENIA (ANC less than 500 cells/cubic millimeters without symptoms).

All 3 patients recovered after mirtazapine was discontinued. The incidence based on these 3 cases was approximately 1.1 per 1000 patients.

Discontinue therapy if the patient develops a sore throat, fever, stomatitis, or signs of infection, along with a low white blood cell (WBC) count.

Other events rarely (incidence less than 1 in 1000 patients) reported in pre-marketing evaluation were PANCYTOPENIA, THROMBOCYTOPENIA, LEUKOPENIA, ANEMIA, LYMPHOCYTOSIS, lymphadenopathy, and petechia (Prod Info Remeron(R), 02a).



Maprotiline - Ludiomil – Ciba Geigy

Extreme caution should be used when this drug is given to:
patients with a history of myocardial infarction; a history or presence of cardiovascular disease
because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes and tachycardia.
Agranulocytosis
CYP2D6 MAOIs

3.8.2 Combination Products (Atypical Antipsychotics & Serotonin Reuptake Inhibitors)

As mentioned earlier there is likely an increased risk of serious and lethal life threatening adverse effects and death if asenapine or a pharmacologically similar drug were to be used in combination with a serotonin Reuptake Inhibitor, (see §3.1.4).

As mentioned in §3.1.4 Symbyax® (Lilly N21520 Approved Dec 24, 2003) a combination of olanzapine and fluoxetine is currently on the market.

Current labeling and safety information for Symbyax® may be found at the following websites³¹.

<http://pi.lilly.com/us/symbyax-pi.pdf>

http://www.symbyax.com/prescribing/consumer_safety.jsp

<http://pi.lilly.com/us/AntiDep-MedGuide.pdf>

Examination of the Clinical Pharmacology, Warnings (including but not limited to orthostatic hypotension), Precautions (including but not limited to pregnancy) sections of the labeling for Symbyax® reveal similar deficiencies in the development program and labeling of Symbyax® as has been noted in the reviews for asenapine.

The following is the indications and usage section from the labeling available at this website:

“INDICATIONS AND USAGE

SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder. The efficacy of SYMBYAX was established in 2 identically designed, 8-week, randomized, double-blind clinical studies.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.”

The highlighted text in red, appears to indicate that:

- a) Symbyax is approved for depression associated with any bipolar disorder.
- b) Symbyax is approved for administration longer than 8 weeks but that it's at the physician's discretion, and that all pertinent information available at approval has been provided to allow for a maximally informed decision for treatment beyond 8 weeks. (This is not to imply that there may be unknown risks however the labeling implies that sufficient information is included in the labeling regarding known potential long term risks.

³¹ Accessed June 15, 2008

With respect to the labeled indication selected text from the clinical studies section of the label follows:

“CLINICAL STUDIES

The efficacy of SYMBYAX for the treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies of patients who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for Bipolar I Disorder, Depressed”

Thus although the indications and usage section indicates approval for any depression associated with bipolar disorder, which clearly implies bipolar I disorder and more recently can be interpreted to mean bipolar spectrum disorder this is clearly not the case.

This interpretation is supported by the following self-assessment tool on Lilly's Symbyax® website (http://www.symbyax.com/tools_downloads/mdq.jsp) which might induce patients to potentially identify bipolar I or bipolar spectrum disorder which may result in patient pressure on primary care providers to inappropriately prescribe Symbyax® for indications for which it was not studied in.

Even stronger evidence suggesting that the sponsor is trying to induce misuse and inappropriate prescribing is the following text from the labeling itself:

“Screening Patients for Bipolar Disorder — A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SYMBYAX is approved for use in treating bipolar depression.”

With respect to item b) the evidence provided in this review indicates that Lilly was also likely aware of the long term risks and even short term risks especially when used in combination with certain other drugs such as carbamazepine.

It is this reviewer's opinion that the labeling for Symbyax® is misleading and is therefore misbranded in violation of the Food Drug and Cosmetics Act § 502 (a), (f) and (j), and that the sponsor is also in violation of FD&CA § 301.

Additional information regarding these laws, as well as preclinical evidence that both some sponsors and more importantly that FDA has been aware of some of the risks associated with both olanzapine and asenapine are included in § 4.5, (Appendix 5 – Additional Information Regarding the Approved Atypical Antipsychotic / SSRI Combination Product- Symbyax®; (Fluoxetine/Olanzapine)).

3.8.3 Quantitative Risk Benefit Analysis

This reviewer is presently working on a new approach to quantify the relative risk to benefit of a drug. This approach may allow a quantitative calculation of a particular drug's risk to benefit that also includes risks of leaving the patient untreated and as compared to presently marketed compounds. Not only may this approach be useful in determining whether the drug should be approved, it may also be useful in assessing if a drug should be removed from the market or whose indications or labeling should be altered.. It is expected that asenapine will be one of the compounds used in developing this methodology. Due to time constraints this quantitative analysis is not included in the present review. If asenapine needs to go to the Drug Safety Oversight Board, this reviewer expects that this review will need to be amended to incorporate some of these analyses.

3.9 Risks with Other Pharmacologically Active Agents

A number of other medications have been reported to have side effect profiles that suggest a common underlying mechanism with asenapine and other antipsychotics.

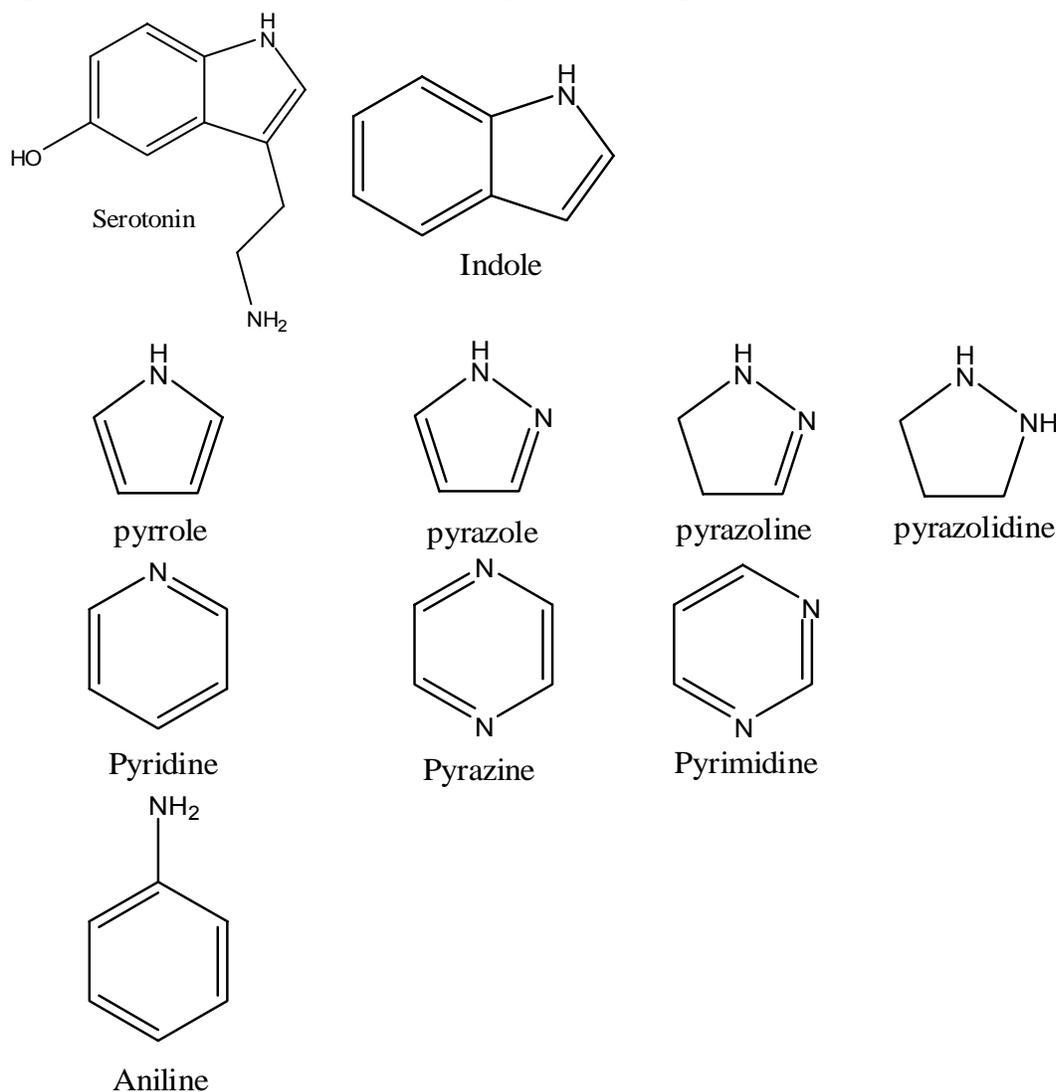
As various serotonin receptors are involved in so many different disease processes similar risks might be seen with receptor nonspecificity with other pharmacologically active agents that tend to bind to different degrees to different serotonin receptors. To this end a quick examination of possible structure activity relationships was undertaken.

3.9.1 Serotonergic Compounds

3.9.1.1 Heteroaromatic Nitrogen Containing Compounds

Figure 17 shows the structure of serotonin and other simple heteroaromatic nitrogen containing compounds that might be expected to bind to serotonin receptors and are common substructures in many drugs. It's clear that serotonin is an indole derivative.

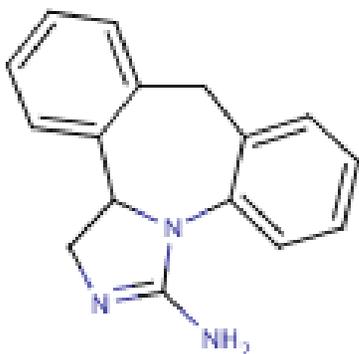
Figure 17 Simple Heteroaromatic Nitrogen Containing Compounds



3.9.1.2 Other Compounds Structurally Similar to Asenapine

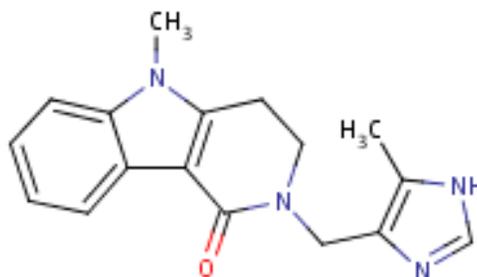
Figure 18 to Figure 20 show other compounds that are structurally similar to asenapine. One of them, epinastine, is a pyrazolidine tetracyclic compound whereas the two 5HT3 antagonists are very similar with both containing an indole and differing primarily in the pyrazole side chain substituent, yet this change results in a significant difference in toxicity in some individuals. In addition to the potential for different 5HT3 receptor subtypes altering efficacy, either this subgroup is cleaved and has different toxicities mediated by vasoconstriction of the intestines and/or minor genetic variations between individuals result in differences in toxicity.

Figure 18 Epinastine (Elestat – Allergan)



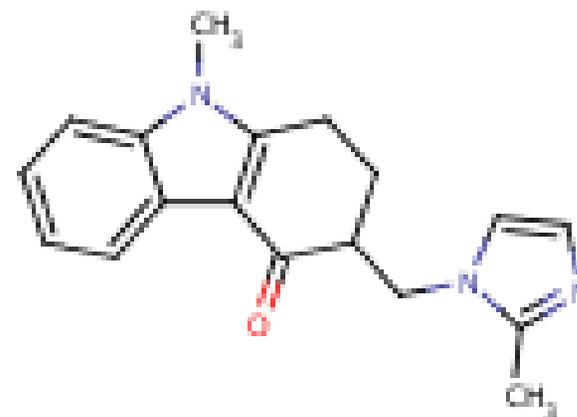
Antihistaminic Ophthalmic used for the prevention of itching associated with allergic conjunctivitis

Figure 19 Alosetron (Lotronex - Glaxo)



5HT3 antagonist used for Irritable Bowel Syndrome, Diarrhea Predominant in Women. Caused Ischemic Bowel Disease in 1 : 300 women, life threatening AE requiring emergency surgery. 4 Cases pre-approval.

Figure 20 Ondansetron (Zofran - Glaxo)



5HT3 antagonist used for the treatment of chemotherapy-induced nausea and vomiting

3.9.1.3 Other Atypical Antipsychotics

The other group of atypical antipsychotics that are structurally different from the tri- and tetracyclic antipsychotics similar to asenapine all include indole substructures and many have multiple substructures that can result in additive toxicities depending on metabolism etc. For example bifeprunox and pimozide each have one or more substructures that might inhibit serotonin reuptake transporters.

Figure 21 Indole Containing Atypical Antipsychotics

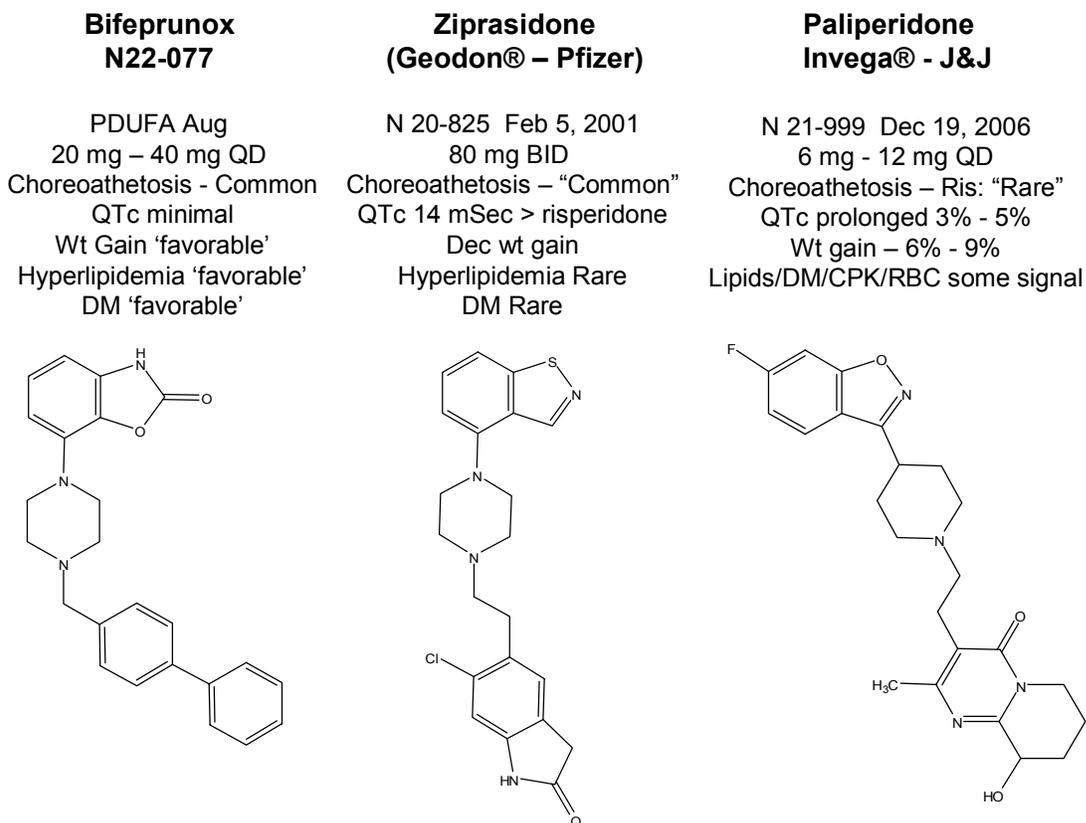
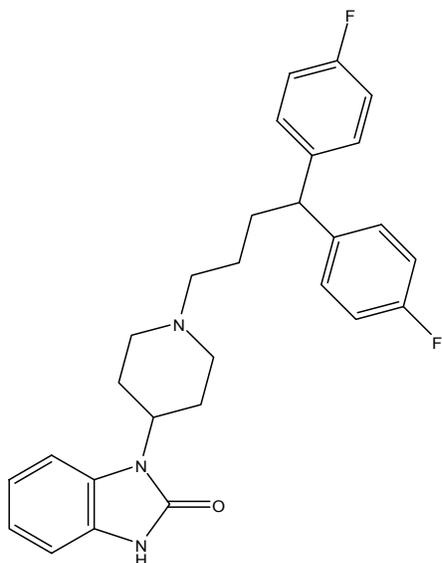


Figure 22 Pimozide – Janssen (1963)



Extremely toxic. Drug of last resort. Structure could cleave at 2 different places both producing different structures that might result in adrenergic or serotonergic reuptake inhibition.

3.9.1.4 Fluoroquinolones

Fluoroquinolones are known to cause QT prolongation and effects on connective tissues, and both type of effects can be mediated by specific serotonin receptors. Of the two fluorquinolones shown in Figure 23 and Figure 24 moxifloxacin has an obvious substructure that would be expected to bind similarly to serotonin, however that does not preclude pharmacologic effects due to the other part of the molecule. Or how a particular serotonin receptor subtype is affected.

Figure 23 Moxifloxacin

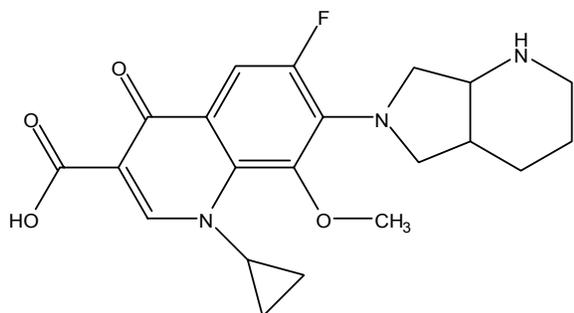
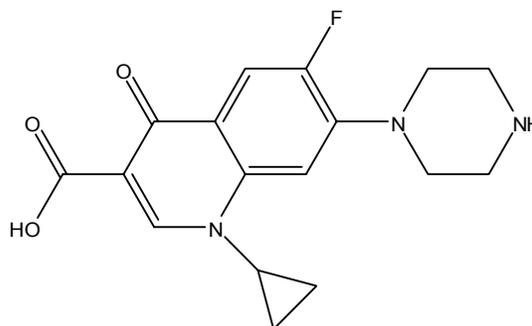


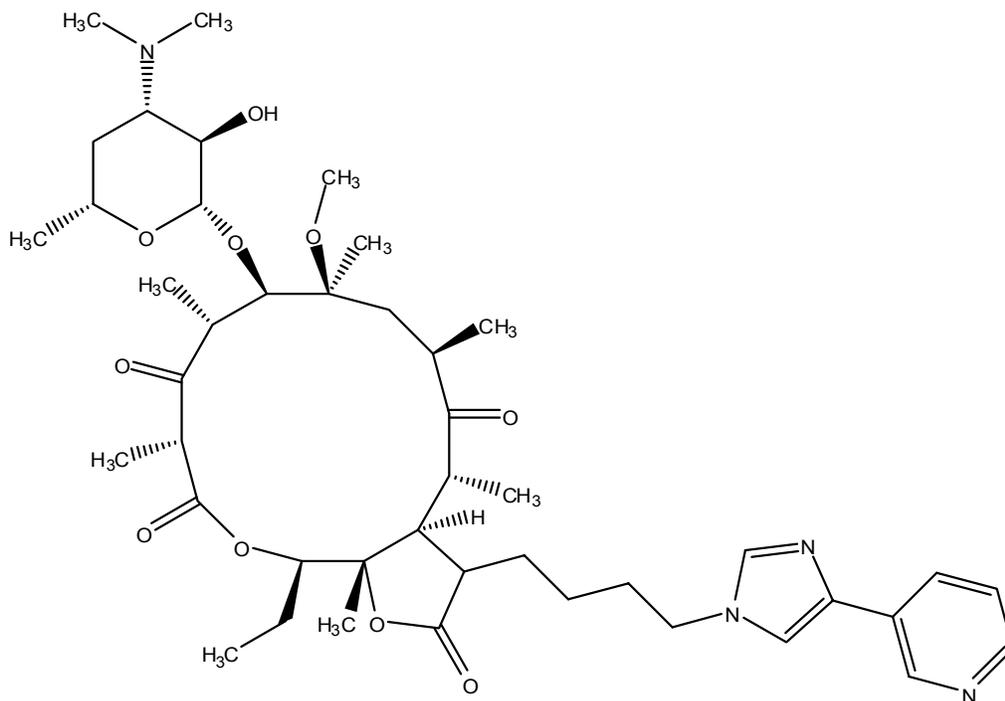
Figure 24 Ciprofloxacin



3.9.1.5 Macrolide Antibiotics

Various macrolide antibiotics also cause hepatotoxicity, the one that has most recently been in the news is Ketek® whose structure is shown in Figure 25. There are various parts of the molecule that might bind to receptors that result in hepatic fibrosis, and this could be used to predict such toxicities in the future.

Figure 25 Telithromycin Ketek®



3.9.1.6 Avermectins

Another drug that has been in the news for cardiac toxicity is moxidectin whose structure is shown in Figure 26. It's clear that moxidectin contains a serotonin like substructure, and it has a degree of similarity to monocrotaline, (see Figure 3). What's more interesting is that moxidectin is extensively used in horses. Since the mid-1990's a number of Kentucky Derby winners have been retired immediately after the Derby due to bone chips in the knee, except for ivermectin most avermectins were not approved for use that early. Avermectins are also used in livestock for food and in farmed fish, (e.g. emamectin in salmon). This raises the possibility that such drugs or compounds with similar pharmacologic activity in the food supply could be causing illness in humans.

Merck has been lauded for their donation of ivermectin to treat parasitic infections in tropical communities, (<http://www.who.int/bulletin/volumes/82/8/editorial30804html/en/index.html> Accessed June 18, 2008). A perhaps unintended benefit to this program is that potentially commercially valuable information has been obtained on side effects in humans and in particular in human populations with especially high genetic diversity which may shed light on the development of personalized medicine.

Figure 26 Moxidectin (Proheart 6)

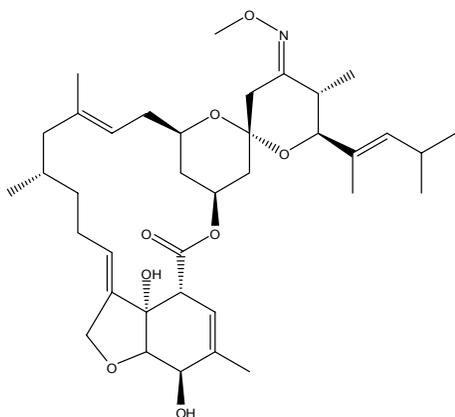


Figure 27 Emamectin

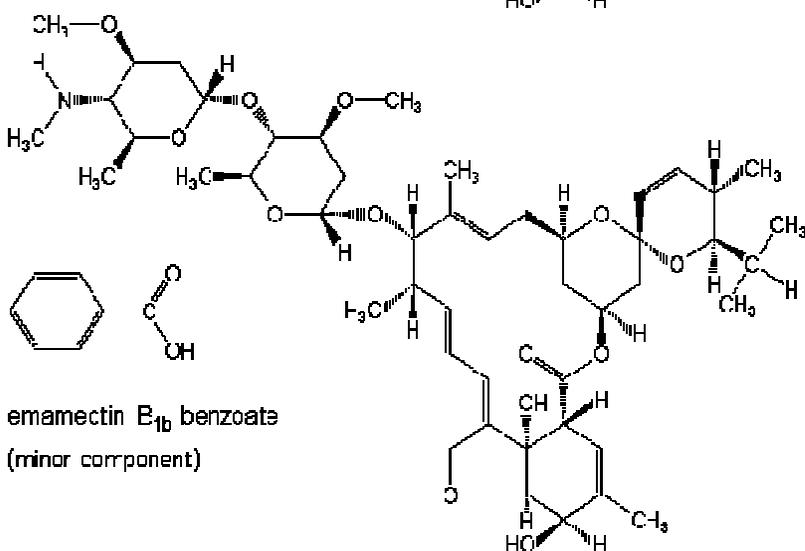
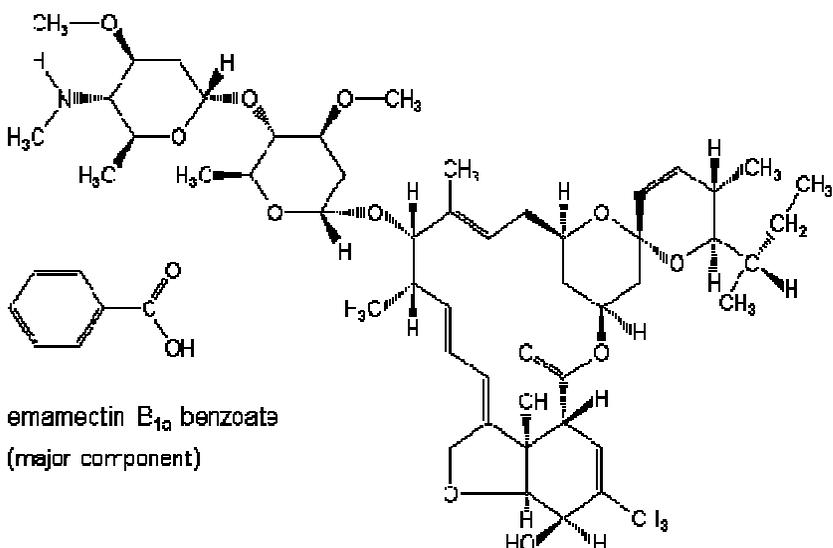
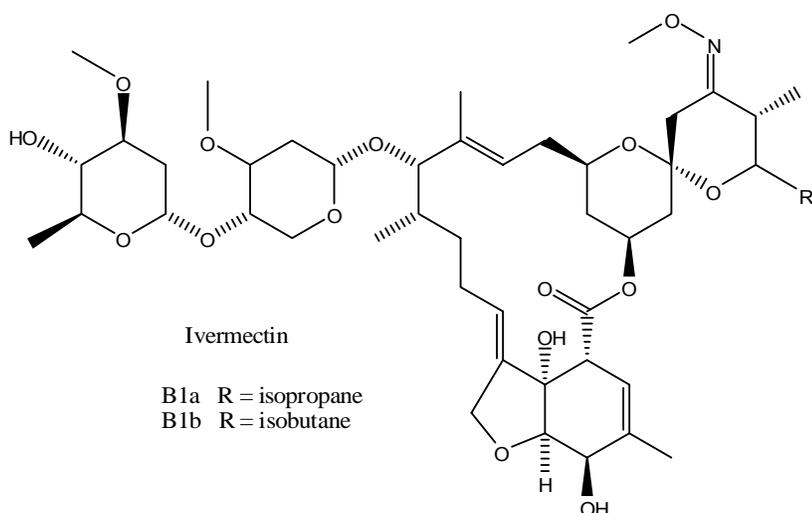


Figure 28 Ivermectin



3.9.1.7 Steroids and Related Compounds

Steroids are well known to have varying effects depending on structure including glucocorticoid, mineralocorticoid, estrogenic and androgenic effects depending on substituents. Steroids all contain a bicyclic 5 and 6 sided ring sub-structure, in addition estrogenic activities have been related to biphenyls. Some of the substructures suggest that some steroidal effects might be mediated via serotonergic receptors. This suggests that perhaps the recent concerns regarding pharmacy compounding of estriol may have a pharmacologic concern underlying it. It also suggests that the varying pharmacologic effects, both positive and negative, seen with conjugated estrogens may be in part mediated via serotonergic effects.

Figure 29 Estriol

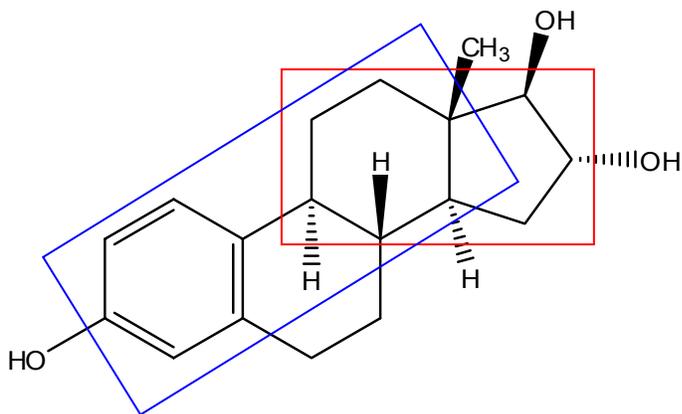
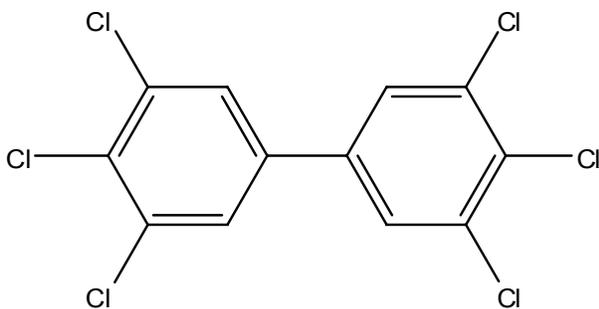


Figure 30 PCBs Polychlorinated Biphenyls



3.9.1.8 Zoloft® Like Compounds

Sertraline (Zoloft® - Pfizer) is a NSRI antidepressant. Comparison of the structure reveals similarities to Bisphenol A, dioxins, including agent organ, and steroids. This also suggests that varying effects for environmental toxins including carcinogenic effects could conceivably be mediated via hormonal or serotonergic effects. In addition, if environmental toxins also affect the 5HT_{2B} receptors and other receptors this provide a mechanistic basis for various maladies such as chronic fatigue syndrome, infertility, the increasing incidence of ADHD, the rising incidence of mitochondrial disorders, possibly autism, and gulf war syndrome.

Figure 31 Sertraline (Zoloft- Pfizer)

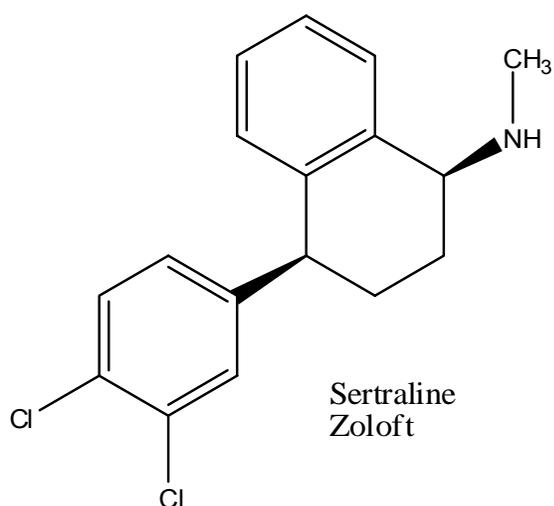


Figure 33 Bisphenol A

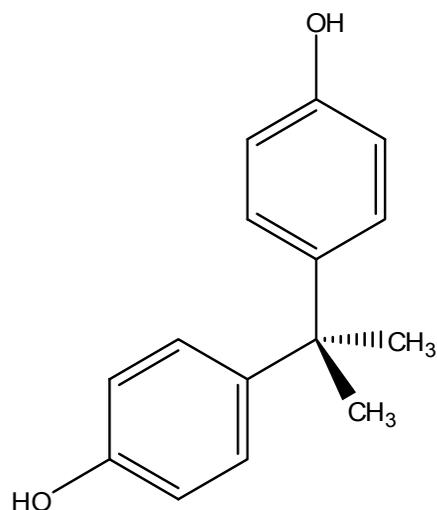


Figure 34 Modafinil

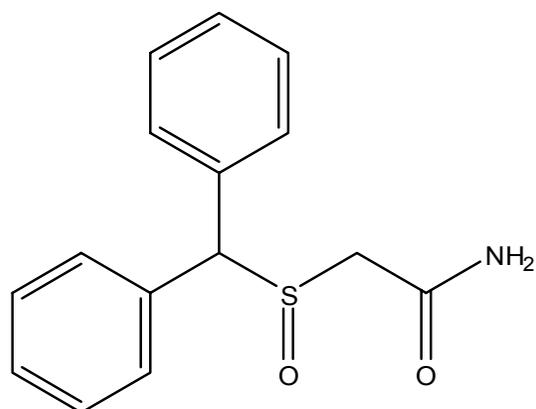


Figure 32 Dioxin 2,3,7,8-p-TCDD

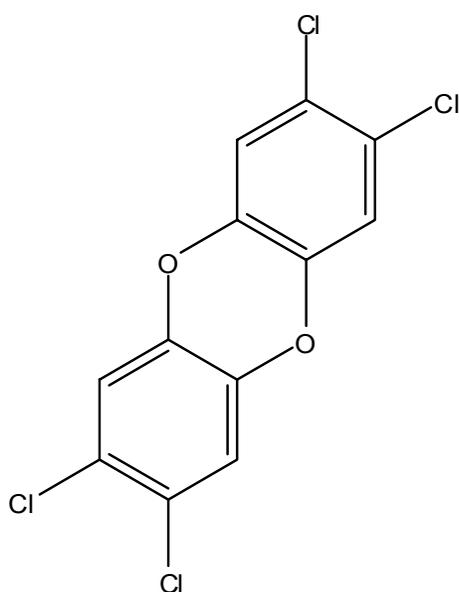
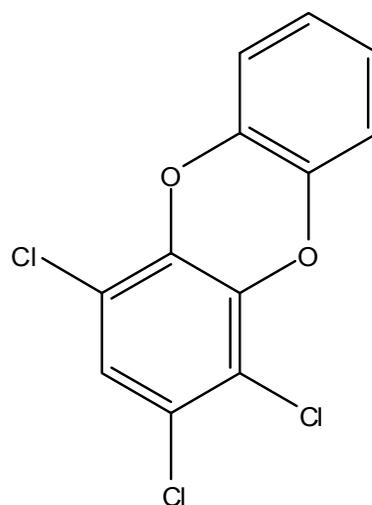


Figure 35 Agent Orange (Equal Mixture of 2,4-DCDD and 2,4,5-TCDD)



3.9.2 Other Structural and Receptor Classes

Several other structural and more importantly receptor drug classes have been shown to have complementary effects all over the body, and that interact with serotonergic systems, that in some cases increase toxicities. Only a few classes are mentioned here.

3.9.2.1 Pyrroles and Pyrrolizidine Plant Alkaloids

Pyrrolizidine plant alkaloids have been implicated in a wide variety of functions related to effects on serotonin, and pyrroles are a primary additive to cigarette tobacco and are among the primary structures in the development of a wide variety of new drug classes including: anti-addictive drugs, anticancer and cancer prevention drugs, drugs for Alzheimers, dementia, psychiatric illnesses, cardiovascular illness, neurologic diseases, stroke, clotting disorders, musculoskeletal disorders, pulmonary and hepatic fibrosis, preeclampsia, etc.. They may also help explain toxicities with a wide variety of drugs presently on the market as well as with tobacco³²

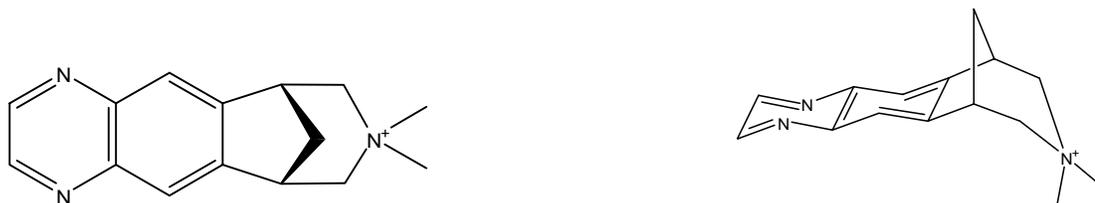
3.9.2.2 Nicotinic Receptor Drugs

A number of drugs are under development that effect nicotinic receptors and indications under investigation include Alzheimer's disease and other dementias, age associated memory impairment (AAMI), mild cognitive impairment (MCI) and other disorders marked by cognitive impairment, Parkinson's disease, pain including neuropathic pain, depression, anxiety, schizophrenia, and addiction.

Recently one of these nicotinic receptor drugs has come under scrutiny for safety reasons³³. Varenicline (Chantix® - Pfizer), has recently been implicated in dizziness, loss of consciousness, seizures, abnormal spasms and movements, and suicidality. Of particular concern are the long term side effects and 224 cases of potential heart-rhythm disturbances. Based on what has been seen in the present submission this raises concerns about effects at serotonin receptors similar to what is observed with asenapine.

Structurally asenapine and varenicline (Chantix® - Pfizer) do not appear similar with possible exception of the single pyrazino nitrogen on varenicline. Since side chain length distance of nitrogen atoms on antipsychotics has been known to affect receptor binding to dopamine receptors since the 1970's this may be involved with binding characteristics to serotonin receptors.

Figure 36 Varenicline Structure (Chantix® - Pfizer)



³² This information was found on my own time and using my own computer equipment while looking up side effects and mechanisms related to ciprofloxacin, BMRP2, and my own or my family's personal health related to drug side effects, i.e. SSRIs, umbilical hernia, COPD, cardiovascular disease etc.. Although I am including this information in this review I want to clearly indicate that this information was not found based upon information I learned through my position and thus I believe I am able to freely discuss it outside of FDA. There will be other information in this review with other drug classes, e.g. drugs for osteoporosis, cancer, etc. that I have also learned about secondary to searches for medical information for personal purposes and although I may include some of my findings in this review, and though I may redo the same google searches that I did at home on my work computer for inclusion in this review, it should not be construed that the searches and information gleaned were based upon information obtained in the course of my job. Therefore I believe I am free to discuss information I use in performing review work but whose origin is completely independent of that work in my private capacity outside. Note the relationship between BMRP2, Smad, and effects on 5HT receptors, etc. as well as structure activity relationships.

³³ <http://www.fda.gov/cder/news/pubpress.htm>

3.9.2.3 Phenylalanine Derivatives

These include the catecholamines dopamine, epinephrine, and norepinephrine.

Figure 37 Dopamine

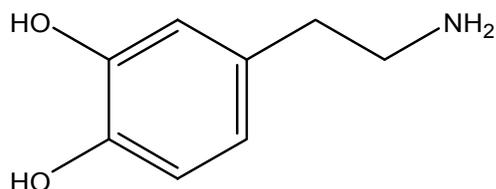
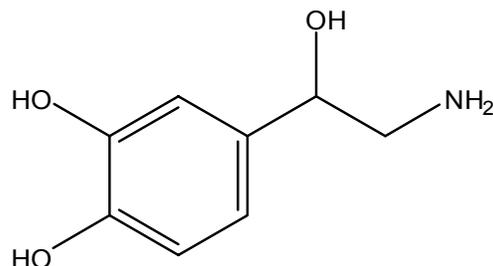


Figure 38 Norepinephrine



3.9.3 Amphetamine Like Compounds

Amphetamine like compounds include ephedra and pseudoephedrine. They may have direct actions on adrenergic receptors or may disrupt cellular reuptake or vesicular release of catecholamine neurotransmitters.

Figure 39 Amphetamine

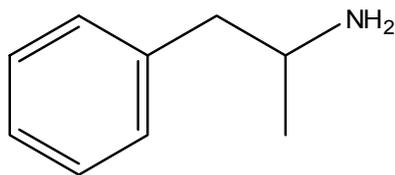


Figure 40 Ephedrine

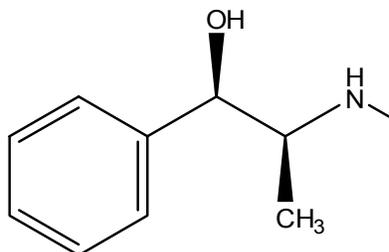
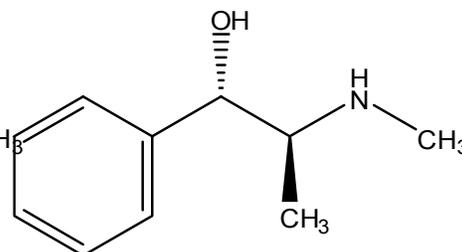


Figure 41 Pseudoephedrine



It's interesting to note that Ephedra was pulled from the market immediately prior to the FDA's warning on Phen-Fen in 1997. Similarly FDA has been issuing repeated warnings about pediatric OTC cough and cold medications that might contain pseudoephedrine since April 2007. This reviewer has also noticed that the dates of these warnings tend to coincide with significant milestones in the submission and review of asenapine, which as treatment for bipolar disorder will likely have a very high off-label market for pediatric bipolar and pediatric bipolar spectrum disorder.

3.9.3.1 Glutamine Derivatives

A number of derivatives of the amino acid glutamine also have pharmacologic effects, for example monosodium glutamate is a common flavoring enhancer and preservative and in some individuals cause intense vasoconstrictive headaches and even seizures. Whereas the structurally similar compound valproate is used as a treatment for a wide variety of seizure disorders as well as a mood stabilizer. More glutamate receptor active agents are currently under development for a variety of neuropsychiatric indications.

Figure 42 Monosodium Glutamate (MSG)

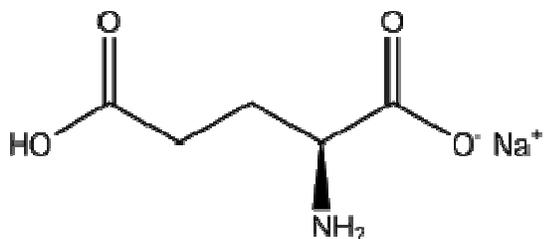
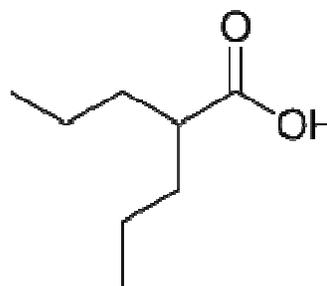


Figure 43 Valproic acid



3.9.3.2 Azo Dyes and Food Colorants

Recently the Center for Science in the Public Interest has petitioned the FDA regarding azo food dyes and has claimed that they may potentially induce or exacerbate ADHD. This seems to be a potentially plausible relationship and should be investigated.

3.9.4 Conclusions

Although still speculative in some regards, the evidence leads to a very simple and elegant unifying hypothesis, that is consistent with previous scientific theories (e.g. evolution), and it leads to important predictions.

The major points of this biologic systems hypothesis follow:

Biologic systems having developed from a limited number of small ubiquitous molecules, such as serotonin, dopamine, and acetylcholine that have over time developed various receptor subtypes in different tissues with varying effects and different degrees of interactions with other systems. Even now evolution is occurring with mutations occurring in these various receptor subsystems, some of which are silent, many of which will have a survival disadvantage, and some of which will have a survival advantage.

Many natural and man-made compounds in the environment are expected to affect these biologic systems, typically in an adverse manner. Different individuals may have different sensitivities based their personal Pharmacogenomics.

In radiation biology there are two major competing theories of toxicity, whether there is a threshold effect or simply a linear effect. A similar issue exists for drugs and it may be a combination of both. However drugs and toxins compound the problem by exposing organisms to varying amounts of different pharmacologically active agents both intentionally and unintentionally via the environment. These active substances would then be expected to have varying effects due to variations in dose and additive, synergistic, and antagonistic effects with other compounds, as well as underlying pathophysiology and Pharmacogenomics.

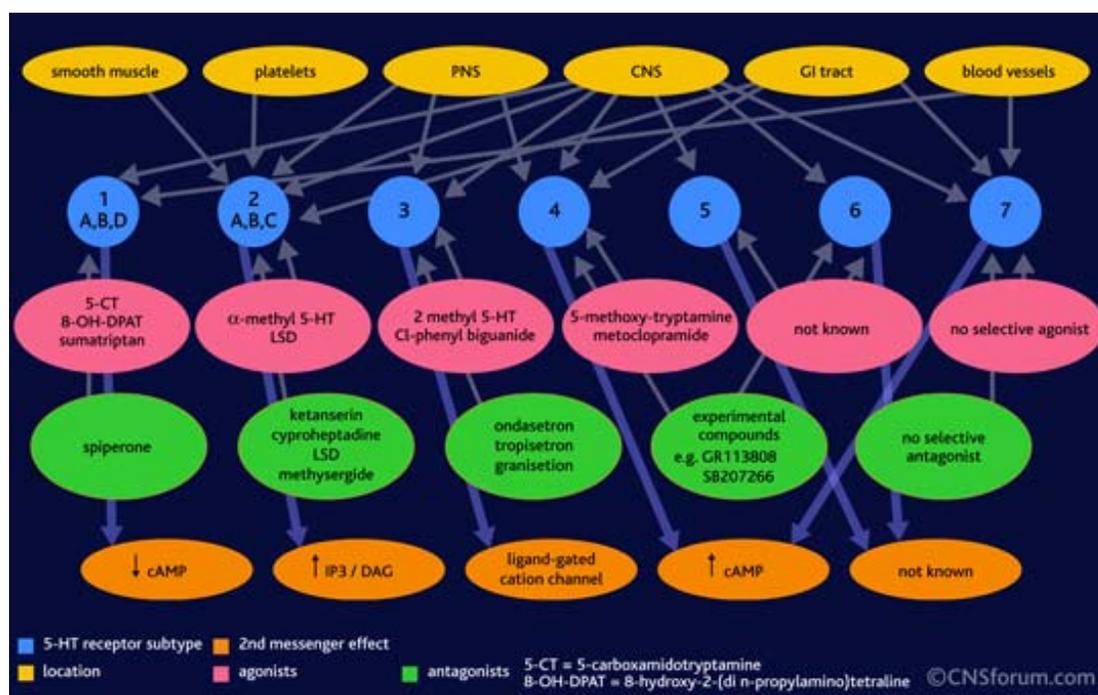
These pharmacologically active agents will enter the environment and may affect someone else. Consequently, the prudent approach would appear to be to try to minimize release and exposure in the first place, and this should include minimizing use of certain food additives, veterinary drugs in food livestock, certain fertilizers, herbicides and pesticides, and use of many drugs if not absolutely necessary.

The alternative is accumulation of environmental toxins that individually might not reach a level of concern but when the total molar exposures and especially over time are considered it becomes clear that a Malthusian effect might develop.

4 Appendices

4.1 Appendix 1 - Description of 5-HT Receptor Subtypes from the Lundbeck Institute

The actions of 5-HT are mediated by a range of different 5-HT receptors. The 5-HT receptors are classified into seven main receptor subtypes, 5-HT₁–7. Six of the seven subtypes are G-protein-coupled receptors; 5-HT₃ is a ligand-gated cation channel. 5-HT₁ receptors occur primarily in the brain and cerebral blood vessels (5-HT_{1D} only), where they mediate neural inhibition and vasoconstriction. They function mainly as inhibitory presynaptic receptors, linked to inhibition of adenylate cyclase. Specific agonists at 5-HT₁ receptors include sumatriptan (used in migraine therapy) and buspirone (used in the treatment of anxiety). Spiperone and methiothepin are specific antagonists of 5-HT₁ receptors. 5-HT₂ receptors are found in the CNS and in many peripheral sites. They act through phospholipase C to produce excitatory neuronal and smooth muscle effects. Specific ligands at 5-HT sites include LSD – acting as an agonist in the CNS and as an antagonist in the periphery – and ketanserin and methysergide (both antagonists). 5-HT₃ receptors occur mainly in the peripheral nervous system, particularly on nociceptive afferent neurones and on autonomic and enteric neurones. The effects of these receptors are excitatory, mediated by receptor-coupled ion channels. 5-HT₃ antagonists (eg ondansetron, tropisetron) are used predominantly as anti-emetic drugs. 5-HT₄ receptors are found in the brain, as well as peripheral organs like the heart, bladder and gastrointestinal (GI) tract. Within the GI tract they produce neuronal excitation and mediate the effect of 5-HT in stimulating peristalsis. A specific 5-HT₄ agonist is metoclopramide used for treating gastrointestinal disorders. Little is known about the function and pharmacology of 5-HT₅, 5-HT₆ and 5-HT₇ receptors.



References

Other peripheral mediators: 5-hydroxytryptamine and purines. In: Pharmacology, 4th edition. Rangsee your doctor to discuss proven treatment options.³⁴

³⁴ http://www.cnsforum.com/imagebank/item/5HT_rcpt_subtypes/default.aspx accessed June 2, 2008

4.2 Appendix 2 – Safety Signal from Original IND Submission

Figure 44 Conclusions and Recommendations from Original IND 30 Day Safety Review for Asenapine - IND 51641 SN 000

VII. Conclusions and Recommendations

At this time, it is recommended that this study be put on hold because of issues regarding safety concerns for subjects and deficiencies in the investigator's brochure (please refer above under Investigator's Brochure). The major safety concern for patients arises in light of cardiotoxic effects of this drug, which induced an asystolic event in a healthy volunteer who required emergency medical resuscitation (Study 25506/ Subject 1/1: blood concentration of 1850 pg/ml of Org 5222 after IV administration). Other studies also demonstrated subjects with asystolic events including Study 25501/Subject 1/1 (at blood concentration of 680pg/ml of Org 5222 after oral dosing), and Study 25511/Subject 9 (at blood level of 69pg/ml of Org 5222 after sublingual administration). The protocol submitted does not sufficiently address this risk or offer details of how subjects will be protected and treated if a catastrophic event such as cardiac arrest were to occur. There is a description of telemetry monitoring by a technician; however, it is unclear how involved a cardiologist will be in the monitoring and care of these subjects and how quickly the telemetry technician and other unit personnel could initiate and activate a medical resuscitation if an event were to occur. A more specific plan ensuring that this study will be conducted in a safe environment is necessary to ensure that subjects are protected against possible risks. It may be desirable to enlist the assistance of a cardiology consultant to devise such a plan.

Also, because of the elevations of liver function studies observed in Study 85136, it would be important to monitor these more frequently in the proposed Study 041-001, especially in the design for Block 3. Based on these previous findings, monitoring liver function studies would be desirable in future protocols as well.

Figure 45 Conclusions and Recommendations from Original IND 30 Day Safety Review for Asenapine - IND 51641 SN 000 (Continued)

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Please refer to the letter to the sponsor dated November 5, 1996 for further detail delineating the rationale for a hold at this time.

Roberta Glass 11/7/96
Roberta Glass, M.D.
Medical Officer, DNDP

CC:
Orig. IND
HAD-120 Div File
HAD-120 TLaughren/SHardeman/LFreed/GFitzgerald/AMosholder/RGlass

11-12-96

There are insufficient details for protocol 041-001 to determine if subjects will be adequately protected. The sponsor has also not adequately explored the plasma level data relative to the cardiac event of concern. In addition, the investigator's approach is deficient. I agree that a hold is appropriate.

Thomas P. Laughren, MD
TL, ADA

4.3 Appendix 3 – Skeletal Exams in Chinchilla Rabbits - Study SDG RR 2914

	GROUP 1 2X0.0 MG/KG	GROUP 2 2X0.5 MG/KG	GROUP 3 2X2.5 MG/KG	GROUP 4 2X15.0 MG/KG
NUMBER OF FETUSES EXAMINED	130	137	140	152
UNLISTED FINDING(S) (SHOWN ON PREVIOUS PAGE(S))	2 2%	2 1%	2 1%	4 3%
STERNUM				
INCOMPLETELY OSSIFIED				
STERNEBRA 1	0	0	0	1 1%
STERNEBRA 2	1 1%	0	2 1%	2 1%
STERNEBRA 3	0	0	0	1 1%
STERNEBRA 4	1 1%	0	1 1%	1 1%
STERNEBRA 5	70 54%	83 61%	60 43% *	104 68% **
NON-OSSIFIED				
STERNEBRA 5	24 18%	16 12%	26 19%	26 17%
ABNORMALLY OSSIFIED				
STERNEBRA 2	0	0	0	1 1%
STERNEBRA 4	0	0	0	2 1%
STERNEBRA 5	0	0	0	1 1%
RIBS				
NON-OSSIFIED				
RIB 12, LEFT	0	1 1%	0	0
RIB 13, LEFT	89 68%	86 63%	85 61%	85 56% *
RIB 9, RIGHT	0	0	0	1 1%
RIB 13, RIGHT	94 72%	91 66%	92 66%	94 62% *
SHORTENED				
RIB 13, LEFT	6 5%	9 7%	12 9%	9 6%
RIB 13, RIGHT	3 2%	7 5%	5 4%	11 7% *
FLYING RIB				
RIB 13, LEFT	3 2%	6 4%	6 4%	11 7% *
RIB 10, RIGHT	0	1 1%	0	0
RIB 13, RIGHT	5 4%	4 3%	1 1%	4 3%
LEFT FORELIMB				
INCOMPLETELY OSSIFIED				
METACARPALIA 1, LEFT	86 66%	86 63%	84 60%	97 64%
DIGIT 1 PROXIMAL PHALANX, LEFT	33 25%	36 26%	36 40% **	43 28%
DIGIT 2 PROXIMAL PHALANX, LEFT	1 1%	0	0	8 5% *
DIGIT 2 MEDIAL PHALANX, LEFT	77 59%	97 71% *	115 82% **	131 86% **
DIGIT 3 PROXIMAL PHALANX, LEFT	1 1%	0	0	8 5% *
DIGIT 3 MEDIAL PHALANX, LEFT	71 55%	93 68% *	98 70% **	123 81% **
METACARPALIA 4, LEFT	0	0	0	2 1%
DIGIT 4 PROXIMAL PHALANX, LEFT	2 2%	3 2%	3 2%	17 11% **
DIGIT 4 MEDIAL PHALANX, LEFT	112 86%	115 84%	115 82%	132 87%
METACARPALIA 5, LEFT	3 2%	10 7%	3 2%	23 15% **
DIGIT 5 PROXIMAL PHALANX, LEFT	31 24%	49 36% *	45 32%	73 48% **
DIGIT 5 MEDIAL PHALANX, LEFT	25 19%	40 29% *	17 12%	9 6% **
NON-OSSIFIED				
METACARPALIA 1, LEFT	4 3%	15 11% *	11 8%	32 21% **
DIGIT 1 PROXIMAL PHALANX, LEFT	12 9%	31 23% **	17 12%	40 26% **
DIGIT 2 MEDIAL PHALANX, LEFT	1 1%	2 1%	2 1%	1 1%
DIGIT 3 MEDIAL PHALANX, LEFT	1 1%	0	0	2 1%
DIGIT 4 MEDIAL PHALANX, LEFT	7 5%	12 9%	19 14% *	15 10%
DIGIT 5 MEDIAL PHALANX, LEFT	105 81%	97 71% *	122 87%	143 94% **
RIGHT FORELIMB				
INCOMPLETELY OSSIFIED				
METACARPALIA 1, RIGHT	82 63%	90 66%	83 59%	99 65%
DIGIT 1 PROXIMAL PHALANX, RIGHT	33 25%	34 25%	37 41% **	43 28%
DIGIT 2 PROXIMAL PHALANX, RIGHT	0	0	1 1%	9 6% **
DIGIT 2 MEDIAL PHALANX, RIGHT	77 59%	96 70% *	115 82% **	124 82% **
DIGIT 3 PROXIMAL PHALANX, RIGHT	0	0	0	9 6% **
DIGIT 3 MEDIAL PHALANX, RIGHT	71 55%	96 70% **	97 69% **	118 78% **
METACARPALIA 4, RIGHT	0	0	0	2 1%

* / ** : Fisher's Exact test significant at 5% (*) or 1% (**) level

	GROUP 1 2X0.0 MG/KG	GROUP 2 2X0.5 MG/KG	GROUP 3 2X2.5 MG/KG	GROUP 4 2X15.0 MG/KG
NUMBER OF FETUSES EXAMINED	130	137	140	152
RIGHT FORELIMB				
INCOMPLETELY OSSIFIED				
DIGIT 4 PROXIMAL PHALANX, RIGHT	4 3%	2 1%	2 1%	17 11% **
DIGIT 4 MEDIAL PHALANX, RIGHT	109 84%	115 84%	115 82%	130 86%
METACARPALIA 5, RIGHT	4 3%	11 8%	4 3%	26 17% **
DIGIT 5 PROXIMAL PHALANX, RIGHT	38 29%	54 39%	51 36%	87 57% **
DIGIT 5 MEDIAL PHALANX, RIGHT	28 22%	45 33% *	19 14%	14 9% **
NON-OSSIFIED				
METACARPALIA 1, RIGHT	6 5%	12 9%	13 9%	29 19% **
DIGIT 1 PROXIMAL PHALANX, RIGHT	14 11%	36 26% **	18 13%	45 30% **
DIGIT 2 MEDIAL PHALANX, RIGHT	2 2%	2 1%	1 1%	1 1%
DIGIT 3 MEDIAL PHALANX, RIGHT	0	0	0	2 1%
DIGIT 4 MEDIAL PHALANX, RIGHT	6 5%	12 9%	20 14% **	17 11% *
DIGIT 5 MEDIAL PHALANX, RIGHT	102 78%	92 67% *	121 86%	138 91% **
LEFT HIND LIMB				
INCOMPLETELY OSSIFIED				
CALCANEUS LEFT	10 8%	8 6%	9 6%	18 12%
TOE 1 PROXIMAL PHALANX, LEFT	1 1%	4 3%	3 2%	11 7% **
TOE 1 MEDIAL PHALANX, LEFT	52 40%	75 55% *	76 54% *	95 63% **
TOE 2 PROXIMAL PHALANX, LEFT	2 2%	5 4%	4 3%	15 10% **
TOE 2 MEDIAL PHALANX, LEFT	36 28%	57 42% *	64 46% **	81 53% **
TOE 3 PROXIMAL PHALANX, LEFT	3 2%	5 4%	5 4%	17 11% **
TOE 3 MEDIAL PHALANX, LEFT	55 42%	79 58% **	79 56% *	94 62% **
TOE 4 PROXIMAL PHALANX, LEFT	13 10%	21 15%	16 11%	30 20% *
TOE 4 MEDIAL PHALANX, LEFT	85 65%	72 53% *	69 49% **	63 41% **
NON-OSSIFIED				
CALCANEUS LEFT	0	0	0	9 6% **
TOE 1 MEDIAL PHALANX, LEFT	0	0	1 1%	2 1%
TOE 2 MEDIAL PHALANX, LEFT	0	0	2 1%	1 1%
TOE 3 MEDIAL PHALANX, LEFT	0	1 1%	1 1%	6 4% *
TOE 4 PROXIMAL PHALANX, LEFT	0	0	0	3 2%
TOE 4 MEDIAL PHALANX, LEFT	45 35%	64 47% *	71 51% **	89 59% **
RIGHT HIND LIMB				
INCOMPLETELY OSSIFIED				
CALCANEUS RIGHT	10 8%	8 6%	9 6%	18 12%
TOE 1 PROXIMAL PHALANX, RIGHT	2 2%	4 3%	3 2%	14 9% **
TOE 1 MEDIAL PHALANX, RIGHT	55 42%	76 55% *	75 54% *	93 61% **
TOE 2 PROXIMAL PHALANX, RIGHT	2 2%	5 4%	3 2%	17 11% **
TOE 2 MEDIAL PHALANX, RIGHT	37 28%	52 38%	59 42% *	74 49% **
TOE 3 PROXIMAL PHALANX, RIGHT	3 2%	5 4%	5 4%	20 13% **
TOE 3 MEDIAL PHALANX, RIGHT	51 39%	69 50% *	78 56% **	85 56% **
TOE 4 PROXIMAL PHALANX, RIGHT	13 10%	21 15%	15 11%	32 21% **
TOE 4 MEDIAL PHALANX, RIGHT	83 65%	75 55% *	67 48% **	65 43% **
NON-OSSIFIED				
CALCANEUS RIGHT	0	0	0	9 6% **
TOE 1 MEDIAL PHALANX, RIGHT	0	0	1 1%	2 1%
TOE 2 MEDIAL PHALANX, RIGHT	0	0	1 1%	1 1%
TOE 3 MEDIAL PHALANX, RIGHT	0	0	1 1%	4 3%
TOE 4 PROXIMAL PHALANX, RIGHT	0	0	0	1 1%
TOE 4 MEDIAL PHALANX, RIGHT	45 35%	61 45%	73 52% **	87 57% **

* / ** : Fisher's Exact test significant at 5% (*) or 1% (**) level

0086

4.4 Appendix 4 – Schering-Plough May 8, 2008 Press Release for Asenapine

Overview of Asenapine Data from Olympia Trial Program Presented at American Psychiatric Association Annual Meeting³⁵

Efficacy and safety data support potential of asenapine in the treatment of [schizophrenia](#) and bipolar I disorder

WASHINGTON, May 08, 2008 /PRNewswire-FirstCall/ -- Schering-Plough Corporation today announced that an overview of asenapine clinical trials from the Olympia program was presented at the 161st Annual Meeting of the American Psychiatric Association in Washington, D.C., May 3-8. Data from the studies, involving patients with [bipolar](#) I disorder and schizophrenia, were presented in two oral presentations (Abstracts # 44 and # 80). Also presented were long-term safety and efficacy data from a clinical trial involving patients with schizophrenia and schizoaffective disorders.

Asenapine, a fast-dissolving, novel psychopharmacologic agent with a unique human receptor signature, was shown to be effective in two short-term [bipolar mania](#) studies with a nine-week extension and in two out of four short-term schizophrenia studies. In the third short-term schizophrenia study, neither asenapine nor the active control differentiated from placebo; in the fourth study, asenapine did not differentiate from placebo, while the active control did. Overall, asenapine was well tolerated in the Olympia trial program.

"Despite having effective treatments available, up to 75 percent of schizophrenia patients(1) and many [bipolar disorder](#) patients stop taking their medicines because of unwanted side effects or lack of efficacy," said Roger McIntyre, M.D., Associate Professor of Psychiatry and Pharmacology at the and head of the Mood Disorders Psychopharmacology Unit at the University Health Network, Toronto, Canada. "Therefore, new therapies that are both effective and well-tolerated would be welcome additions to the treatment options currently available for improving patient care."

Schering-Plough acquired asenapine in November 2007 through its combination with Organon BioSciences, which developed the investigational antipsychotic agent. The [Food and Drug Administration](#) is reviewing a new drug application (NDA) for asenapine in the treatment for schizophrenia and acute manic or mixed episodes associated with bipolar I disorder. The asenapine Olympia clinical trial program thus far has involved over 3,000 patients and has included bipolar mania and acute schizophrenia trials.

"Based on results from the Olympia trial program, we believe asenapine has the potential to address a clinically important unmet need for patients with schizophrenia and bipolar disorder," said Robert J. Spiegel, M.D., Chief Medical Officer and Senior Vice President, Schering-Plough Research Institute.

Olympia Data: Bipolar I Disorder

The bipolar I disorder program includes two placebo- and active-controlled, three-week trials followed by an extension study totaling one year of treatment involving nearly 1,000 patients with bipolar I disorder. Treatment response was measured using the Young Mania Rating Scale (YMRS) score, an 11-item scale used to evaluate manic symptoms.

In the trials, both asenapine and the active-control drug olanzapine* produced greater mean reductions in YMRS total scores versus placebo after three weeks of treatment. Asenapine produced 13- and 14-point reductions in the YMRS total score from baseline to day 21 (P<0.05 versus placebo; olanzapine was also demonstrated to be statistically superior to placebo; there was no direct comparison between asenapine

³⁵ http://www.drugs.com/clinical_trials/overview-asenapine-data-olympia-trial-program-presented-american-psychiatric-association-annual-4220.html Accessed June 15, 2008

and olanzapine). In a 9-week extension of the 3-week trials, asenapine was found to be noninferior to olanzapine on the primary efficacy measure, change in YMRS.

The overall incidence of treatment-related adverse events (AEs) in the trials was 60.8 percent in the asenapine group, 52.9 percent in the olanzapine group, and 36.2 percent in the placebo group. The most commonly reported adverse events (greater than or equal to 5 percent and twice the rate of placebo) with asenapine included sedation, dizziness, somnolence, oral hypoesthesia (numbness) and weight increase.

Presentation of the overview of the Olympia Program in bipolar I disorder (oral abstract #44) was on Tuesday, May 6, at 12:00 pm in Room 151A.

Olympia Data: Schizophrenia

The schizophrenia program includes four placebo- and active-controlled, six-week trials involving more than 1,300 patients with schizophrenia. In two of the trials involving almost 700 patients, asenapine produced 19- to 20-point reductions in Positive and Negative Syndrome Scale (PANSS) total score and was significantly superior to placebo. PANSS total score is a measure of positive symptoms (e.g., hallucinations and delusions), negative symptoms (such as lack of emotional expression), and general psychopathology symptoms (such as anxiety and [depression](#)).

The third study in approximately 260 patients was considered a failed trial as neither asenapine nor the active control olanzapine differentiated from placebo. A fourth trial of approximately 400 patients with acute schizophrenia was considered a negative trial, as the active-control (olanzapine) differentiated from placebo whereas asenapine did not.

The most commonly reported AEs (greater than or equal to 5 percent and twice the rate of placebo) among patients taking asenapine in the short-term schizophrenia trials were somnolence, akathisia (restlessness) and oral hypoesthesia (numbness).

"Schizophrenia is a lifelong illness that requires ongoing treatment to effectively manage the spectrum of symptoms that patients suffer from. As such, new treatments need to demonstrate an acceptable long-term safety profile," said Steven Potkin, M.D., Professor, Department of Psychiatry and Human Behavior, . "We are encouraged that in the long-term trial, asenapine had a lower incidence of clinically significant [weight gain](#) (15%) vs olanzapine (36%)."

Presentation of the overview of the Olympia Program in schizophrenia (oral abstract #80) is on Thursday, May 8, at 11:00 am in Room 101.

Long-term Safety and Efficacy Data

In a year long, double-blind, randomized study of 1200 patients with schizophrenia or schizoaffective disorder treated with asenapine or olanzapine (3:1 randomization), the safety evaluation showed that the overall rates of AEs were similar for the asenapine 5-10 mg BID arm and olanzapine 10-20 mg QD arm (drug-related AEs, 60 percent and 61 percent respectively; withdrawal due to serious adverse events, 6.3 percent and 6.8 percent, respectively). On efficacy measures, improvements in PANSS total score were greatest for both asenapine and olanzapine within the first six to eight weeks of treatment and were maintained throughout the 52-week study period. In an exploratory secondary analysis, the between-group difference at 52 weeks favored olanzapine. Most commonly reported AEs (greater than or equal to 10 percent) in both treatment groups were [insomnia](#), worsening psychotic symptoms, weight gain and depression.

Additional Asenapine Data Presentations

Additional asenapine data were presented in poster sessions during the meeting.

About Bipolar Disorder

Bipolar disorder, commonly referred to as manic-depressive disorder, is a chronic, episodic [illness](#) characterized by mania (episodes of elevated moods, extreme irritability, and increased energy), depression (overwhelming feelings of sadness, suicidal thoughts), or a combination of both. It affects approximately 1 to 5 percent of adults, including more than 10 million adults in the U.S. and more than four million people in Europe.(2,3,4) The condition can start early in childhood or later in life, with the average age of onset between 15 and 25 years old.(5) Bipolar disorder is the sixth leading cause of disability in the world.(3) About half of the patients with bipolar disorder who recover in response to treatment experience recurrence two years later.(6)

About Schizophrenia

Schizophrenia is a chronic, disabling brain disorder characterized by hallucinations, delusions, and disordered thinking. About 24 million people worldwide (or seven in every 1,000 adults in the population) have schizophrenia,(7) including more than two million people in the U.S.(8) and more than four million people in Europe.(9) People with schizophrenia may hear voices other people don't hear or may believe others are trying to harm them. As a result, they may become socially withdrawn, fearful, and agitated.(8)

About Schering-Plough

Schering-Plough is an innovation-driven, science-centered global [health care](#) company. Through its own biopharmaceutical research and collaborations with partners, Schering-Plough creates therapies that help save and improve lives around the world. The company applies its research-and-development platform to human prescription and consumer products as well as to animal health products. Schering-Plough's vision is to "Earn Trust, Every Day" with the doctors, patients, customers and other stakeholders served by its colleagues around the world. The company is based in Kenilworth, N.J., and its Web site is www.schering-plough.com.

SCHERING-PLOUGH DISCLOSURE NOTICE: The information in this press release includes certain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements relating to the development of, and potential market for, asenapine. Forward-looking statements relate to expectations or forecasts of future events. Schering-Plough does not assume the obligation to update any forward-looking statement. Many factors could cause actual results to differ materially from Schering-Plough's forward-looking statements, including market forces, economic factors, product availability, patent and other intellectual property protection, current and future branded, generic or over-the-counter competition, the regulatory process, and any developments following regulatory approval, among other uncertainties. For further details about these and other factors that may impact the forward-looking statements, see Schering-Plough's Securities and Exchange Commission filings, including Part I, Item IA. "Risk Factors" in Schering-Plough's 2008 Q1 10-Q.

*Olanzapine is marketed as Zyprexa(R) by Eli Lilly

(1) Liu-Seifert H, Adams DH, Kinon BJ. Discontinuation of treatment of schizophrenic patients is driven by poor symptom response: a pooled post-hoc analysis of four atypical antipsychotic drugs. BMC Med. 2005;3:21. Available at www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16375765. (Due to the length of this URL, please copy and paste it into your Internet browser to view) Accessed on April 8, 2008.

(2) National Institute of Mental Health. Available online at: www.nimh.nih.gov/publicat/bipolar.cfm

(3) Depression and Bipolar Support Alliance (DBSA). Bipolar Disorder Statistics, accessed on May 10, 2007. http://www.dbsalliance.org/site/PageServer?pagename=about_statistics_bipolar (Due to the length of this URL, please copy and paste it into your Internet browser to view)

(4) World Health Organization. WHO European Ministry Conference on Mental Health. Available online at: <http://www.euro.who.int/document/MNH/emnhqa.pdf>. Accessed on October 2, 2007.

(5) National Alliance on Mental Health. Understanding Bipolar Disorder and Recovery. Available online at: http://www.nami.org/Template.cfm?Section=bipolar_disorder&template=/ContentManagement/ContentDisplay.cfm&ContentID=44951 (Due to the length of this URL, please copy and paste it into your Internet browser to view)

(6) Perlis RH, Ostacher MJ, Patel JK. Predictors of Recurrence in Bipolar Disorder: Primary Outcomes from the Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry. 2006; 163:210-224.

(7) World Health Organization. Available online at: http://www.who.int/mental_health/management/schizophrenia/en/. Accessed on October 2, 2007.

(8) National Institute of Mental Health. Available online at: <http://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml>

(9) World Health Organization. WHO European Ministry Conference on Mental Health. Available online at: <http://www.euro.who.int/document/MNH/emnhqa.pdf>. Accessed on October 2, 2007.

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Web site: <http://www.schering-plough.com/>

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Ticker Symbol: (NYSE:SGP)

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4.5 Appendix 5 – Additional Information Regarding the Approved Atypical Antipsychotic / SSRI Combination Product- Symbyax®; (Fluoxetine/Olanzapine)

4.5.1 Selected Sections of the Food Drug and Cosmetics Act

FD&CA Sec. 502 [21 USC 352]

- (a) False or misleading label. If its labeling is false or misleading in any particular.
- f) Directions for use and warnings on label. Unless its labeling bears
 - (1) adequate directions for use; and
 - (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users,
- (j) Health-endangering when used as prescribed. If it is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.

FD&CA Sec. 301 [21 USC 331]

Sec. 301. Prohibited acts

The following acts and the causing thereof are prohibited:

- (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

4.5.2 Information on Risk of Phen-Fen Like and Developmental Risks with Symbyax® from FDA Reviews

The FDA recommendation for a repeat of the prenatal/postnatal development study in rats as a Phase 4 commitment is based on these findings as well as on the fact that no meaningful toxicological conclusions about these (and other) developmental endpoints in F1 generation can be made on the basis of the submitted postnatal developmental study. This study employed only two olanzapine/fluoxetine combination (OFC) dose levels: high and low. The high dose combination induced excessive mortality in the progeny early in life that did not allow assessment of postnatal developmental endpoints other than survival and body weight. For this reason, the sponsor did not provide data on developmental endpoints in the progeny (including those of the reproductive system) at the HD combination. No proper toxicological assessment or meaningful conclusion about OFC postnatal developmental toxicity can be made based on the available results at only one (LD) dose level. In conclusion, there is obviously a need for a repeated pre/postnatal study (as a phase 4 commitment) with a more appropriate dose selection that would allow a reliable assessment of postnatal developmental toxicity parameters and their dose-effect relationships and NOAEL.

6.

In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity.

7.

In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination [low-dose: 2 and 4 mg/kg (1 and 0.5 times the MRHD on a mg/m² basis), respectively, high-dose: 4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m² basis) respectively] and alone [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m² basis), respectively]. Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

FDA Comment: Accepted with corrections (correction included in the corresponding paragraph in December 11, 2003 PI as reproduced below):

SYMBYAX Embryofetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4

mg/kg/day (low dose) (1 and 0.5 times the MRHD on a mg/m² basis, respectively) and 4 and 8 mg/kg/day (high dose) (2 and 1 times the MRHD on a mg/m² basis, respectively). In rabbits, the doses were: 4 and 4 mg/kg/day (low dose) (4 and 1 times the MRHD on a mg/m² basis, respectively) and 8 and 8 mg/kg/day (high dose) (9 and 2 times the MRHD on a mg/m² basis, respectively).

4.6 Appendix 6 - Review of Amendment 027 Submitted June 13, 2008

Comments were apparently sent to the sponsor without the knowledge of this reviewer and that this amendment is in response to these comments. No information on what comments the sponsor is replying to is included and this reviewer can find no record of any communication of comments to the sponsor in DFS. Upon review it appears that these slides are in response to a memo to the file from the OCP team leader labeled Asenapine.Doc and dated June 10, 2008 at 1:50 PM. It is unclear why comments from a memo to the file would be sent to the sponsor without going through proper channels including being signed off on by the OCP division director. For ease of reference the comments from this memo to the file follow:

Figure 46 OCP Team Leader's Memo to File

OCP Team Leader's Memo to File

Date: June 10, 2008

From: Raman Baweja, Ph.D.
Team Leader
DCP 1, OCP

To: File NDA 22117, Asenapine

This writeup pertains to OCP dfs'ed review of May 15, 2008.

From a clinical pharmacology standpoint it should be noted that the sponsor has not adequately ascertained what moieties are circulating in plasma. In the mass balance study both the data in the table, and the figure show that the plasma concentrations of ¹⁴C asenapine (equivalents) greatly exceeds that of asenapine (cold drug) as well as the metabolites measured. Further, that the moieties looked for are asenapine, desmethylenapine, and the N-oxide. The total AUC counts for total radioactivity (¹⁴C) is around 1550 AUC units whereas the summation of all the AUCs for the three measured moieties accounts for about 55 AUC units. There is a vast amount of circulating material in plasma that has not been ascertained. As the review indicates that at least 96.6% of the circulating species have not been identified. This is a matter for concern and the sponsor should be requested to explain this vast gap between circulating radioactivity, and, moieties circulating and identified in plasma.

Another issue that raises concern is that the mass balance has not been adequately characterized. In a generalized manner, after the administration of the radioactive dose about 88 % of the dose is recovered with 49 % in the urine and 39 % in the feces; this is like providing the generalized presentation of where did the radioactivity go. When it comes to specifics regarding what moieties are involved, what is known is that direct glucuronidation accounts for 12-21% of the dose. Further, that 5-16 % of the dose is that of unchanged drug, asenapine. When these two are added up, it represents 17-37 % of the dose. Therefore, a subtraction shows that 63-83 % of the dose has not been adequately characterized for the primary elimination pathways.

The metabolism issues mentioned above, viz., what moieties are circulating in plasma, and the characterization of elimination pathways, should be clearly and properly addressed by the sponsor.

Another area of concern stems from the administration a low single sublingual dose of 5mg to healthy subjects for the conduct of a bioequivalence (BE) study. In this BE study according to the sponsor's report, 10 subjects experienced bradycardia, 8 subjects experienced tachycardia, 7 subjects experienced sinus pause, 3 subjects experienced junctional rhythms, and one subject experienced bradycardia with junctional rhythm. Then also in another study following a 5 mg sublingual dose one subject experienced bradycardia which occurred while the subject was supine. Overall then, these adverse events raise concern about the use of this drug even when administered as low single doses based on what is seen with the administration of the drug in healthy subjects.

Nine slides were submitted in the amendment that is presumably in response to the above comments. The following table includes a description of each slide's content and review comments.

Table 28 Critique of Slides Include in Amendment 027 (BB) Submitted June 13, 2008

Slide #	Summary of Slide Content	Review Comments
Slide 1	Title Slide	
Slide 2	Sponsor claims asenapine and N-desmethyl account for only 3% of circulating radioactivity	Does not address appropriate time interval Does not address dose. Even if we accept this it is still problematic.
Slide 3	Sponsor's proposed metabolic scheme	Compare with reviewer's scheme. Neither is certain at this time. This does not change conclusions.
Slide 4	Sponsor shows comparative metabolic concentration v. time profiles of asenapine, the 11-O-Sulfate and Asenapine Glucuronide in Study 25546	Study 25546 was a 6 day multiple dose study in young healthy nonsmoking and light smoking Japanese and Caucasian males. From the raw data it's not clear what dose is represented. Neither is the race, demographics or other features. Although the 11-O-Sulfate exposure is similar to asenapine this does not address exposure to other species. Even when the reviewer did a similar analysis and estimated exposures to the 11-O-Sulfate and the glucuronide from better characterized studies the analysis revealed at least 85% of the circulating species are still unknown. Performing the same analysis again with data from study 25546 will not change the conclusions.
Slide 5	Sponsor claims radiometric quantification was difficult.	It was difficult to quantify because the sponsor apparently designed the study in such a manner so as to make it difficult. This is not a valid justification for not performing appropriately designed studies.
Slide 5 and 6	Sponsor indicates that at single time points up to 30% of the radioactivity was identified. Four species were quantified and No AUCs can be calculated.	Single time points do not represent total exposure over time which is the appropriate metric. The reason only 4 species were identified is because the sponsor a priori decided to measure these particular 4 species as cold drug by HPLC and thus did not even attempt to look at exposures via other species. No AUCs can be calculated because of the sponsor's methodology. Larger single radioactive doses could have been used and samples from a number of subject could have been pooled. In addition this does not report data from 0 to 1.5 hours after dosing and is thus skewed this is data from HPLC System 1 which is the least sensitive method the sponsor has.
Slide 7	Sponsor claims all 'major' peaks identified, the remaining peaks are minor and quantification of the pooled data is not possible.	The guidance defines major as >10% of parent (peak 20) a cursory examination reveals that the 'minor' peaks are likely greater than 10% of asenapine, the sponsor does not even include the integrated AUCs which it is possible to obtain which would help definitely answer this. Thus the sponsor hasn't even attempted to support their claim with data that they can easily go back and generate. Even 'minor' peaks or a combination of 'minor' peaks can be clinically relevant and likely are in asenapine's case. Even if what the sponsor claims is true, an alternative study design would have overcome these problems.
Slide 8	Sponsor claims 71% of dose (fully/tentatively/partly) identified via excreta.	Agree however the partly identified part is a claims mixture or multiple possible metabolites whose structures are not clear and so it is not possible to assign the relative contributions of the primary pathways. While the slide is technically correct it is misleading and the data is insufficient for assessment of safety and labeling purposes.
Slide 9	Conclusions	See previous comments.

4.7 Appendix 7 – Quality of the Submission

To be included in a separate amendment to the NDA review.

4.8 Appendix 8 – Evaluation of Pilot NDA Review Process

To be included in a separate amendment to the NDA review.

4.9 Appendix 9 – Lessons Learned and Feedback on FDA Policies, Procedures and Regulations

To be included in a separate amendment to the NDA review.

4.9.1 Future Predictions

To be included in a separate amendment to the NDA review.

4.9.2 Recommendations re: FDA Policy Procedures, Guidances, Regulations, and Laws

To be included in a separate amendment to the NDA review.

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/s/

Ron Kavanagh
6/18/2008 04:30:25 PM
BIOPHARMACEUTICS

Per our discussion I have cc'ed all parties reviewing
asenapine for whom this might impact their reviews,
as well as individuals in Neuro for whom
this information may impact drugs that will eventually
be used for psychiatry indications

John Duan
6/18/2008 04:34:18 PM
BIOPHARMACEUTICS

OCP secondary reviewer's memo to file

From: John Duan, Ph.D., Acting Team Leader, DCP1, OCP

Through: Mehul Mehta, Ph.D., Division Director, DCP1, OCP
Ramana Uppoor Ph.D., Division Deputy Director, DCP1, OCP

To: File NDA 22-117, Asenapine

Re: Review amendment by Ronald Kavanagh, Pharm. D., Ph.D.

1. Background

Asenapine NDA is proposed for the treatment of schizophrenia or acute episodes of bipolar I disorder. The original clinical pharmacology review by Dr. Kavanagh was signed off on May 15, 2008. After the completion of the review, Dr. Kavanagh changed his recommendation to “not approvable”, which is the subject of his review amendment.

Since he has broad knowledge and interest and thus the scope of his review are beyond the normal range of regular Clinical Pharmacology review, I do not think I am qualified to make appropriate judgment on the issues Dr. Kavanagh has raised. This memo will first briefly summarize his concerns and comment on these issues divided into several categories.

2. A brief summary of issues Dr. Kavanagh has raised

A glimpse on the thought flow of Dr. Kavanagh in his review may be helpful for quicker grasping his view of points.

He started with a hypothesis that correlates the adverse events mechanistically with binding on 5HT_{2B} receptor based on his observations; followed by introducing the signs and symptoms associated with 5HT_{2B} agonism, he emphasized on pulmonary arterial hypertension, cardiotoxicity, connective tissue disorders, and effects on neonates; then, he restates the clinical observations emphasizing the deaths, SAE and AEs in the clinical studies to provide evidences to support his hypothesis, not only from clinical, but also from preclinical data (especially for neonatal risks and bone remodeling); after that, structure-activity relationship is sought to further expand his hypothesis; finally, he puts his concerns in the context of broader picture addressing implications of his hypothesis on other drugs.

Following is a list of his major concerns.

1. Serious cardiovascular toxicities including death due to pulmonary arterial hypertension, direct and indirect effects on the myocardium, and (likely via indirect) effects on platelet aggregation.

2. Pulmonary arterial hypertension in neonates, resulting in death, maiming of children, and infant death via breast feeding by mothers taking drug postnatally.
3. Bone remodeling and ossification from Pharm/Tox data concerning the effects in pregnancy, growing children, and in other populations where bone remodeling is an issue, e.g. elderly women and renal failure patients.
4. Other connective tissue disorders, such as hernias and rupture of tendons.
5. Increase in motor activity from animal studies concerning that could induce prescribers to inappropriately increase the dose, which would increase the risk of chronic cardiopulmonary toxicity.
6. Possible risk of aplastic anemia due to agranulocytosis.
7. Effects on platelet aggregation and strokes.
8. Sudden death without warning in otherwise young healthy individuals due to arrhythmias or strokes with symptoms misattributed to something else such as orthostatic hypotension.
9. Likely cumulative serious cardiovascular toxicities resulting in Phen-Fen type toxicities especially when dosed for over a year.

Based on these concerns, Dr. Kavanagh concludes that asenapine is less safe than competing agents and offers few if any advantages. He indicates that asenapine “is unacceptably dangerous at this time” and he also mentions: “there was inadequate information submitted to assess safety.”

In addition, Dr. Kavanagh believes that the entire development program of asenapine appears designed to minimize detection and quantification of risks and thereby precludes his ability to write appropriate labeling. He also believes that in several instances the sponsors’ actions were unlawful and must be reported to the criminal investigators.

Therefore, he recommends that N22-117 submitted on August 30, 2007 not be approved, other drugs and drug classes be re-evaluated and the safety issue be communicated to the public. He also recommends criminal investigation of individuals in various companies and organizations for failure to report deaths, attempting to mislead reviewers. He made a formal request for such investigation.

3. Comments

Dr. Kavanagh’s comments, recommendations and requests can be divided into following categories.

First of all, clinical safety and efficacy, such as cardiovascular toxicities, are his major concerns. I am not qualified to make judgments and comments on these issues.

Secondly, preclinical concerns including receptor binding activity, bone remodeling and motor activity are closely related to clinical safety issues. I am not qualified to make judgments and comments on these issues.

Thirdly, structure-activity relationship is a prosperous field in chemistry. Expert judgments on this are needed.

Fourthly, legal issues such as request of criminal investigation are unusual items in Clinical Pharmacology review. Dr. Kavanagh insists on putting it in the review, although I am not sure whether it is the right procedure to follow.

Lastly, he restates the comments from his original review regarding clinical pharmacology issues although they are not the focus of this review amendment. It is not necessary for me to reevaluate the studies submitted in the original NDA as the review memo from Team leader Dr. Raman Baweja have already made the relevant conclusions (please see the memo from Dr. Baweja).

In a word, this review amendment concentrates on the clinical safety issues, in a manner out of the range of regular Clinical Pharmacology review and beyond my qualification for a secondary review.

Recommendations

Due to the range beyond regular Clinical Pharmacology review and comprehensive nature of this review amendment, I am not qualified to make judgments and comments.

The clinical, pharm/tox, and chemistry reviewers should evaluate and consider Dr. Kavanagh's comments and recommendations.

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/s/

John Duan
6/20/2008 04:28:07 PM
BIOPHARMACEUTICS

Mehul Mehta
6/20/2008 04:34:19 PM
BIOPHARMACEUTICS

OCP Team Leader's Memo to File

Date: June 10, 2008

From: Raman Baweja, Ph.D.
Team Leader
DCP 1, OCP

To: File NDA 22117, Asenapine

This writeup pertains to OCP dfs'ed review of May 15, 2008.

From a clinical pharmacology standpoint it should be noted that the sponsor has not adequately ascertained what moieties are circulating in plasma. In the mass balance study both the data in the table, and the figure show that the plasma concentrations of ¹⁴C asenapine (equivalents) greatly exceeds that of asenapine (cold drug) as well as the metabolites measured. Further, that the moieties looked for are asenapine, desmethyiasenapine, and the N-oxide. The total AUC counts for total radioactivity (¹⁴C) is around 1550 AUC units whereas the summation of all the AUCs for the three measured moieties accounts for about 55 AUC units. There is a vast amount of circulating material in plasma that has not been ascertained. As the review indicates that at least 96.6% of the circulating species have not been identified. This is a matter for concern and the sponsor should be requested to explain this vast gap between circulating radioactivity, and, moieties circulating and identified in plasma.

Another issue that raises concern is that the mass balance has not been adequately characterized. In a generalized manner, after the administration of the radioactive dose about 88 % of the dose is recovered with 49 % in the urine and 39 % in the feces; this is like providing the generalized presentation of where did the radioactivity go. When it comes to specifics regarding what moieties are involved, what is known is that direct glucuronidation accounts for 12-21% of the dose. Further, that 5-16 % of the dose is that of unchanged drug, asenapine. When these two are added up, it represents 17-37 % of the dose. Therefore, a subtraction shows that 63-83 % of the dose has not been adequately characterized for the primary elimination pathways.

The metabolism issues mentioned above, viz., what moieties are circulating in plasma, and the characterization of elimination pathways, should be clearly and properly addressed by the sponsor.

Another area of concern stems from the administration a low single sublingual dose of 5mg to healthy subjects for the conduct of a bioequivalence (BE) study. In this BE study according to the sponsor's report, 10 subjects experienced bradycardia, 8 subjects experienced tachycardia, 7 subjects experienced sinus pause, 3 subjects experienced

junctional rhythms, and one subject experienced bradycardia with junctional rhythm. Then also in another study following a 5 mg sublingual dose one subject experienced bradycardia which occurred while the subject was supine. Overall then, these adverse events raise concern about the use of this drug even when administered as low single doses based on what is seen with the administration of the drug in healthy subjects.

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/s/

Raman Baweja
6/10/2008 01:50:16 PM
BIOPHARMACEUTICS

**New Drug Application
Memo to File - Clinical Pharmacology
Change in Recommendation**

NDA:	22-117
Type of Submission:	Original NDA
Submission Date:	August 30, 2007
Associated INDs:	51,641 September 30, 1996 (Treatment of Psychosis) 70,329 August 3, 2004 (Treatment of Acute Mania in Bipolar I)
Generic Name:	Asenapine Maleate
Formulation: Strengths:	Sublingual Tablets 5 mg, 10 mg
Route:	Sublingual (N.B. Route is mislabeled in Application Form 356h)
Brand Name:	Sycrest®
Sponsor:	Organon / Schering-Plough
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Kavanagh, Ronald E

From: Kavanagh, Ronald E
Sent: Friday, May 16, 2008 10:21 AM
To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert
Subject: NDA 22-117 Asenapine Change in Recommendation

Mehul,

Per my 9 AM verbal notification I am changing my recommendation for asenapine (NDA 22-117) to nonapproval per FD&CA Sec. 505 d) 1) b); d) 2); d) 5; and c) 7.

As I was writing the labeling and trying to figure out how to discuss the drug interactions I realized that the information in the review indicates that asenapine causes pulmonary arterial hypertension and cardiac effects.

All of the cardiac and respiratory toxicities can potentially be explained by this, and appears to be the mechanism for the death 2 months after adding an antidepressant and may be an alternative mechanism for several deaths including the patient with Quincke's edema and the death of the neonate.

I'm also afraid that the nasal congestion and respiratory symptoms seen in many patients will be self mediated with OTC decongestants and will increase toxicity.

It appears that this toxicity is mediated by agonism at the 5HT2B receptor and is likely due to an active metabolite produced in the 11-hydroxylation cascade. Based on the sponsor's receptor binding information the metabolite involved might be the 11-O-Sulfate but it could be others.

The metabolic scheme, the mechanism, and the observed toxicities along with the study designs used by the sponsor in the drug-drug interaction studies, and the lack of many specific pieces of information in the submission as well as other things indicate that the sponsor knew about this toxicity and specifically tried to prevent our detecting it.

The potentially toxic metabolites are formed via CYPs 3A4 and 1A2, and based upon the use of this medication it will be used in subjects who have increased formation via these pathways and the long term toxicities may be subtle and not appreciated until well after marketing. Although based on the asenapine paroxetine drug interaction study at least ~60% of the patients taking this drug may be at risk and it is likely even higher in African Americans and children. (AA due to expression of 3A5 and children due to factors already mentioned.)

I simply do not believe there is anything we can do that would adequately educate physicians and patients to the risks and that with off-label use we will be looking at an epidemic of potentially lethal cardiac and pulmonary toxicities in children several years from now.

I believe that the pop PK findings in blacks are likely either erroneous or spurious and a dedicated PK study in appropriate subjects will demonstrate why pop PK studies are unreliable.

This only a brief summary and I intend to amend my review to include more details and request adequate time to fully document my concerns.

Ron

Tracking:	Recipient	Delivery	Read
	Mehta, Mehul U	Delivered: 5/16/2008 10:21 AM	
	Baweja, Raman K	Delivered: 5/16/2008 10:21 AM	Read: 5/16/2008 10:31 AM
	Laughren, Thomas P	Delivered: 5/16/2008 10:21 AM	Read: 5/16/2008 10:28 AM
	Temple, Robert	Delivered: 5/16/2008 10:21 AM	Deleted: 5/16/2008 4:35 PM

Kavanagh, Ronald E

From: Laughren, Thomas P
To: Kavanagh, Ronald E
Sent: Friday, May 16, 2008 10:28 AM
Subject: Read: NDA 22-117 Asenapine Change in Recommendation

Your message

To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert
Subject: NDA 22-117 Asenapine Change in Recommendation
Sent: 5/16/2008 10:21 AM

was read on 5/16/2008 10:28 AM.

Kavanagh, Ronald E

From: Temple, Robert
To: Kavanagh, Ronald E
Sent: Friday, May 16, 2008 4:35 PM
Subject: Not read: NDA 22-117 Asenapine Change in Recommendation

Your message

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Subject: NDA 22-117 Asenapine Change in Recommendation
Sent: 5/16/2008 10:21 AM

was deleted without being read on 5/16/2008 4:35 PM.

Kavanagh, Ronald E

From: Mehta, Mehul U
Sent: Friday, May 16, 2008 4:55 PM
To: Kavanagh, Ronald E
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
Subject: RE: NDA 22-117 Asenapine Change in Recommendation

Ron,

Please go ahead with your plan to undertake further evaluation of this new safety issue that has just been identified. Please send me a brief e mail COB Wednesday, May 21st, describing your progress, whether more time is needed and if so, how much more and to evaluate what remaining information.

Mehul

Note: New Address

Mehul Mehta, Ph.D.
*Director
Division of Clinical Pharmacology I
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Silver Spring, MD 20993
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fax (301)847-8712
mehul.mehta@fda.hhs.gov*

From: Mehta, Mehul U
Sent: Friday, May 16, 2008 1:37 PM
To: Kavanagh, Ronald E
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
Subject: RE: NDA 22-117 Asenapine Change in Recommendation

Ron,

I am trying to get in touch with Tom to discuss how much extra time can be made available and will let you know as soon as we are able to finalize it. In the meanwhile, please complete your labeling comments by the end of today to the extent you can, based on what you know so far.

Mehul

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Mehul Mehta, Ph.D.
*Director
Division of Clinical Pharmacology I
Office of Clinical Pharmacology*

OTS, CDER, FDA
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Sent: Tuesday, May 20, 2008 4:54 PM
To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
Subject: RE: NDA 22-117 Asenapine Change in Recommendation

Mehul,

As you are aware from previous discussions I do not believe it is possible to write labeling with the present lack of information, and I was excused from writing labeling.

Today Ray told me that he is writing labeling. Since this must be based on the current version of my review prior to any amendment that you indicated I have until COB tomorrow to write, I must indicate my objection.

Ron

From: Mehta, Mehul U
Sent: Friday, May 16, 2008 1:37 PM
To: Kavanagh, Ronald E
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
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/s/

Ron Kavanagh
5/20/2008 05:10:26 PM
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**New Drug Application
Clinical Pharmacology Review**

NDA:	22-117					
Type of Submission:	Original NDA					
Submission Date:	August 30, 2007					
Associated INDs:	51,641 September 30, 1996 (Treatment of Psychosis) 70,329 August 3, 2004 (Treatment of Acute Mania in Bipolar I)					
Generic Name:	Asenapine Maleate					
Formulation: Strengths:	Sublingual Tablets 5 mg, 10 mg					
Route:	Sublingual (N.B. Route is mislabeled in Application Form 356h)					
Brand Name:	Sycrest®					
Sponsor:	Organon / Schering-Plough					
Submission Date(s):	SN	Date	Code	Descriptor	Contents	OCP
	000	8-30-07		Original Submission		X
	001	9-28-07	BM / BB	Minor Amendment - Medical / OCP	Highlights of Clinical Pharmacology Requested by Medical Reviewer	X
	002	10-24-07	BM	Minor Amendment - Medical	Response to MO request for Regulatory History	X
	003	11-20-07	XS	Change in Ownership	Change in ownership	
	004	11-30-07	BZ	Minor Amendment – Multiple Disciplines	Response to QT group questions	(x)
	005	12-3-07	BS	Minor Amendment – Statistical	Response to statistical reviewer	
	006	12-7-07	BB	Minor Amendment – OCP	PK Datasets	X
	007	12-10-07	C / BC	Minor Amendment – CMC	Response to CMC Request	
	008	12-21-07	BC / BL	Minor Amendment – CMC / Labeling	Update CMC information	
	009	12-21-07	BC	Minor Amendment – CMC	Response to CMC Request	
	010	12-27-07	SU	Safety Update	4 month Safety Update Exposure Response Analysis and interim report of PK in elderly	
	011	12-28-07	BB	Minor Amendment – OCP	PK Datasets and other requested information	X
	012	1-11-08	BP	Minor Amendment – Pharm/Tox	Effect on Prolactin in Rats	
	013	1-11-08	BM	Minor Amendment Medical	Summary of Clinical Safety - Rhabdomyolysis	
	014	1-17-08	BC	Minor Amendment Chemistry	CMC Information - Packaging	
	015	1-30-08	BC	Minor Amendment Chemistry	CMC Information – Drug Substance	
	016	2-21-08	BP	Minor Amendment – Pharm/Tox	Response to request for information	
	017	2-21-07	BC / BL	Minor Amendment – CMC / Labeling	Update CMC Blister labeling	
	018	3-11-08	BP	Minor Amendment – Pharm/Tox	Response to request for information	
	019	3-27-08	BP	Minor Amendment –	Response to request for information	

				Pharm/Tox		
	020	3-27-08	GC	General Correspondence	Lack of appropriate birth control used in study. Exclusion of data from Bipolar efficacy study.	
	021	4-10-08	BL	Minor Amendment – Labeling	Cartoning and Proposed Tradename	
	022	4-18-08	BC	Minor Amendment – Chemistry	Changes in Manufacturing Process	
	023	4-29-08	BP ^a	Minor Amendment – Pharm/Tox	Response to questions re: carcinogenicity studies.	
	024	4-30-08	BC	Minor Amendment – Chemistry	Response to Comments: Stability and Impurity Specifications	
Reviewer:		Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.				
Team Leader:		Raman Baweja, Ph.D.				

a Mislabeled as BB

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2 Executive Summary

2.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology I (OCP/DCP-1) has reviewed NDA #22-117 with an initial submission date of August 30, 2007.

OCP finds this application unacceptable for the following reasons:

1. Studies examining clinical pharmacology and exposure response were designed, conducted and reported in such a manner that it is not possible to determine how it may or may not be possible to mitigate risks; and in particular in the most vulnerable populations (i.e. children and elderly) who are also expected to be the primary users of this medication.

Major deficiencies include:

1. The vast majority of circulating species in plasma have not been identified.
2. The mass balance data provided only allows the unambiguous assignment of the primary elimination pathways of 1/5 to 1/3 of the dose.
3. Inappropriate design and lack of the appropriate information in drug interaction studies.

Comments may be found under section 2.3 on page 42.

2.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

2.2.1 Introduction and Background

Chemistry and Mechanism of Action

Asenapine is a heterocyclic dibenzo-oxepino pyrrole antipsychotic, i.e. a tetracyclic D2 antagonist that includes a pyrrole as the fourth ring.

Proposed Indications

Schizophrenia

Acute manic or mixed episodes associated with bipolar I disorder

Proposed Formulation and Strengths

5 mg and 10 mg Fast Dissolving Sublingual Tablets

Proposed Dosage Regimen

Schizophrenia: The recommended dose range of Sycrest[®] is 5 mg to 10 mg given twice daily (BID). Sycrest[®] should be administered at an initial daily dose of 5 mg BID. An increase in dose to 10 mg BID is recommended only after clinical assessment. (2.1)

Bipolar disorder: The recommended dose of Sycrest[®] is 10 mg given twice daily (BID). (2.2)

Administration: Sycrest[®] Sublingual Tablets should be placed under the tongue and left to dissolve completely; do not swallow tablet. Eating and drinking should be avoided for 10 minutes after administration.

2.2.2 Summary of Major Conclusions

Asenapine appears to be efficacious in the treatment of severe cases of acute mania, with baseline YMRS scores of greater than or equal to approximately 27, although additional studies might be needed prior to an approval.

There appears to be no margin of safety with regards to cardiac toxicity. Various serious cardiac toxicities including asystole, supraventricular arrhythmias and conduction disturbances, and myocardial infarction occurred in healthy volunteers, as did a death due to congestive heart failure in a patient. Many of the cardiac toxicities appear unrelated to effects on QT although there is a positive QT effect that appears more pronounced in women.

Other life threatening toxicities observed include neutropenia, and presumptive agranulocytosis with pancytopenia resulting in death. This appears to be time dependent occurring after approximately 1.2 years of treatment and may be due to a cumulative effect of toxic metabolites. The incidence of death due to agranulocytosis was approximately 1/313 in subjects treated for 1 year and when other suspicious deaths due to respiratory arrests are included the incidence of death due to agranulocytosis may be twice as high (i.e. ~ 1/150). However it should be remembered that this does not include other causes of drug induced death.

Dose and time dependent drug induced liver injury also occurs and appears related to the amount of drug swallowed and is of special concern in children. It may also be worse when used in combination with other psychoactive drugs.

There is evidence of significant pharmacodynamic interactions, including CNS effects, with commonly coadministered drugs (including drugs of abuse and OTC drugs) that result in serious AEs (i.e. coma and psychosis).

Desmethyl-asenapine is a noncompetitive inhibitor of CYP2D6 and drug-drug interactions with other CYP2D6 substrates including OTC allergy and cough and cold medications are likely to occur. As a noncompetitive inhibitor interactions may continue to occur for a substantial period after discontinuing asenapine until enzyme regenerates.

A neonatal death was also reported but no detailed information was submitted so the potential mechanism cannot be determined and any labeling recommendations would likely be insufficient.

Due to differential first pass effect with swallowing, the relative weight normalized dosage in children and frail elderly, and the likely heightened risk with comorbid diseases, these populations may be especially at risk.

The incidence of suicidality in schizophrenics after short term treatment appears similar to olanzapine and placebo however the numbers are likely too small for a definitive conclusion. The peak incidence of suicidality in schizophrenic subjects occurs 1 – 2 weeks after discharge from inpatient care. Based on the available data an examination on whether a longer duration of residence in an inpatient setting or continued residence in a structured environment for several weeks may be more effective in preventing suicides in schizophrenics. For subjects with bipolar disorder there was no suicidality in the placebo group where as there was a 1% incidence of suicidality for both asenapine and olanzapine with a peak incidence of completed suicides (0.3%) for both compounds after 2 weeks of therapy and during inpatient treatment.

The clinical development program appears to be designed and reported in such a manner so as to minimize the detection and acknowledgment of expected and observed toxicities. Consequently, there is insufficient information to allow labeling recommendations that might mitigate risks. In addition quantitative estimates of the relative benefits of asenapine relative to the risks are likely to be unreliable.

2.2.3 Pertinent Clinical Pharmacology and Biopharmaceutic Questions

What formulations were used in the phase I, phase II, and phase III studies and how do these compare to the formulations proposed for marketing?

(b) (4)

The proposed To-Be-Marketed, (TBM), formulation is a (b) (4) sublingual tablet that contains (b) (4) and water which is removed by (b) (4). Four changes have been proposed for the To-Be-Marketed formulation from the Clinical-Trial-Formulation.

- (b) (4)
- Change (b) (4)
- Change (b) (4)
- (b) (4)

Typically for a (b) (4) sublingual formulation changes to the formulation would generally be considered to be unlikely to be clinically significant however for asenapine faster dissolution means more drug being absorbed sublingually with higher peaks and greater AUCs, and slower *in vivo* dissolution would result in more drug being swallowed with greater first pass effect and more N-desmethyl-asenapine being formed and changes in metabolic profiles and greater changes in time dependent kinetics. In the case of asenapine this might be clinically significant due to the dose and time dependent hepatotoxicity observed with oral administration, metabolite concentration dependent cardiac arrhythmias, as well as significant drug-drug-interactions.

Are the proposed to-be-marketed formulations bioequivalent to the clinical-trial-formulations?

Two pivotal bioequivalence studies were conducted. Study A7501015 examined the effect of changing the (b) (4) source and study A7501016 examined the effect of a (b) (4). The sponsor concluded that both changes resulted in bioequivalence.

For the change in (b) (4), geometric mean ratios were high but within the acceptance limits of 0.80 – 1.25 for both C_{max} and AUC, with the change in C_{max} with the (b) (4) resulting in increased bioavailability, (GMRs for C_{max} 1.09 (b) (4) and AUC 1.07 (b) (4). However this required a large sample size (n = 36) due to the large variability. On average a large percent of the AUC_{inf} was extrapolated (7.4%). This is not surprising as sampling was only conducted to 48 hours and there is a long half-life. Unfortunately the datafiles could not be opened to determine whether the results are acceptable or not.

For the change in (b) (4) the geometric mean ratios were just barely within the acceptance limits of 0.80 – 1.25 for both C_{max} (LL 90%CI: 0.808) and AUC (LL 90%CI: 0.837), even with a large sample size (n = 35), with the change in (b) (4) resulting in decreased bioavailability. This is presumably due to (b) (4). On average a large percent of the AUC_{inf} was extrapolated (8.4%). Unfortunately the data files could not be opened to determine whether the results are acceptable or not. With decreased bioavailability and the narrow therapeutic window there is a concern for greater hepatotoxicity and cardiac toxicity. In fact the sponsor conducted telemetry monitoring during the study and reports the following:

“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).”

In total 20 of the 35 subjects experienced some form of cardiac arrhythmia.

As this study was conducted in young healthy male and female volunteers with a single low dose this is very concerning.

Does asenapine exhibit linear kinetics over the dosage range?

No. Absorption is nonlinear.

When administered sublingually, linearity over a range of 0.02 mg to 5 mg is apparent from the mean C_{max} and AUC data from a number of other studies.

Above a dose of 5 mg, sublingual absorption decreases. This is due to more of the drug being swallowed, and is expected based on the solubility of asenapine in water and pH 4.0 buffer being in the range of 3.7 - 3.8 mg/ml. Consequently, there is greater first pass of the portion of the dose that is swallowed with less exposure to asenapine and a corresponding increased exposure to N-desmethyl-asenapine.

What are the pharmacokinetic characteristics of asenapine?

Asenapine is a high intrinsic clearance drug with an intrinsic clearance that is likely equal to hepatic blood flow. It has an extremely large volume of distribution of roughly 100 - 200 L/kg, and an initial phase half-life of around 5 hours with a terminal phase half-life of around 1 – 1½ days and up to 2½ days in the PET study.

With sufficiently large doses and extended sampling a third compartment can be discerned.

Absorption after sublingual administration is rapid with a median T_{max} of 0.5 – 1.0 hours

There were no significant diurnal variation in the overall concentration time profiles however, predose concentrations show clear diurnal variation when dose normalized, however the absolute amount of diurnal variation is small and does not raise any obvious concerns.

What is the metabolic profile of asenapine?

Asenapine appears to be metabolized via four primary metabolic pathways to N-desmethyl-asenapine, 11-hydroxy-asenapine, asenapine N-oxide and asenapine N- glucuronide.

With the exception of the glucuronide the primary metabolites are all further metabolized extensively. For example the 11-hydroxy is also hydroxylated at the 10 position with further O-sulfation, O-glucuronidation and O-methylation by COMT.

As expected the N-glucuronide is formed by UGT1A4 which typically glucuronidates tertiary amines, whereas the enzymes responsible for the 11-hydroxylation, N-oxidation, and N-desmethylation are not as clear. However, it appears that 11-hydroxy is mediated by CYP1A2 and possibly 3A4, N-desmethylation may be mediated by CYP2C9 and possibly other enzymes with secondary N-oxidation by CYP2D6, whereas enzymes responsible for formation of N-oxide asenapine are not clear.

Presently the metabolic profile is only tentative due to limitations in the reporting of the data, (see §6.5 (Requests to Sponsor) on page 477).

What are the pharmacokinetic characteristics of the metabolites?

Desmethyl-asenapine has peak concentrations of 30% of asenapine's at 5 mg BID and below, and around 60% of asenapine's at 10 mg BID. AUCs of desmethyl-asenapine are 3 fold asenapine's at doses of 5 mg BID and below, and 11 fold at 10 mg BID. Desmethyl-asenapine has monoexponential decline during a single dosage interval and although the half-lives reported 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.

Exposures to asenapine glucuronide are several fold higher than asenapine but are otherwise unnoteworthy and N-oxide concentrations in plasma were frequently barely detectable possibly due to binding to tissues.

Are the metabolites adequately characterized in plasma?

No.

The mass balance study utilized a single 0.3 mg dose of ¹⁴C-labeled asenapine administered in addition to asenapine 10 mg SL BID. The sponsor also compared the plasma concentrations of selected species determined by standard bioanalytic methods, (i.e. asenapine, desmethyl-asenapine, and asenapine N-oxide) to total plasma radioactivity as determined by scintillation counting. The plasma concentration profiles for total radioactivity and identified circulating species indicated that at least 96.6% of the circulating species have not been identified. In order to compare the exposure to asenapine and the two metabolites to total circulating species the total radioactivity needs to be dose normalized. Examination of the raw data indicates that the sponsor did not do this. Dose normalization would increase the total radioactivity 34.3 fold (i.e. 10.3 mg / 0.3 mg). In addition the AUC_τ of these selected species need to be compared to AUC_∞ for total dose normalized radioactivity.

When this is done, 99.9% of the circulating species have not been identified. In addition, when dose normalized radioactive C_{max} is compared to the C_{max} of asenapine the total radioactivity is 223 – 552 fold higher, (i.e. 3145/14.1 and 3008/5.44).

When chromatograms of pooled plasma samples over the dosage interval are examined, there are 10 or more unidentified peaks with peak areas apparently greater than 10% of the peak area for asenapine. This means that there are at least this many and possibly more metabolites that may not have been adequately qualified in toxicology studies.

Has the mass balance of asenapine been adequately characterized?

No.

After administration of a radioactive dose on average 88% of the dose was recovered, with approximately 49% recovered in urine and 39% recovered in feces.

Except for direct glucuronidation by UGT1A4 which accounts for 12% - 21% of the dose and elimination of unchanged asenapine which accounts for 5% - 16% of the dose, the relative contribution of the 3 primary oxidative pathways cannot be definitively assigned. This is due to the fact that multiple metabolites were identified for each peak and is also due to lack of identification of other peaks. Consequently the metabolic scheme is uncertain. Consequently the enzymes responsible for each of 3 of the primary pathways and their relative contributions have not been adequately characterized for 64.5% – 82.8% of the dose.

What are the receptor affinities for asenapine and metabolites?

Asenapine has high receptor affinities for all dopamine, serotonin, alpha-adrenergic, and histamine receptors tested, as well as for norepinephrine and dopamine reuptake transporters based upon typical

C_{max} in the range of 3 - 30 nMol/L (1 - 10 ng/ml) with doses of 5 – 10 mg SL BID, and typical IC₅₀'s in the range of 0.1 – 4 nMol/L..

In addition to the receptors mentioned, the evidence presented by the sponsor suggests that asenapine has effects on potential down-stream intracellular mediators.

Unfortunately the sponsor does not indicate whether binding at the various receptors result in antagonism or agonism, and this would be needed to predict potential pharmacologic effects such as cardiac valvulopathy with agonism of the 5HT_{2B} receptor.

Effects on other potential receptors, e.g. ion channels, were not found during this review, however the QT review mentions effects on canine calcium channels that are consistent with certain cardiac toxicities that have been seen in humans.

Until more information is available on the unidentified circulating species and receptor affinities are available for them the clinical significance of metabolites cannot be assessed.

What transporters are involved in asenapine's disposition?

Asenapine itself is not a substrate for pGP, however the sulfate and glucuronide conjugates probably are although active transport of metabolites was not studied.

What is asenapine's protein binding and the effects of changes in protein binding?

Protein binding of asenapine was 95% and is primarily to low molecular weight non-albumin plasma proteins.

What is the effect of pharmacogenetic polymorphisms on asenapine pharmacokinetics and pharmacodynamics?

This was not studied however as a CYP 2D6 and 2C9 substrate these might be clinically significant.

What are pharmacokinetic characteristics of the enantiomers of asenapine?

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. 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. 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 exposures to other metabolites and potentially different in risk : benefit ratios for the different enantiomers if administered separately. In addition this makes the interpretation of drug-drug interactions more difficult as binding to both on- and off-target receptors are frequently different between enantiomers.

Are there any indications of time dependent kinetics based on the *in vitro* data, i.e. enzyme activated inhibition?

Yes. N-desmethyl-asenapine is potentially a time-dependent inhibitor of CYP2D6 as it is a suicide substrate inhibitor. Consequently, the effect of inhibition might be small with a single dose but would increase upon multiple dosing due to the cumulative inhibition due to multiple doses. In addition, the effect of inhibition could be quite long lived based on the time needed to regenerate enzyme. This could be significant even with a single dose if the amount of enzyme inhibited with a single dose is sufficiently large.

Does asenapine exhibit time invariant kinetics *in vivo*?

There was no *in vitro* evidence of induction by asenapine on CYPs 1A2 or 3A4.

With regards to inhibition, N-desmethyl-asenapine is a suicide substrate inhibitor of CYP2D6. Although was not expected to affect the kinetics of asenapine it was expected to result in time dependent kinetics for N-desmethyl-asenapine. However nonlinear kinetics for both asenapine and desmethyl-asenapine were observed in the elderly PK study with maximal exposures several fold greater than in healthy volunteers. (See the question on food effect on the following page for further discussion.)

What is the absolute bioavailability of asenapine?

The absolute bioavailability after an oral dose is approximately 2% - 3%, whereas after sublingual administration the average absolute bioavailability for a single 5 mg dose is approximately 35%. This decreases with higher dosages (i.e. 10 mg) although quantitative values are not available and the variability and range are needed to be able to thoroughly assess safety.

The lower bioavailability with higher doses is likely due to solubility issues and as decreased bioavailability and differences in metabolism have safety implications this is especially important for smaller children who may have lower bioavailability with similar doses.

What is the relative buccal and supralingual bioavailability?

Both the supralingual and buccal routes had lower C_{max}s, AUCs and delayed T_{max}s as compared to the sublingual route, with absorption via the supralingual route being less than the buccal route. The supralingual route was not bioequivalent to sublingual administration and although the buccal route met the criteria for bioequivalence, it barely did so. The formulation used is different than the to-be-marketed formulation and has a 20% lower bioavailability, and the dose used is in the range where bioavailability is greater than with clinical dosages, which would minimize the chance of seeing toxicities in this study. Thus buccal and supralingual bioavailability is expected to be much less than after sublingual administration and is a safety concern with clinical dosages.

What is the effect of drinking water in close proximity to taking asenapine?

When water is taken less than 10 minutes after asenapine administration the exposure to asenapine decreases, presumably due to transfer of unabsorbed asenapine from the oral cavity to the stomach and increased first pass effect by way of GI absorption as compared to sublingual administration.

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

There is little to no difference in mean exposures to asenapine and desmethyl-asenapine when water is administered 10 or 30 minutes after dose administration.

What is the effect of food on the bioavailability of asenapine?

Food decreases exposure to asenapine by about 20% when administered concurrently. In addition when food is administered 4 hours after asenapine dosing it decreases asenapine exposures by about 10% (but not peak concentrations), apparently due to slowed hepatic and splanchnic blood flow.

This food effect study was not conducted under true fasted conditions as the 'fasted' individuals were administered a 'liquid breakfast' and an 'isotonic sports drink' 1 hour prior to taking asenapine. Thus the magnitude of the decrease in bioavailability especially when taken with a meal may actually be larger. As asenapine has a narrow therapeutic window with regards to hepatotoxicity even small changes and metabolic shunting could be clinically significant.

What is the effect of activated charcoal?

Charcoal administration affects oral absorption more than sublingual absorption. When administered with charcoal there is a decrease in asenapine exposure after oral administration of approximately 50% compared to a decrease in asenapine exposure of approximately 25% after sublingual administration. In addition the effect of charcoal administration on desmethyl-asenapine exposure is even greater than the effect on asenapine, and this is especially true with oral administration.

Does asenapine exhibit route dependent pharmacokinetics?

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. Data indicates it is not due to biliary excretion of asenapine and it 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. In drug interaction studies virtually no information was included on formation by 11-hydroxylation. Consequently, the true effects of drug interactions and shunting cannot be determined.

Are there pharmacokinetics differences by Race or 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.

Single and multiple dose pharmacokinetics for asenapine, desmethyl-asenapine, asenapine glucuronide and asenapine 11-O-sulfate in Japanese and Caucasians did not show any clear differences between the groups. However, due to the small sample size (n = 8 / group) no firm conclusions can be drawn from this study. In addition, this reviewer noticed only 1 Ethiopian reported as being enrolled in other studies.

Are there pharmacokinetics differences by 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 need to be examined.

This omission should be noted as agranulocytosis with structurally similar compounds may be greater in women.

Does asenapine's pharmacokinetics change with increasing age?

It was thought that no study in the elderly had been performed. However, on April 11, 2008 an abbreviated study report in the elderly was found. It had been submitted in Amendment 010 the 120 safety update report, under Reports of Efficacy and Safety / Schizophrenia / Other Study Reports / Study A7501021 a phase III efficacy and safety study in the elderly under the legacy study report under an entirely different study number with no description.

This abbreviated study only provides interim pharmacokinetic summary statistics with no raw data or safety information. On average C_{max} and AUCs in the elderly (65 – 85 years of age) were 30% - 40%

higher for asenapine compared to younger adults and for desmethyl-asenapine they were double. When the range of exposures in the elderly are examined the highest exposure for asenapine is 3 fold higher than the highest exposures in younger subjects and for desmethyl-asenapine it is 11 fold higher. However, the relatively high amount of N-desmethyl-asenapine indicates that there is likely some type of metabolic shunting occurring that will either increase inhibition of CYP2D6 or cause shunting to desmethyl-asenapine and /or toxic metabolites such as the N-oxide. Thus without adequate information on the metabolic scheme risks cannot be mitigated. In fact we don't even have safety data from this study to help identify the incidence of side effects. In addition without individual data the effect of predictive factors such as age and gender on the exposures cannot be determined.

As asenapine is a sublingual formulation the degree of dementia might have an impact on the amount of drug swallowed and this should be examined as use in this elderly population is expected to be especially high. Unfortunately significant cardiac safety signals have been observed that are not typically observed with other classes of antipsychotics, although they are seen to varying degrees with structurally similar compounds, and that are generally considered to be of particular clinical importance in the elderly.

In addition, the risk of agranulocytosis with structurally similar compounds is increased in the elderly, possibly due in part to lower baseline WBCs, so lack of information in the elderly is an important omission in the clinical development program.

What are the pharmacokinetic characteristics in children?

No raw pharmacokinetic data or metrics in children were supplied. As with the pharmacokinetic study in the elderly only an abbreviated report was provided with summary statistics for pharmacokinetic metrics. 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.

Examination of patient demographics revealed that 0 / 17 females and only 5 / 23 males had body weights of \leq 45 kg. This is significant as 45 kg is the median population weight in adolescents between 12 – 17 years of age. Thus the pharmacokinetic data from this population 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 normal weight adolescents at the lower end of the age range. This is concerning since, there appears to be a very narrow safety margin for hepatotoxicity if dosage is not adjusted. This is especially worrisome with off label use in even younger children as a sublingual formulation 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 significantly 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.

What is the effect of renal insufficiency on asenapine?

Two “full” studies were conducted on the effects of renal impairment on the pharmacokinetics of asenapine and desmethyl-asenapine. One study was conducted at a low dose 0.3 mg, possibly for safety reasons and this was followed by a second study with a single 5 mg dose (n = 8 / group).¹ The findings

¹ 9 for normal renal function in the 5 mg study

were mixed however it appears that desmethyl-asenapine exposures are lower in moderate and severe renal insufficiency (GMRs 0.82 and 0.73 respectively), possibly indicating a decreased formation of desmethyl-asenapine. It is known that CYP2D6 activity is decreased in end stage renal failure however this doesn't adequately explain the findings regarding desmethylasenapine.

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

What is the effect of hepatic insufficiency on asenapine?

Two "full" studies were conducted on the effects of hepatic impairment on the pharmacokinetics of asenapine and desmethyl-asenapine. One study was conducted at a low dose 0.3 mg, possibly for safety reasons and this was followed by a second study with a single 5 mg dose (n = 8 / group).¹ Average exposures to asenapine are over 5 fold higher in subjects with severe hepatic impairment, although some individual patients with mild hepatic impairment (n = 2) also had higher exposures to asenapine and N-desmethyl-asenapine. In addition the increased exposure to free drug was much higher, (3 fold the UL of exposures in normal volunteers making the average increase similar to the average increase of nearly 2 fold in moderately impaired subjects).

Since only slightly higher than the likely clinical dosage appears to be associated with hepatotoxicity, the presence of even 1 or 2 individuals in the mild hepatic impairment groups with much higher total exposures and others with normal total exposures and much higher free exposures leaves no margin of safety. Thus even if the risk : benefit ratio turns out to be acceptable for patients with normal hepatic function; it is unlikely to be acceptable for patients with even mild degrees of hepatic function.

What is the effect of smoking on asenapine pharmacokinetics?

Asenapine is a CYP1A2 substrate which forms 11-hydroxy-asenapine -sulfate. As tobacco use induces CYP1A2 a decreased exposure to asenapine due to induction is expected. In addition there is a possibility of decreased absorption secondary to vasoconstriction due to nicotine.

When examined no effect of smoking was seen on the pharmacokinetics of asenapine or desmethyl-asenapine. Although neither the effect on 11-hydroxy-asenapine or downstream metabolites such as sulfate conjugates were studied. However the study was conducted in chronic smokers and during the smoking phase of the study the subjects smoked from 5 minutes before to 10 minutes after asenapine administration. Thus the true effect of smoking on asenapine is unknown, as chronic smokers would not be expected to have any induction secondary to a single cigarette. In spite of this the low peak concentrations and AUCs seen in this study as compared with other studies may be indirect evidence of induction or slowed absorption.

As schizophrenics tend to be heavy smokers the effect of smoking is more likely to be evident in patients with bipolar illness where intermittent smoking may be more relevant, or if the drug is used off label for schizoaffective disorder. However since the clinical importance of metabolism by 11-hydroxylation is still unknown the true effects of smoking in schizophrenics are also unknown.

What is the potential for asenapine to inhibit CYP2D6?

The effect of asenapine to inhibit CYP2D6 was examined with 3 cosubstrates under varying conditions:

- Asenapine 5 mg BID administered for 11 days on a single dose of paroxetine 20 mg
- Asenapine 5 mg BID administered for 9 days on a single dose of dextromethorphan
- A single dose of asenapine 5 mg followed by a 4 day washout on the multiple dosing of paroxetine 20 mg qd for 1 week and the effect on dextromethorphan 9 days after the single dose of asenapine.

¹ 6 for severe hepatic impairment in the 5 mg study

- Effect of a single dose asenapine 5 mg on a single dose of imipramine 75 mg

Effect of multiple doses of asenapine on a single dose of paroxetine

A low dose of asenapine 5 mg BID resulted in a doubling of paroxetine. The mechanism for this interaction, e.g. effect on CYP3A4 or another enzyme, is unknown.

Effect of a single dose of asenapine on multiple doses of paroxetine

Even after 7 days of dosing paroxetine 20 mg qd, trough concentrations were still increasing. Although paroxetine does exhibit nonlinear kinetics, even at a higher dose of 30 mg mean half-life is 15 -22 hours with maximal half-lives of 65 hours. Consequently, steady-state should have already been reached). Instead it's possible that irreversible inhibition from the initial single dose of asenapine 7 days before was still inhibiting the elimination of paroxetine. This has clear implications for switching from asenapine to other antipsychotics or adding other drugs that are CYP2D6 substrates, e.g. antidepressants or narcotics.

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

Comparative Effect of Asenapine and Paroxetine on Exposure to Dextromethorphan

The DX/DM ratio after paroxetine 20 mg po qd is about 7.5% of the DX/DM ratio after asenapine 5 mg SL BID demonstrating that paroxetine is a more potent inhibitor. Based upon these DX/DM ratios it appears that paroxetine is 13.4 fold more potent. However the degree of effect on the DX/DM ratio is due to a combination of changes in both dextrothorphan and dextromethorphan. A better indicator of the degree of inhibition of CYP2D6 is by examination of the relative change in exposures to dextromethorphan in the presence of each compound. Although not examined, this can be determined indirectly by comparing the amounts of dextromethorphan recovered in urine in the presence and absence of each inhibitor.

For paroxetine the post-dosing to pre-dosing GMR for dextromethorphan for an 8 hour timed urine collection is 13.1 compared to 1.55 for asenapine. Consequently paroxetine causes on average an 8.45 greater increase in dextromethorphan than asenapine, although it should be noted that a low dose of asenapine was used and the effect of asenapine on dextromethorphan with a 10 mg dose is likely greater. When individual values are compared some subjects in the paroxetine group have exposures of nearly 45 times higher than baseline, whereas no one receiving asenapine had an increase of even 10 fold. Although with the 10 mg dose the effect is likely greater and may approach the degree of inhibition with paroxetine. The primary concerns are if children receive the 10 mg dose, greater effects with swallowing, inhibition for several days after stopping, and severe AEs due to dextromethorphan or other CYP2D6 substrates such as antidepressants, cough and cold remedies, or narcotics should they be given in combination, particularly in children and the elderly.

Imipramine

No effect of a single dose of asenapine 5 mg SL was seen on a single dose of imipramine 75 mg in 24 subjects, although there was trend for higher asenapine concentrations (~10%) in the presence of imipramine. However this was a single dose study and asenapine is a mechanism based inhibitor. Consequently when the drugs are administered simultaneously there may not be time for inactivation of CYP2D6 by asenapine to occur. Although the rationale for dosing imipramine prior to asenapine is so that ingestion of water will not send asenapine to the stomach this is also likely to minimize inhibition because

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

Consequently, the results of this study cannot be considered representative of what is expected during clinical use and the studies with paroxetine and especially dextromethorphan are thus more informative.

Based on the study numbers it appears that this study (25525) was designed after the multiple dose paroxetine interaction study (25526).

What is the effect of CYP2D6 inhibition on asenapine?

There was a slightly lower exposure to asenapine in the presence of steady-state dosing of paroxetine 20 mg qd in 26 subjects but this was within acceptable limits with a GMR of 0.87 for C_{max}, (90% CI 0.80 - 0.96), and 0.91 for AUC, (90% CI 0.85 - 0.97).

In contrast, there was a 26% increase in exposure (AUC) to desmethyl-asenapine, (90% CI 1.11 – 1.42), presumably due to inhibition of CYP2D6 N-oxidation.

Thus addition of asenapine to a potent CYP2D6 inhibitor could result in metabolic shunting with unknown clinical consequences.

How do other drugs effect the metabolism of asenapine by glucuronidation?

Valproate

The effect of valproic acid 500 mg PO BID on the pharmacokinetics of asenapine, N-desmethyl asenapine, and asenapine N-glucuronide following a single 5 mg dose of asenapine was assessed in 24 healthy male subjects.

There was clearly no effect of valproate on total asenapine C_{max} or AUC.

In contrast the extent of exposure for desmethyl - asenapine as expressed by GMR of AUC_∞ was on average 30% lower in the presence of valproate (90% CI: 0.64 – 0.77) whereas no effect was seen on C_{max}. This may indicate decreased formation of desmethyl–asenapine by inhibition of CYP2C9, which is polymorphic.

The effect of valproate on the pharmacokinetics of asenapine–glucuronide was to decrease both AUC_∞ and C_{max} on average by 85%, meaning exposure in the presence of valproate was 1/7 the exposure in the absence of valproate. This appears to indicate that valproate competes with glucuronidation by UGT1A4 with not much effect on active secretion.

The lack of effect on asenapine kinetics and the decreases in both asenapine glucuronide and desmethyl asenapine indicates that coadministration with valproate likely results in shunting to 11-hydroxylation. This is likely primarily mediated by CYP1A2, consequently coadministration of asenapine with valproate and a 1A2 inhibitor such as fluvoxamine could be quite dangerous. This is expected to occur occasionally in practice and might be predicted to occur most frequently in patients with bipolar spectrum disorder.

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

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

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

What is the effect of likely co-administered inducers on asenapine, e.g. Carbamazepine?

The effect of a low dose of carbamazepine, (200 mg PO BID), on the pharmacokinetics of asenapine, N-desmethyl asenapine, asenapine N-glucuronide, and asenapine N-oxide following a single 5 mg dose of asenapine was assessed in 24 healthy male subjects.

Carbamazepine induces the elimination of asenapine resulting in a secondary decrease in glucuronidation. Lower concentrations early on in both of their concentration vs. time profiles with more similar concentration vs. time curves later on indicates that elimination is driving the earlier phase of the declining profile while redistribution may be driving the later phase.

There is a much greater percentage decrease in N-desmethyl-asenapine exposure (30%) compared with the decreases in asenapine and asenapine glucuronide exposures (i.e. 15% for each). This may indicate that elimination of N-desmethyl-asenapine is also mediated by oxidation to 11-OH-desmethyl-asenapine by CYP3A4. Consequently formation of 11-OH-asenapine by CYP3A4 may also be increased and shunting to metabolites of 11-hydroxylation may be behind the apparent increase in severe fatigue when the drugs are taken in combination. N-oxide concentrations were largely below the limit of quantitation and were more frequently measured following asenapine alone as compared with in the presence of carbamazepine.

What is the effect of the nonspecific CYP450 inhibitor cimetidine on asenapine?

The effect of cimetidine, (800 mg PO BID), on the pharmacokinetics of asenapine, N-desmethyl asenapine, asenapine N-glucuronide, and asenapine N-oxide following a single 5 mg dose of asenapine was assessed in 12 healthy male subjects.

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

It's interesting that cimetidine was studied and only 12 subjects were evaluated as compared to other studies that enrolled more subjects. In addition to the potential for drug interactions cimetidine causes agranulocytosis at a rate of approximately 1 in 100,000 and there have been reports that coadministration of cimetidine with compounds that are structurally related to asenapine might increase the risk of agranulocytosis.

In the presence of cimetidine exposure to asenapine doesn't change although C_{max} is lower (GMR 0.87 90% CI 0.77 – 0.98) and although the exposure to asenapine glucuronide increases slightly, (GMR 1.22 90% CI 1.11 – 1.34 on average); the exposure to desmethyl-asenapine approximately doubles (GMR 2.22 90% CI: 1.91 – 2.58).

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

As only a single dose of asenapine was examined the full implications of the increase in desmethyl-asenapine exposure was not examined. It is expected that there may be a quicker onset of time dependent irreversible metabolism. In the cimetidine arm there were more subjects who experienced hypotension and dizziness. In addition it's also possible that the slightly higher N-oxide exposures might translate into an increase in toxicity, which for an N-oxide would expect to include hematologic toxicities.

What is the effect of the CYP1A2 inhibitor fluvoxamine on asenapine?

The effect of a low dose of fluvoxamine 25 mg bid on the kinetics of asenapine, D-desmethyl-asenapine, and asenapine 11-O-sulfate following a single 5 mg SL dose of asenapine was examined in 26 healthy nonsmoking males.

Fluvoxamine increased the exposure to asenapine by 30%, (90% CI 1.14 – 1.46), decreased exposure to asenapine 11-O-sulfate by at least 30%, (90% CI 0.52 – 0.98 for AUC_{tlast}), and increased exposure to desmethyl-asenapine by 2 fold, (90% CI 1.82 – 2.43).

Since the clinical dose of fluvoxamine is up to 300 mg daily the effects that are likely to be seen in clinical practice are much larger. In addition it should be noted that this study was conducted in nonsmokers, whereas most schizophrenics are smokers who will have CYP1A2 induced. Thus blocking 1A2 by fluvoxamine will result in an even greater effect in smokers, and will likely result in a much different risk profile compared to what was seen in the safety database.

The increase in exposure to desmethyl-asenapine is likely due to inhibition of 11-hydroxylation of desmethyl-asenapine. This will result in shunting to N-oxidation, although increased formylation is also a possibility. The shunting to N-oxidation will result in greater inhibition of CYP2D6 and as a suicide substrate result in even greater inhibition and thus result in nonlinear accumulation of desmethyl-asenapine upon multiple dosing. It's also possible that the increased inhibition of CYP2D6 will result in increased hepatotoxicity.

What is the effect of CYP1A2 inducers on asenapine?

This was not studied, however as this is expected to increase the formation of the catechol there may be increased interactions with COMT and the possibility of increased cardiotoxicity.

What is the effect of CYP2C9 inhibitors on asenapine?

This was not studied and the incomplete information on mass balance and the metabolic scheme makes the clinical consequences difficult to predict.

Are there any potential pharmacodynamic interactions that may be of concern with asenapine?

Yes. It is becoming more apparent that many toxicities and even the efficacy of many psychoactive drugs are mediated via effects on mitochondria. Thus even in the absence of pharmacokinetic interactions pharmacodynamic interactions are expected to be present. Any antipsychotic used for bipolar disorder is likely to be used as an add on therapy to other drugs such as carbamazepine, valproic acid and lithium thus the increase in AEs seen in the pharmacokinetic interaction studies is worrisome and the side effect profiles in larger combination studies should be examined prior to any marketing.

Are there any concerns with asenapine with other drug metabolizing enzymes?

The most obvious enzyme of potential concern is COMT, however the effect of asenapine on COMT has not been studied. In addition, prescribing information from the sponsor on a structurally similar compound, mirtazapine, indicate that mirtazapine should not be used within 14 days of the use of an MAOI because of the risk of serious effects such as hypertensive crisis and hyperthermia. Similar advice is probably appropriate for asenapine.

Is there any need for clinical pharmacology and biopharmaceutic review of the dissolution method and specifications?

This cannot be determined without actually performing such a review, however the clinical data suggests that changes in dissolution *in vivo* is clinically significant, whether an *in vitro* method could be developed that is sufficiently sensitive to detect such changes is presently unknown.

Are there any issues with switching antipsychotic medications?

Asenapine appears to be a suicide substrate inhibitor for CYP2D6. 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. As most psychiatric medications are CYP2D6 substrates, this would make switching from asenapine to most other psychiatric medications or addition of other psychoactive drugs problematic and would likely result in overdosing.

What was the effect of asenapine on hormones?

This was not reviewed. However increases in prolactin are expected.

What was the effect of asenapine on sleep?

This was not studied however antipsychotics typically have variable effects on sleep patterns. Although a number of cases of nightmares and other sleep disturbances were noted and are also included in the labeling for structurally similar compounds.

*** What was the effect of asenapine on QTc?**

Asenapine clearly prolonged QTc. However the effect was greater at the proposed clinical dose of 10 mg BID than at 20 mg BID with an UL of the 90% CI of the peak mean effect on $\Delta\Delta\text{QTcF}$ at 10 mg of 17.1 mSec. This paradoxical inverse U may be due to a dose dependent effect on calcium channels resulting in an increase in the PR segment and a shortening of QTc, or could be due to the effects of metabolites on other receptors such as 5HT receptors. An effect on calcium channels is worrisome as this can be associated with AV block and junctional rhythms which are particularly dangerous in the elderly and which have been observed in a number of healthy young subjects receiving asenapine.

*** Are there any other important clinical pharmacology / safety issues?**

Yes. Cardiac asystole and sinus pause have been observed with asenapine as well as a number of other cardiac arrhythmias and an apparent myocardial infarction and death due to cardiac failure.

Cardiac asystole was seen after a 30 minute 0.7 mg IV infusion. Although attributed by the sponsor to a vasovagal response cardiac massage stimulated nodal bradycardia, however the patient reverted to asystole and again responded to cardiac massage but with bradycardia and with intermittent nodal complexes and AV dissociation until two doses of atropine and Haemaccel was administered. Even though this occurred with IV dosing the exposures to asenapine with this regimen is similar to what is seen with clinical sublingual dosing.

In the multiple rising oral dose study one subject had asystole for 8.7 seconds with a junctional escape rhythm following a single 30 mg oral dose. The asenapine exposures in this study are low compared with sublingual dosing however the desmethyl-asenapine exposures are similar.

In the paroxetine interaction study a black male experienced atrial fibrillation approximately 2 hours after paroxetine 20 mg and 1.5 hours after a single dose of asenapine 5 mg SL. It appears that the Afib may have lasted nearly 24 hours as it required cardioversion with sotalol the following day. In the multiple dose asenapine arm one subject had pain between the scapulae and SOB along with a negative T wave in leads II, III and AVF on the second day of dosing with asenapine.

In the pivotal BE study comparing single 5 mg sublingual doses of (b) (4) formulations 20 of 35 subjects had cardiac effects observed on telemetry, 10 subjects experienced bradycardia, 8 tachycardia, 7 sinus pause, 3 junctional escape rhythms, and 1 bradycardia with junctional rhythm.

In another study a subject experienced bradycardia following a single 5 mg SL dose with the (b) (4) tablet. Although this was explained by the sponsor as being neurally mediated it occurred while the subject was supine.

In an ongoing study, (246021), there was also a death due to cardiac failure 2 months after maprotiline was added. Based on labeling from structurally similar compounds and the information in this submission, it appears this could be a pharmacokinetic interaction with asenapine and / or a pharmacodynamic interaction.

Many of the other cardiac toxicities seen are known AEs with multiple structurally similar drugs. In fact MI fitting the description of the case in the paroxetine interaction study is a labeled AE with the structurally similar drug clozapine.

The most common cardiac AEs were bradycardia (3.6%) and tachycardia (2.8%). The thorough QT review as well as a number of the phase I studies reported numerous changes in ECG morphology and more detailed review would be needed to assess their significance. The concern with asenapine is that so many of these serious AEs are being seen in healthy volunteers without cardiac problems at low doses and short treatment durations. Thus this is much greater concern compared with other drugs in the class as these AEs are known to occur at anytime during treatment without prior warning and the intended patient population which has a high prevalence of comorbid cardiovascular disease.

“Dose and time dependent” liver injury was seen in 9 of 20 subjects and in 7 subjects the increases were greater than 2x ULN. In these 7 subjects the increases occurred between days 2 and 10 with oral doses of 3 mg – 30 mg BID. In two of the seven, increases in LFTs were approximately 5 and 10 times the upper limits of normal. The increases in LFTs in this study are associated with desmethyl-asenapine and asenapine exposures seen with clinical dosing i.e. 5 mg – 10 mg SL.

There was one case of increased total bilirubin at day 2 and 10 with a 20 mg oral dose in this study, (85136) and is listed among the 7 cases of suspected drug induced liver injury. This needs to be looked in further as to whether it's hepatic in origin or has another cause, e.g. hematologic.

There were also 3 cases of increased LFTs (> 3 x ULN) in two BE studies with formulations that are expected to dissolve slower and have more drug swallowed. Study 41009 comparing polymorphic forms had two cases and study 41026 had one case after administration of a (b) (4) sublingual tablet. This is 5% of the subjects in these studies. In study 41009 one case might have been an exacerbation of an underlying condition and detailed information was not provided on the second case. However the third case in study 41026 occurred after only a single 5 mg dose.

There were also 4 cases of elevated LFTs in the paroxetine interaction study out of 24 subjects, only one of which was > 3x ULN. However all cases were in the asenapine treatment arm. Two cases occurred after co-administration of asenapine. One subject exhibited mildly increased ALATs beginning on day 7 (3 days after beginning dosing; ALAT 119), and this apparently remained stable until day 26 (10 days after discontinuing asenapine) and finally decreased to 59 U/L 7 days later. This subject also had a mildly elevated GGT (60 U/L) and bilirubin (18 µM/L) prior to beginning asenapine. The fourth subject's ALAT began to increase after 6 days of treatment reached a maximal increase with an ALAT of nearly 10x ULN a few days after coadministration of the single dose of paroxetine and finally declined to 78 U/L 2 weeks after discontinuation. These cases suggest that coadministration of even a single dose of paroxetine may induce hepatic injury and it is worse in the subjects who already may be more sensitive to the hepatic injury with asenapine.

There were also a number of increases in bilirubin that were associated with the thorough QT study mentioned in the pop PK analysis. The TQT study employed higher doses than would be used clinically

15 mg - 20 mg BID and the medical reviewer was informed of the possible increased bilirubins. However it appears that the sponsor has only submitted the summary statistics for laboratory values prior to and after treatment with asenapine and not during treatment.

Many antipsychotics commonly cause drug induced liver injury, both cholestatic and non-cholestatic in origin. However fatal cases are not unknown and the risk appears to vary with the drug. In particular elevations in liver enzymes are especially common with the structurally related drug olanzapine. For asenapine it appears that dose and swallowing the drug are risk factors. Thus this may be an especially important risk in children or frail demented elderly who may be smaller and swallow more asenapine.

Also in study 41009 a subject had a “schizophrenic reaction” to asenapine, however it appears that the subject may have also taken ‘robitussin’, and pseudoephedrine for seasonal allergies at the same time. There is the possibility that the ‘robitussin’ may have contained dextromethorphan.

Hematologic toxicity was not systematically looked into however, due to the structural and metabolic similarity to clozapine and other compounds in the class, virtually all of which are known to cause to agranulocytosis to varying degrees it was expected that it might occur. Due to the lower molar dose of asenapine as compared to clozapine the incidence would also be expected to be lower even though this effect might be immunologically mediated. In addition the relative risk of agranulocytosis or alternatively aplastic anemia appears to be genetically linked. In addition to the one case of neutropenia that the sponsor notes in the integrated summary of safety this reviewer found a probable death due to aplastic anemia from August 2005 in one of the ‘ongoing’ clinical trials that would not have been included in the safety database. The death occurred in a 44 yo F who was just listed as having died with no explanation provided. The lab reports showed clear evidence of progression toward pancytopenia over an 8 month period prior to the death with a differential leukocyte pattern (i.e. relative lymphocytopenia) which is what is described for clozapine. In addition the lab reports indicated an alert for sponsor notification 2 months prior to the death. In addition, the lab reports for the woman who died from Quincke’s edema are also suspicious for a similar downward trend in hematologic parameters after year on asenapine.

Other serious AEs seen in ongoing studies include acute MI, several cases of chest pain, Afib, Right Bundle Branch Block, 145 cases of psychosis, neonatal death, a toxic skin reaction, acute respiratory failure resulting in death including a death due to an allergic reaction with Quincke’s angioedema, a number of injuries some due to falls, renal failure and urolithiasis.

What were the results of PK/ PD modeling and simulation of the PET study data?

The modeling and simulation did not result in a better dose estimate than simply fitting an Emax model to the D2 receptor binding PET data and eyeballing the doses needed to achieve these concentrations. However, the quantitative estimations of having a positive or failed study under various scenarios would be quite useful for business decisions, although additional model refinement is clearly needed as shown by the poor predictability of the current model.

Fits of the asenapine D2 occupancy data from studies 25510 and 25516 to an Emax model indicates that a peak concentration of 3 – 9 ng/ml is needed to achieve 90% occupancy and that extrapolation of the data available at the time of the study indicated that a daily dosage of 5 - 10 mg is necessary to achieve this assuming dose linearity.

In retrospect it appears that the early low dosages used in clinical trials were due to toxicity concerns with the exposures achieved with asenapine.

What conclusions can be drawn from exposure response analysis of acute schizophrenia trials?

For study 41004 all treatments result in the same final value of total PANSS score. The difference from placebo for the asenapine group in change in total PANSS score is due to a higher initial baseline score in the asenapine group. In addition the active comparator risperidone did not show an effect, which is

quite unusual for risperidone. Thus this is a 'failed' study and the major problems noted in this review have already been described in the financial press¹.

For study 41023 the active treatments did result in final values different from placebo but the decrease in PANSS scores were only about 5 units greater than with placebo and the higher 10 mg dose failed to differentiate from placebo.

The sponsor claims a dose response based on modeling, however, close examination of the sponsor's plots indicate that the true values plateau and there is no increased response to a 10 mg dose over a 5 mg dose.

What were the results of the use of mixed models of repeated measures?

The reason for dropping out especially by treatment and duration on treatment was poorly explained and therefore modeling dropouts while possible may not be especially accurate in the present ER analysis. Specifically the large proportion of drop-outs categorized as lost to follow-up, other, and especially withdrew consent is troubling. In addition, that only one subject was assigned to worsening of schizophrenia is not believable as this appears to be inconsistent with spaghetti plots of response vs. time

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

What are the results of the exposure response analysis in acute mania?

According to the sponsor these studies were performed in subjects with 'moderate' or 'severe' mania and mixed mania with baseline YMRS scores ≥ 20 . Based upon clinical practice until the a few years ago, this reviewer performed an exploratory assessment of response by baseline disease severity.

Examination of the YMRS score over time by quintile reveals that for placebo the final score at 3 weeks is correlated with the initial baseline score, indicating that initial disease severity is a good predictor of placebo response. When the plots for asenapine and for the active control olanzapine are examined the mean final score at the end of 3 weeks of treatment is approximately 10 – 13 regardless of the initial baseline score. Scores of 11 – 12 are consistent with hypomania. Comparison of the responses with active treatments to placebo by quintile of severity reveals that the responses to the lowest two quintiles are virtually identical between active treatment and placebo and only differentiate with the 3 more severe quintiles. In addition, there appears to be a greater difference from placebo as severity increases.

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

This raises two important points. First until about 2000 practice treatment guidelines for the use of antipsychotics in mania were limited to subjects essentially who were hypermanic. Thus by inclusion of all subjects with full blown mania in drug trials we may have driven the mean results by the more severely ill subjects. Secondly, it indicates that promotion of off-label use and current 'expert opinion' practice treatment guidelines for the off-label use of antipsychotics in hypomania and especially in bipolar spectrum disorder such as promoted by NIMH in a May 5th, 2007 press release are inappropriate. This is especially true for the use in children since the YMRS scores in children for whom mania might be diagnosed in practice, based on certain recommendations, are on the order of 4 for a few hours at a time.

¹ [http://www.glgroup.com/News/Does-The-FDA-Acceptance-of-The-NDA-for-Asenapine-Signal-A-Good-Outlook-for-Schering-Plough-\(NYSE--SGP\)--19717.html](http://www.glgroup.com/News/Does-The-FDA-Acceptance-of-The-NDA-for-Asenapine-Signal-A-Good-Outlook-for-Schering-Plough-(NYSE--SGP)--19717.html)

Whereas in this study efficacy only appears to occur with YMRS scores equal to or greater than 27 and the drugs barely bring the YMRS scores to 5 after 3 months.

The patterns seen in this study was also confirmed by analysis of data from studies with other antipsychotics from other NDAs and there are even hints in some of the statistics reviews for other NDAs.

Based on these analyses and the severe side effects associated with antipsychotics, including death, and the increasingly common practice and recommendations for using antipsychotics in children with ADHD there is a major public health concern and these concerns should be communicated to the public as soon as possible regardless of whether further review of asenapine is warranted and before a final decision on this drug is made.

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

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

What are the results of the exposure response analysis for maintenance effect for mania?

After 3 weeks of treatment during the acute treatment phase with asenapine mean YMRS falls to approximately 10 - 12 regardless of initial severity. This is in contrast to placebo treated subjects in whom YMRS falls to 10 - 12 in the lowest two quintiles but not in the more severely ill subjects.

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

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

What is the exposure response for EPS?

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

There was insufficient time for the reviewer to perform a detailed critique of the study report and data submitted however examination of the sponsor's graphical analysis indicates a dose response relationship with symptoms of EPS over a period of six weeks. However, this was only an analysis of

SARS scores which measures Parkinsonian symptoms. Although the frank SARS scores decrease over 6 weeks, over a longer period of time we might see a dose response with tardive dyskinesia. Although haloperidol had higher SARs scores observations, consistent with what has been seen with other atypicals this could also be due to the nonlinear bioavailability with asenapine. In contrast study 25517 in spite of comparable dosing of asenapine and Olanzapine showed nearly twice the incidence of total EPS with asenapine. In addition there has been a high incidence of restless legs syndrome with asenapine in many of the phase I studies with incidences of over 75% in some of the larger , which conceivably might actually be symptoms of akathisia. Thus comparative risks of various types of EPS cannot be determined from the current analyses with respect to tardive or with respect to other atypical antipsychotics, and further analysis is needed.

What is the exposure response analysis for suicidality?

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

Are there any broader implications of the exposure response analyses?

The lack of differentiation in the time course of response for asenapine from placebo along with improvements in the drug effect with baseline YMRS of less than 27 suggests that response in mildly and moderately ill patients may be due to simply environmental factors and not drug.

What was the quality of this submission, and how did it affect the quality and reliability of this review?

Please refer to §6.9 Submission Quality in the appendices.

What feedback is there for the Good Review Management Practice pilot program?

Please refer to §6.10 Good Review Management Practice – Pilot Program - Critique in the appendices.

2.3 Comments

2.3.1 Comments to the Medical Division

2.3.1.1 Comments Previously Provided to the Medical Review Team

On Friday May 1, 2008 this reviewer went to the medical division to discuss a death in the ongoing studies. Due to workload the medical review team requested followup midweek the following week. On Thursday May 8th, 2008 a followup e-mail was sent to the medical review team informing them of a possible case of aplastic anemia.

2.3.1.2 Comments to be Provided to the Medical Review Team

Plasma metabolic exposure profiles, the metabolic scheme, mass balance, and enzymes responsible for various elimination pathways need to be clarified. This will likely require additional studies.

Many issues in the clinical pharmacology development program remain unanswered. These include the effects of age, gender, smoking, race/ethnicity and pharmacogenetics, as well as pharmacokinetic and pharmacodynamic drug-drug interaction studies. Design of the future studies including assess of effects on various metabolic pathways should be based upon more complete metabolism information. A follow-up meeting between OCP and the sponsor to discuss details of any future development is recommended.

Data suggests that there may be pharmacodynamic interactions with other psychotropic medications that increase cardiac, hepatic, and hematologic toxicities in addition to any pharmacokinetic interactions.

Psychometric testing indicates that asenapine has an adverse effect on both short term and long term memory. This may be significant on historicity in schizophrenics as well as elderly patients with dementia. Whether this is particular to asenapine or a class effect cannot be determined from the information in the submission. Consideration should be given to following up on this with other antipsychotics.

The exposure response analysis in bipolar disorder I disorder that indicates that efficacy is limited to only those patients with the most severe mania and that this is a class effect it is recommended that an adequately powered confirmation study be conducted prior to any approval.

Based upon the suicides and suicidality seen in the acute mania trials in both the asenapine and active control arms and the lack of any suicides or suicidality seen in the placebo arm, in addition to other adverse effects and the lack of response in subjects with YMRS scores less than approximately 27, it is recommended that a public health warning for a class effect be considered at the earliest possible time even before any final decision is made regarding whether asenapine is deemed approvable. Alternatively, at the very least it is recommended that a public advisory committee hearing be held as soon as possible.

Additional analyses will need to be performed including comparison of suicidality / suicides in dropouts and by drop out type, and for subjects remaining on treatment how they were responding to treatment. However these should be able to be completed in 1 day and almost certainly in less than a week. In addition even if other antipsychotics are examined the required analyses should not take greater than a few weeks. Consequently it is recommended that data analysis begin as soon as possible so that risk communication is not delayed.

It is recommended that full sets of case report forms be obtained for subjects who have died (including full autopsy reports). Submission of full case reports for cases of serious adverse events observed during development might also be considered. Specifically the cases of particular interest include the

schizophrenic reaction in the pivotal bioequivalence study and possible signs of cardiovascular abnormalities. In addition, the medical division is referred to previous comments from OCP.

If asenapine is eventually approved it is recommended that the Risk Mitigation Plan include surveillance and possibly other strategies for cardiac, hepatic, and hematologic toxicities particularly in the most vulnerable populations. For hematologic toxicities this may need to include monitoring of laboratory values and possibly pharmacogenomic assessments when available.

Please also see the comments to the other review disciplines and to the sponsor.

2.3.2 Comments to the Pharm/Tox Team

2.3.2.1 Comments Previously Provided to the Pharm/Tox Reviewer

At the mid-cycle review meeting held Friday, February 1, 2008 the Pharm/Tox team made a request to the OCP team leader whether there were any new human metabolites of interest. On Wednesday, February 6th, 2008 OCP met with the Pharm/Tox and Pharm/Tox was informed verbally that there were at least 10 metabolites in humans that likely had exposures greater than 10% of asenapine and thus may not have been adequately qualified. Pharm/tox asked the identities of these metabolites and was told by OCP that the sponsor did not identify them and it was not known.

At a later date (~ 1 month later) the OCP review team discussed the possibility of a followup communication and a second verbal followup was provided.

2.3.2.2 Comments to be Provided to the Pharm/Tox Review Team

Please remember to request appropriate pharmacology / toxicology studies when and if appropriate human and preclinical studies are conducted to identify and quantify human metabolites.

To assess potential clinical safety issues agonism and antagonism at the various receptors is needed by the clinical pharmacology team. We were unable to find this information in the submission and if it is available we request assistance in finding it in any future review cycle.

Information on screening at other receptors and in particular effects on ion channels also is needed and may need to be requested if not already provided.

2.3.3 Comments to the Statistical Review Team

2.3.3.1 Comments Previously Provided to the Statistical Reviewers

Several discussions were held with the statistical review team.

With regard to the bipolar efficacy studies, OCP pointed out the difference in efficacy observed based on initial disease severity, and statistics pointed out findings regarding Asians having a greater response to drug. Based upon this information from statistics further analyses were performed by OCP that showed that Asians were overrepresented among the most severely ill patients and underrepresented among less severely ill subjects. This distribution by race was presented at the OCP briefing.

Multiple attempts were made to informally discuss the schizophrenia studies with the statistical review team however in spite of attempts due to schedule conflicts no discussions were able to be held.

2.3.3.2 Comments to be Provided to the Statistical Review Team

The use of Mixed Models of Repeated Measures (MMRM) in the efficacy analysis for schizophrenia was intriguing and research in this area should be continued with better documentation regarding why subjects dropped out.

Factors that should be assessed include, initial disease severity, duration of illness, duration of current episode, subtype, and prior response to different structural classes of compounds.

2.3.4 Comments to the Chemistry Review Team

2.3.4.1 Comments Previously Provided to the Chemistry Reviewer

This reviewer met with the Chemistry reviewer to find out about drug particle sizes in clinical and developmental study batches due to the potential for hepatotoxicity and other toxicities with swallowing.

2.3.4.2 Comments to-be Provided to the Chemistry Review Team

Due to the low solubility of asenapine small delays in dissolution of particles post disintegration are likely to result in more drug being swallowed. Due to the potential increased risk of hepatotoxicity, cardiac, and hematologic toxicity with even small increases in the amount of drug absorbed any changes in manufacturing may have clinical implications and the post-marketing chemistry reviewer team needs to be aware of this.

2.3.5 Comments to the Sponsor

2.3.5.1 Comments Previously Provided to the Sponsor

Please refer to comments previously provided in §6.5 (Requests to Sponsor) on page 477.

2.3.5.2 Comments to be Provided to the Sponsor

- 1) The mass balance data provided only allows the unambiguous assignment of the primary elimination pathways of 1/5 to 1/3 of the dose.
- 2) The plasma concentration profiles for total radioactivity and identified circulating species indicated that at least 96.6% of the circulating species have not been identified, and when the total radioactivity is dose normalized it indicates that potentially 99.9% of the circulating species have not been identified. In addition chromatograms of pooled plasma samples from over a dosage interval indicate at least 10 unidentified species with exposures greater than 10% of asenapine.
- 3) Based upon incomplete information mentioned in items 1 and 2 we are unable to determine the appropriateness of metabolite assessments in the drug-drug interaction studies.
- 4) OCP is available for a follow-up meeting with the sponsor to discuss details of the NDA review to assist them in any future development of this or other compounds.

**2.3.5.2.1 Commitments to be Performed Prior to Approval
(Prior Approval Commitments)**

To be discussed with medical division.

2.3.5.2.2 Labeling Comments

Labeling comments will be included in an amendment to the review.

**2.3.5.2.3 Commitments to be Performed Post-Approval
(Phase IV Commitments)**

None presently.

2.4 Signatures

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Date

Senior Reviewer
Division of Clinical Pharmacology I

Ramen Baweja, Ph.D.

Date

Team Leader
Division of Clinical Pharmacology I

OCP Briefing Meeting:

Date: Monday, May 12th, 2008

Time: 1:00 PM – 2:30 PM

Location: Building 51 Room 1211

Level: Required Office Level CPB Briefing

Attendees: **Psychiatry** LevinRo, ZornbergG, MathisM, LaughrenT

Pharmacology Chalenka-FranaszekE, FossomL, AtrakchiA

Statistics TBD

Chemistry

Office of Clinical Pharmacology

KavanghR, BawejaR, MehtaM, UppoorR, HuangS, LeskoL,
RamanA, LazorJ, Urs Meyers, IyerG

Others StrongJ

cc: DFS NDA 22-117 (DFS)
HFD-130 (LevinRo, ZornbergG, MathisM, LaughrenT, Chalenka-FranaszekE, RosloffB,
OliverT, ChenYF, KordzakhiaG, YangP, HungJ, TeleC, OliverT, UpdegraffK,
KiedrowK)
HFD-860 (KavanaghR, BawejaR, UppoorR, MehtaM)

45 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

4 Signatures

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Date

Senior Reviewer
Division of Clinical Pharmacology I

Ramen Baweja, Ph.D.

Date

Team Leader
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Pharmacology

Chalenka-FranaszekE, AtrakchiA, FossomL

Office of Clinical Pharmacology

KavanaghR, BawejaR, UpoorR, MehtaM, RahmanA, LazorJ,
HuangSM, LeskoL, IyerG, Urs Meyers

Others

StrongJ

cc: DFS NDA 22-117 (DFS)
HFD-120 (ZornbergG, MathisM, LaughrenT, Chalenka-FranaszekE, RosloffB, TeleC,
OliverT, ChenYF, KordzakhiaG, YangP, HungJ, KeidrowK, UpdegraffK)
HFD-860 (KavanaghR, BawejaR, UpoorR, MehtaM)

5 Review

5.1 Chemistry

The following chemistry information is as reported by the sponsor.

5.1.1 Drug Substance

5.1.1.1 Nomenclature

Recommended Modified International Nonproprietary Name (rINNM)

asenapine maleate

Recommended International Nonproprietary Name (rINN)

asenapine (for Org 5222 active entity)

US Adopted Name (USAN)

asenapine maleate

Systematic chemical name(s)

CA Index Name

(3aR,12bR)-rel-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (2Z)-2-butenedioate (1:1)

Other names

trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (Z)-2-butenedioate (1:1)

CAS Registry Number 85650-56-2

Company or Laboratory Code Org 5222

5.1.1.2 Molecular formula

Asenapine base: $C_{17}H_{16}ClNO$

Asenapine maleate: $C_{17}H_{16}ClNO.C_4H_4O_4$

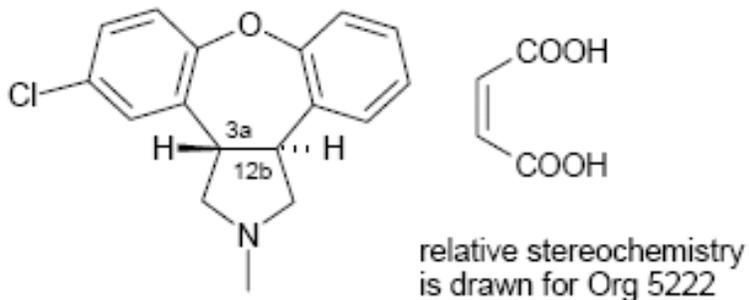
5.1.1.3 Relative Molecular Mass

Asenapine base: $MW = 285.77$

Asenapine maleate: $MW = 401.84$

5.1.1.4 Structure

Figure 1 Asenapine Maleate Structure



5.1.1.5 Physico-Chemical Properties

5.1.1.5.1 Polymorphism

(b) (4)

5.1.1.5.2 Physical Form and Appearance

White to off-white powder.

5.1.1.5.3 Melting Point

The melting point has an average onset temperature of 139.9°C.

5.1.1.5.4 Hygroscopicity

Org 5222 polymorphic (b) (4) displays almost no affinity for water as was studied by (b) (4)

5.1.1.5.5 Partition coefficient

The logarithm of the *n*-octanol/water coefficient (*log P*) is 4.9 (neutral species) and 1.4 (cationic species) at 21.5 - 23.8°C.

5.1.1.5.6 pH in Solution

At 23.5°C, the pH in a 0.1% m/v solution of Org 5222 in water is 4.6 and the pH in a saturated solution in water is 4.2.

5.1.1.5.7 pKa in Solution

The pKa value of the protonated free base of Org 5222 (extrapolated from various methanol/water ratios to water) is 8.6 at 21.5-23.8 °C.

5.1.1.5.8 Solubility

Table 1 Solubility of Asenapine Base

Solvent	Temperature °C (at which solubility was determined)	Solubility (mg/mL)
DMSO	Ambient**	≥71
0.1 M Phosphate buffer pH 7.4*	Ambient	2.7
Dichloromethane	Ambient	≥17
Ethanol	Ambient	14
Methanol	Ambient	≥17
Acetone	Ambient	≥18
Iso-octane	Ambient	0.005
Heptane	Ambient	0.003
Ethyl acetate	Ambient	4.0
Water	Ambient	3.7
0.1 M Hydrochloric acid	Ambient	13
0.2 M Phosphate buffer pH 4.0*	Ambient	3.8
0.1 M Phosphate buffer pH 7.0*	Ambient	3.0
Ammonia-ammonium chloride buffer pH=10.0*	Ambient	0.010
Gelatin/mannitol (0.5 %/5 %)	Ambient	4.1
Gelatin/mannitol in 0.1 M hydrochloric acid (0.5 %/5 %)	Ambient	12
Gelatin/mannitol in 0.2 M phosphate buffer pH 4.0* (0.5 %/5 %)	Ambient	4.3
Gelatin/mannitol 0.1 M phosphate buffer pH 7.0* (0.5 %/5 %)	Ambient	3.4
Water 5.4 0.01 M Hydrochloric acid	37	6.0
Acetate buffer pH 4.5*	37	5.5
0.2 M Phosphate buffer pH 6.8*	37	4.5

* Type of Buffer

Buffer pH 4.0: 0.1 M Citric Acid + 0.2 M Na₂HPO₄

Buffer pH 4.5: 0.028 M Acetic Acid + 0.022 M sodium acetate + 0.0009 M aqueous sodium hydroxide solution

Buffer pH 6.8: 0.2 M KH₂PO₄ + 0.2 M aqueous sodium hydroxide solution

Buffer pH 7.0: 0.1 M NaH₂PO₄ + 0.2 M Na₂HPO₄

Buffer pH 7.4: 0.1 M NaH₂PO₄ + 0.2 M Na₂HPO₄

Buffer pH 10.0: 1.31 M NH₄Cl + 1.34 M NH₃-solution

** At ambient temperature, the temperature was not controlled.

5.1.2 Drug Product

(b) (4)

5.1.2.4 Physical Chemical Stability

Asenapine maleate salt was selected for use in asenapine tablet drug product based on chemical stability, melting point, good purification upon crystallization, and acceptable solubility in water.

Asenapine maleate drug substance is not readily susceptible to heat, pH, light, or oxidative agents. During long term and accelerated stability studies asenapine maleate drug substance has been shown to be chemically stable for at least 18 months when stored at 25 °C/60% RH and at least 6 months when stored at 40 °C/75% RH.

5.1.2.5 Method of Manufacture

Asenapine tablets are (b) (4) sublingual tablets formed (b) (4) in their aluminum blisters.

5.1.2.6 Qualitative – Quantitative Composition

Table 2 Qualitative-Quantitative Composition of Asenapine Tablets

Component	Reference Standard	Function(s)	5 mg Tablet		10 mg Tablet	
			Mass (mg)	% (wt/wt)	Mass (mg)	% (wt/wt)
asenapine maleate ¹	In-house standard	active ingredient	7.03	28.7	14.06	46.1
Gelatin	Ph. Eur. / NF / JP	structure forming agent	(b) (4)			
Mannitol	Ph. Eur. / USP / JP	structure forming agent				
(b) (4)	Ph. Eur. / USP / JP	(b) (4)				
Total						

1 1.40617 g of asenapine maleate salt is equivalent to 1.0 g of asenapine (active entity).

2 Essentially removed during processing

5.1.2.7 Container Closure System

Asenapine tablets of both 5 mg and 10 mg strengths are filled into all-aluminum blister packs which may be also referred to as (b) (4) aluminum blister packs.

One blister pack contains 10 tablets

(b) (4)

5.2 Overview of Clinical Development Program

To be filled in post briefing.

5.3 In Vitro Pharmacology

5.3.1 Receptor Binding

pK_is and IC₅₀s for various receptors from humans and other species are shown in Table 4, Table 5, and Figure 2 on the following pages.

Asenapine has high receptor affinities for all dopamine, serotonin, alpha-adrenergic, and histamine receptors tested, as well as for norepinephrine and dopamine reuptake transporters based upon typical C_{max}s in the range of 3 - 30 nMol/L (1 - 10 ng/ml) with doses of 5 – 10 mg SL BID, (see Table 53, Table 55 and Figure 51) and typical IC₅₀'s in the range of 0.1 – 4 nMol/L, (see Table 4 and Table 5). Although this estimate does not take into account free concentrations which are around 5% of total it's likely that the receptor binding experiments were conducted in the presence of albumin and so a correction is not needed. In addition, the results of PET studies also suggest that corrections for protein binding are unnecessary, (see Table 155).

In addition to the receptors mentioned, above Figure 2 also shows that asenapine has effects on potential down-stream intracellular mediators.

Unfortunately the sponsor does not indicate whether binding at the various receptors result in antagonism or agonism, and this would be needed to predict potential pharmacologic effects such as cardiac valvulopathy with agonism of 5HT_{2B} receptors.

Table 4 Reported pKis for Human Receptor Binding and Transporters

Receptor	R&DRR INT0002643					Study 00003223				
	Asenapine	(-)asenapine	(+)asenapine	N-desmethyl	N-oxide	Org 191634-0 N-sulfated- N-Desmethyl	Org 213772-0 11-OH	Org 214025- 0 11-O-sulfate	Org 216761-0 N-Gluc	Org 220473-0 7-OH
5-HT1A	8.60 ± 0.04	8.04 ± 0.03	8.57 ± 0.02	8.21 ± 0.09	5.97 ± 0.01	8.0	8.4	7.5	<5	7.6
5-HT1B	8.40 ± 0.08	8.77 ± 0.11	8.60 ± 0.02	6.70 ± 0.01	7.45 ± 0.02					
5-HT2A	10.15 ± 0.09	10.21 ± 0.08	10.40 ± 0.11	8.62 ± 0.04	8.22 ± 0.14	7.6	10.0	9.9	<6	9.9
5-HT2B	9.75 ± 0.03	9.42 ± 0.29	9.04 ± 0.40	8.61 ± 0.27	7.42 ± 0.09	8.0	10.0	9.4	<6	9.5
5-HT2c	10.46 ± 0.15	10.00 ± 0.13	10.38 ± 0.28	8.73 ± 0.25	8.22 ± 0.04	7.7	9.9	9.4	<6	9.9
5-HT5A	8.84 ± 0.21									
5-HT6	9.60 ± 0.04	9.58 ± 0.11	9.90 ± 0.08	7.86 ± 0.07	7.07 ± 0.02	7.7	10.0	9.7	<6	9.1
5-HT7	9.94 ± 0.04	10.04 ± 0.05	9.67 ± 0.13	7.98 ± 0.05	7.24 ± 0.08	7.5	9.8	9.6	<6	8.8
D1	8.85 ± 0.04	8.80a	8.82 a	6.92 a	6.69 a					
D2L	8.90 ± 0.08	8.69 ± 0.13	8.72 ± 0.14	7.26 ± 0.04	6.20 ± 0.14					
D2S	8.84 ± 0.05	8.86 ± 0.13	8.96 ± 0.16	7.32 ± 0.09	6.32 ± 0.15	7.0	8.4	7.8	<6	8.4
D3	9.38 ± 0.06	9.37 ± 0.29	9.32 ± 0.07	7.72 ± 0.05	6.69 ± 0.03	7.4	8.4	8.1	<6	9.1
D4	8.95 ± 0.07	8.98 ± 0.08	8.61 ± 0.07	7.01 ± 0.11	6.35 ± 0.08					
D4.7						6.9	9.0	8.4	<5	8.6
α1A	8.93 ± 0.04	8.84 ± 0.04	8.99 ± 0.06	7.56 ± 0.07	6.50 ± 0.04	7.8	9.0	8.3	<6	8.4
α2A	8.94 ± 0.05	9.07 ± 0.07	8.62 ± 0.05	7.76 ± 0.02	6.26 ± 0.03	7.1	8.2	7.7	<6	8.2
α2B	9.49 ± 0.02	9.66 ± 0.03	9.40 ± 0.11	8.64 ± 0.10	6.89 ± 0.05					
α2c	8.91 ± 0.12	8.96 ± 0.09	8.31 ± 0.02	7.43 ± 0.02	6.21 ± 0.05	7.2	8.0	7.8	<6	8.0
H1	9.00 ± 0.13	8.48 a	8.92a	7.20 a	6.48 a	7.7	8.9	8.8	<6	9.9
H2	8.21 ± 0.10	7.92 a	7.25 a	5.39 a	5.48 a					
M1	5.09 ± 0.03	5.14 ± 0.01	4.99 ± 0.12	5.08 ± 0.04	4.22 ± 0.04					
M2	4.50 ± 0.09	4.41 ± 0.09	4.48 ± 0.08	4.44 ± 0.08	4.19 ± 0.01					
M3	4.67 ± 0.03	4.81 ± 0.06	4.66 ± 0.27	4.59 ± 0.05	4.17 ± 0.01					
M4	5.04 ± 0.10	5.14 ± 0.07	5.21 ± 0.05	5.03 ± 0.08	4.43 ± 0.01					
M5	<5					<5	<5	<5	<5	<5
SERT	<5					<5	<5	<5	<5	<5
NET	<5.5					<5.5	<5	<5	<5	<5
DAT	<5					<5	<5	<5	<5	<5

Table 5 Estimated IC50s (nMol/L) for Human Receptor Binding and Transporters Based on Reported pKis

Receptor	R&DRR INT00002643					Study 00003223				
	Asenapine	(-)asenapine	(+)asenapine	N-desmethyl	N-oxide	Org 191634-0 N-sulfated- N- Desmethyl	Org 213772-0 11-OH	Org 214025-0 11-O-sulfate	Org 216761-0 N-Gluc	Org 220473-0 7-OH
5-HT1A	2.5	9.1	2.7	6.2	1,071.5	10.0	4.0	31.6		25.1
5-HT1B	4.0	1.7	2.5	199.5	35.5					
5-HT2A	0.1	0.1	0.0	2.4	6.0	25.1	0.10	0.13		0.13
5-HT2B	0.2	0.4	0.9	2.5	38.0	10.0	0.10	0.40		0.32
5-HT2c	0.03	0.1	0.0	1.9	6.0	20.0	0.13	0.40		0.13
5-HT5A	1.4									
5-HT6	0.3	0.3	0.1	13.8	85.1	20.0	0.1	0.2		0.8
5-HT7	0.1	0.1	0.2	10.5	57.5	31.6	0.2	0.3		1.6
D1	1.4									
D2L	1.3	2.0	1.9	55.0	631.0					
D2S	1.4	1.4	1.1	47.9	478.6	100.0	4.0	15.8		4.0
D3	0.4	0.4	0.5	19.1	204.2	39.8	4.0	7.9		0.8
D4	1.1	1.0	2.5	97.7	446.7					
D4.7										
α1A	1.2	1.4	1.0	27.5	316.2	15.8	1.0	5.0		4.0
α2A	1.1	0.9	2.4	17.4	549.5	79.4	6.3	20.0		6.3
α2B	0.3	0.2	0.4	2.3	128.8					
α2c	1.2	1.1	4.9	37.2	616.6	63.1	10.0	15.8		10.0
H1	1.0					20.0	1.3	1.6		0.1
H2	6.17									
M1	8,128	7,244	10,233	8,318	60,256					
M2	31,623	38,905	33,113	36,308	64,565					
M3	21,380	15,488	21,878	25,704	67,608					
M4	9,120	7,244	6,166	9,333	37,154					
M5	2.5	9.1	2.7	6.2	1,071.5	10.0	4.0	31.6		25.1
SERT	4.0	1.7	2.5	199.5	35.5					
NET	0.1	0.1	0.0	2.4	6.0	25.1	0.10	0.13		0.13
DAT	0.2	0.4	0.9	2.5	38.0	10.0	0.10	0.40		0.32

Figure 2 Asenapine Enantiomer Binding to Various Receptors by Species – Report SDGRR 4393

Table 1. Pharmacology of Org 5222 and enantiomers *in vitro*

Test	Receptor	Parameter	Org 5222	Org 10968 (-)	Org 10969 (+)
Serotonin					
5-HT binding (human receptor clone)	5-HT _{1A}	pK _i	7.1		
8-OH-DPAT binding (rat hippocampus)	5-HT _{1A}	pK _i	7.6		
8-OH-DPAT binding (human receptor clone)	5-HT _{1A}	pK _i	8.1	7.7	8.1
GTPγS binding (human receptor clone)	5-HT _{1A}	pIC ₅₀	*	7.0	*
		α	0.3	0	0.5
cAMP turnover (human receptor clone)	5-HT _{1A}	pIC ₅₀	7.1	7.0	7.2
		α	0.5	0	0.5
5-HT binding (pig striatum)	5-HT _{1D}	pK _i	7.1	7.1	7.3
5-HT release (guinea pig cortex)	5-HT _{1D}	%increase	50% at 10 ⁻⁷ mol/L		
Ketanserin binding (rat cortex)	5-HT _{2A}	pK _i	10		
Ketanserin binding (human receptor clone)	5-HT _{2A}	pK _i	10.4	10.3	10.3
PI turnover (human receptor clone)	5-HT _{2A}	pIC ₅₀	10.6	10.3	10.4
5-HT binding (pig choroid plexus)	5-HT _{2C}	pK _i	10.1	10.0	10.1
5-HT binding (human receptor clone)	5-HT _{2C}	pK _i	9.1	9.6	9.8
Mesulergine binding (human receptor clone)	5-HT _{2C}	pK _i	10.1	10.0	10.5
PI turnover (human receptor clone)	5-HT _{2C}	pIC ₅₀	8.9	8.6	8.5
* Accurate IC ₅₀ value could not be calculated due to a biphasic effect					
Dopamine					
Spiperone binding (human receptor clone)	D _{2S}	pK _i	8.8		
Spiperone binding (human receptor clone)	D _{2L}	pK _i	8.8		
Spiperone binding (human receptor clone)	D ₃	pK _i	9.1		
Spiperone binding (human receptor clone)	D ₄	pK _i	8.9		
Antagonism of quinpirole adenylyl cyclase inhibition (human receptor clone) control	D _{2L}	pIC ₅₀	6.3		
+ Org 5222	D _{2L}	pIC ₅₀	4.1		
		agonist/antagonist shift	138		
Acetylcholine					
Oxotremorine M binding (rat cortex)	M _{1,2}	pK _i	5.2		
Pirenzepine binding (rat brain)	M ₁	pK _i	4.4		
QNB binding (rat brainstem)	M _{1,2}	pK _i	6.0		

Effects of acute and chronic (21 days, b.i.d.) s.c. treatment of rats with Org 5222 on the levels of dopamine (DA) and serotonin (5-HT) and their major metabolites [3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxy-4-hydroxyphenylacetic acid (HVA) and 5-hydroxy indoleacetic acid (5-HIAA)] in the nucleus accumbens with olfactory tubercles and the caudate nucleus.

		DA	DOPAC	HVA	5-HT	5-HIAA
Acute ¹⁾	60 min	NC	increase	increase	NC	NC
	12 h	NC	increase	NC	NC	NC
Chronic ²⁾	21 days(A)	NC	NC	NC	NC	NC
	21 days(B)	NC	increase	increase	NC	NC

NC = no significant change

1) Single doses were administered 60 min or 12 h before decapitation and the subsequent determination of DA, 5-HT and their major metabolite levels in the brain areas.

2) The last injection was given 12 h (A) or 30 min (B) before decapitation and the subsequent determination of DA, 5-HT and their major metabolite levels in the brain area.

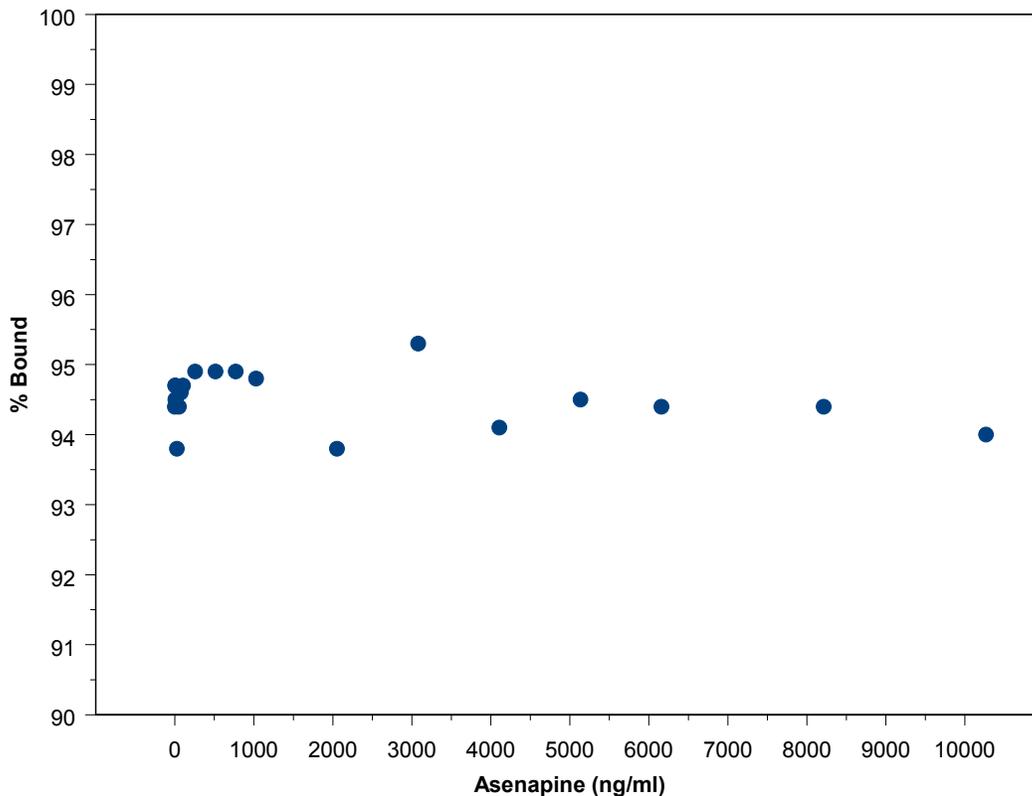
5.3.2 Protein Binding

Asenapine binding to human plasma proteins assessed by equilibrium dialysis was non-saturable over a concentration range of 1.4 to 10,268 ng/ml, with a mean free fraction of 5.5%, (see Table 6 and Figure 3).

Table 6 Asenapine Plasma Protein Binding over a Concentration Range of 1.4 to 10,268 ng/ml – Study SDGRR 2972

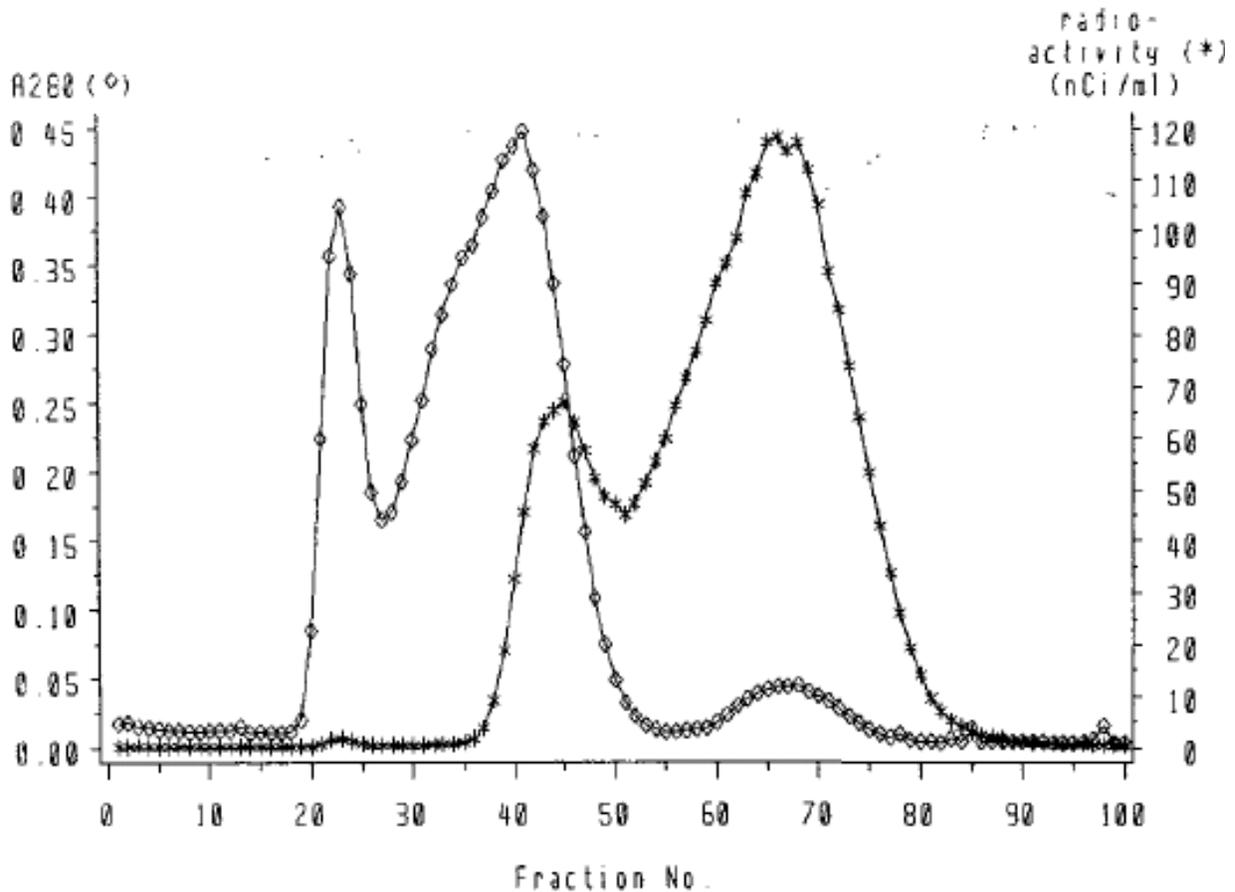
Fraction Bound fBnd (%)	Fraction Unbound fu (%)
94.5 + 0.4 (0.4)	5.5 + 0.4 (7.0)
93.8 – 95.3	4.7 – 6.2

Figure 3 Asenapine Plasma Protein Binding over a Concentration Range of 1.4 to 10,268 ng/ml – Study SDGRR 2972



The elution profile of radiolabeled [³H]-asenapine from a Sephadex G-200 column indicates that the majority of radioactivity comes off the column as unbound radioactivity whereas a small fraction comes off with a retention time similar to that of low molecular weight proteins. This indicates that asenapine is likely primarily bound to albumin, (see Figure 4).

Figure 4 Elution Profiles of Plasma Proteins (A280) and Radiolabeled [³H]-Asenapine 80 ng/ml from a Sephadex G-200 Column — Study SDGRR 2972



In two other studies, high binding (>95%) to plasma proteins was shown for asenapine, desmethyl-asenapine and asenapine 11-O-sulfate. For asenapine and desmethyl-asenapine total binding was higher in women than in men. However the binding to albumin and to AAG is much lower and these should only account for binding of around 81.5% and 53.2% of asenapine and desmethyl-asenapine respectively. Consequently, a significant fraction of the binding of these species is due to some other unidentified plasma protein, (see Table 7 - Table 9).

Thus it's unclear what changes in plasma proteins might result in changes in free fraction. Since asenapine is a high intrinsic clearance compound, changes in protein binding might result in differences in kinetics.

Table 7 Asenapine and Desmethyl-Asenapine Binding in Human Plasma by Equilibrium Dialysis over 4 hours – Study DM2005-005222-007

Conc. (ng/ml)	Fu (%)			
	Asenapine		Desmethyl-Asenapine	
	Males	Females	Males	Females
1	4.01 ± 2.01	1.66 ± 0.23	3.97 ± 2.30	2.45 ± 0.46
25	2.81 ± 1.03	1.72 ± 0.38	0.872 ± 0.111	1.84 ± 0.48
500	3.10 ± 1.30	2.07 ± 0.55	3.24 ± 4.10	1.86 ± 0.90
Average	3.28 ± 1.47	1.81 ± 0.40	2.86 ± 2.89	2.08 ± 0.65

N = 3 - 7

Table 8 Equilibrium Dialysis Plasma Protein Binding of 11-Hydroxy- Asenapine Sulfate (ORG-214025) 200 ng/mL – Study DM2006-005222-015

Species	% Free	% Bound
Human	2.88 ± 0.12 (4.05)	97.1 ± 0.12 (0.12)
	1.75 - 3.03	97.0 - 97.2
Rat	0.98 ± 0.05	99.0 ± 0.05
Rabbit	0.23 ± 0.02	99.8 ± 0.02

Table 9 Asenapine and Desmethyl-Asenapine Binding to Human Serum Albumin and α1-Acid Glycoprotein by Equilibrium Dialysis over 4 hours – Study DM2005-005222-007

Conc. (ng/ml)	Fu (%)			
	Human Serum Albumin		α1-Acid Glycoprotein	
	Asenapine	Desmethyl-Asenapine	Asenapine	Desmethyl-Asenapine
1	47.1 ± 1.9	38.3	25.4 ± 4.6	45.8 ± 5.1
25	45.8 ± 3.0	36.9 ± 3.1	18.9 ± 3.5	58.0 ± 16.2
500	45.4 ± 1.4	37.2 ± 2.9	25.2 ± 2.1	68.7 ± 14.1
Average	46.1 ± 2.1	37.3 ± 2.5	23.0 ± 4.6	57.5 ± 15.1

Table 10 Reviewer's Estimated Total Asenapine and Desmethyl-Asenapine Binding to Plasma Proteins based on Binding to HSA and AAG in Study DM2005-005222-007

Substrate	Asenapine		Desmethyl - Asenapine	
	HSA	AAG	HSA	AAG
fBnd (%)	46.1 ± 2.1	37.3 ± 2.5	23.0 ± 4.6	57.5 ± 15.1
Additional % Bound due to AAG	(100 - 46.1) * 37.3 = 20.1%		(100 - 23.0) * 57.5 = 44.1%	
Estimated Total % Bound	46.1 ± 20.1 = 60.2%		23.0 ± 44.1 = 67.1%	
Estimated Total % Free	39.8%		32.9%	

5.3.3 Binding to Red Blood Cells

Asenapine and or a metabolite binds to and sequesters in red blood cells such that the radioactivity measured in RBCs is higher than expected concentration based on passive diffusion alone. Table 11 shows the sponsor's value for the extent of binding, whereas Table 12 shows the reviewer's calculations.

Even though they differ slightly there is probably minimal to any pharmacokinetic significance, although pharmacodynamic significant is unknown.

N.B. These calculations do not account for free concentrations consequently the fraction bound is approximately 20 fold higher.

Table 11 Sponsor's Calculated *In Vitro* Binding of [³H]-Asenapine to male human erythrocytes Study R&DRR NL0029630

[³ H]-Org 5222 ^a (ng/mL)	Time (min)	Hcrit	Whole blood Radioactivity (Bq/mL)	Plasma Radioactivity (Bq/mL)	R	E
0	60	0.395	3772	5185	0.73	0.18
5		0.395	3855	5280	0.73	0.18
25		0.405	3766	5123	0.73	0.18
200		0.400	3905	5471	0.72	0.17
1000		0.400	3941	5304	0.74	0.19
10000		0.410	3814	5001	0.76	0.22
Mean ± SD (%CV)					73.5 ± 1.4 (1.9%)	18.7 ± 1.75 (9.4%)

^a Blood samples were spiked with 0, 5, 25, 200, 1000 and 10000 ng/mL unlabeled Org 5222 and 3.66 kBq/mL [³H]-Org 5222 (equivalent to 2.1 ng·mL⁻¹)

E = fraction bound to erythrocytes

R = whole blood to plasma radioactivity ratio

Table 12 Reviewer's Calculated *In Vitro* Binding of [³H]-Asenapine to male human erythrocytes Study R&DRR NL0029630

[³ H]-Org 5222 ^a (ng/mL)	Time (min)	Hcrit	1- Hcrit	Plasma Radioactivity (Bq/mL)	Expected Whole Blood Radioactivity with Passive Diffusion [Plasma Radioactivity/(1- Hcrit)]*Hcrit	Measured Whole blood Radioactivity (Bq/mL)	RBC:Plasma Ratio
0	60	0.395	0.605	5185	3137	3772	1.114
5		0.395	0.605	5280	3194	3855	1.118
25		0.405	0.595	5123	3048	3766	1.080
200		0.400	0.600	5471	3283	3905	1.071
1000		0.400	0.600	5304	3182	3941	1.114
10000		0.410	0.59	5001	2951	3814	1.097
Mean ± SD (%CV)							1.099 ± 0.02 (1.8%)

^a Blood samples were spiked with 0, 5, 25, 200, 1000 and 10000 ng/mL unlabeled Org 5222 and 3.66 kBq/mL [³H]-Org 5222 (equivalent to 2.1 ng·mL⁻¹)

E = fraction bound to erythrocytes

R = RBC to plasma radioactivity ratio

5.3.4 Cell Transport - Pgp

The sponsor reported the following results for cell transport studies with asenapine and N-desmethyl-asenapine:

'Bi-directional transport studies were performed in MDCK and MDR1-MDCK (MDR1) cells to determine the extent of P-glycoprotein (P-gp) mediated transport of [³H]- asenapine and [³H]-N-desmethyl asenapine. The bi-directional transport studies were carried out at 31.6, 100 and 316 nM of asenapine and N-desmethyl asenapine. In addition, [3H]-diazepam (1 μM), [³H]-prazosin (2 μM) and [³H]-quinidine (2 μM) were included as negative, weak positive, and moderate positive P-gp controls, respectively.

The apical to basolateral (A→B) transport of asenapine across the MDCK and MDR1 cell monolayers was characterized by mean effective permeability (Pe, ×10⁶ cm/s) values of 3.12 – 3.51, and 1.90 – 2.43, respectively, over the concentration range studied (31.6 – 316 nM). The corresponding values for N-desmethyl asenapine are 2.24 – 2.94, and 1.82 – 2.25, respectively. The efflux ratios of asenapine in MDCK and MDR1 cells ranged from 0.862 – 1.02, and 0.914 – 1.29, respectively, and the corresponding values for N-desmethyl asenapine were 0.677– 0.836, and 0.596 – 0.720, respectively.

The MDCK normalized efflux ratio of asenapine and N-desmethyl asenapine in MDR1 cells ranged from 1.02 – 1.34 and 0.767 – 1.06, respectively. The corresponding values for P-gp control substrates were 0.903, 0.982, and 2.49 for diazepam, prazosin and quinidine, respectively.' (See Table 13 and Figure 5).

These results suggest that asenapine and N-desmethyl asenapine have low to moderate effective permeability under our experimental conditions and at best are weak substrates of the human P-gp transporter. Thus, it is unlikely P-gp will have a significant impact on the in vivo disposition of asenapine and N-desmethyl asenapine.'

Due to the high binding to the cell membranes effective permeability coefficients, (Pe), are reported for asenapine and desmethyl-asenapine, whereas apparent permeability coefficients, (Papp), are reported for the control substrates.

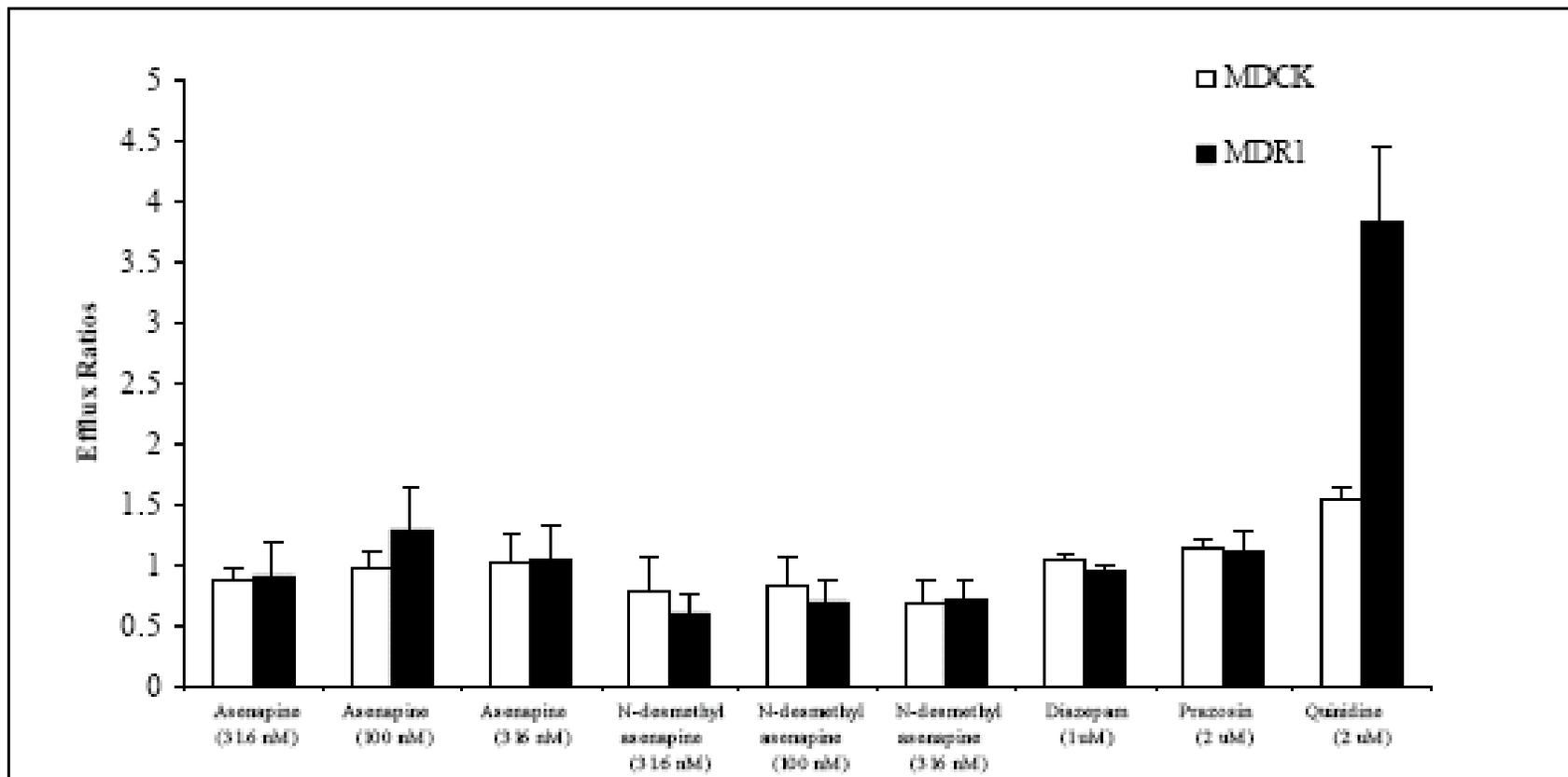
As a highly lipophilic substances these results are expected, however different results might be found for the 7- and 11- Hydroxy metabolites and especially for the sulfate and glucuronide conjugates. Also, other transporters in addition to P-gp may be involved and these other potential substrates and transporters have not been examined.

Table 13 P-gp Cell Transport of [³H] Asenapine and [³H] N-Desmethyl-Asenapine – Study DM2005-005222-008

	Substrate	Type of Control	Concentration	A → B Pe or Papp	B → A Pe or Papp	P-gp Efflux Ratios
				(cm/sec x 10 ⁶ cells)		$\frac{B \rightarrow A P_i}{A \rightarrow B P_i}$
				MDCK	MDR1	
Controls	Diazepam	Negative	1.0 μM	1.04 ± 0.04	0.939 ± 0.047	0.903
	Prazosin	Weak positive	2.0 μM	1.14 ± 0.08	1.12 ± 0.18	0.982
	Quinidine	Strong positive	2.0 μM	1.54 ± 0.11	3.83 ± 0.63	2.49
Test Substrates	Asenapine		31.6 nM	0.862 ± 0.101	0.914 ± 0.256	1.06
			100.0 nM	0.960 ± 0.152	1.29 ± 0.35	1.34
			316.0 nM	1.02 ± 0.23	1.04 ± 0.29	1.02
	N-Desmethyl asenapine		31.6 nM	0.777 ± 0.291	0.596 ± 0.160	0.767
			100.0 nM	0.836 ± 0.226	0.698 ± 0.185	0.835
			316.0 nM	0.677 ± 0.186	0.720 ± 0.158	1.06

a Mean ± SD, n = 4

Figure 5 Efflux Ratios of [³H]-Asenapine, [³H]-N-desmethyl asenapine, and [³H]-P-gp Control Substrates for MDCK and MDR1 Cells – Study DM2005-005222-008



*: Efflux ratios for asenapine and N-desmethyl asenapine were calculated using Pe due to extensive membrane retention, while Papp was used for calculating efflux ratios of diazepam, prazosin, and quinidine.

5.4 *Drug Metabolism*

5.4.1 **Overview of Human Drug Metabolism**

Come back to post briefing.

5.4.2 In Vivo Drug Metabolism

5.4.2.1 Location of Information

In vivo drug metabolism and mass balance was formally examined at steady-state in study 25532. Results were reported in the clinical trial report for study 25532, (including sub-reports) as well as the reports INT00008145 (AKA 040105) and INT00003211 (AKA 40218). The additional reports were not always cross referenced appropriately and were found by accident. The manner of reporting the information from the mass balance study was confusing as it required extensive cross checking of documents that were labeled with different report codes on the page headers. For future reference these are included in Table 14.

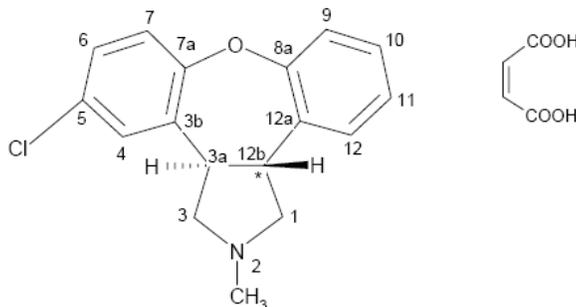
Table 14 Cross References of Reports of Differing Aspects of Mass Balance Study 25532

Study Report Code	Additional Coding inside Main Report	Report Title
25532		Open, non-randomized, single center trial to determine the excretion balance, metabolic profile and pharmacokinetics of asenapine after a sub-lingual dose of [¹⁴ C]-labeled asenapine.
	NL0057152	Bioanalysis of Asenapine, Org 30526 and Org 31437 in human plasma samples from Clinical Trial 25532
	PBR-041201	The Determination of [¹⁴ C]-Asenapine in Human Plasma, Urine and Faeces Samples Originating From a Human ADME Study With Liquid Scintillation Counting
INT00003211	040218	Profiling of a Metabolism Study with [¹⁴ C]-Labeled Asenapine in Healthy Volunteers (Additional to Clinical Trial Protocol 25532)
INT00008145	040105	Isolation and Identification of Metabolites of Asenapine (ORG 5222) in Various Types of Samples

5.4.2.2 Study Design

Study 25532 utilized a single 0.3 mg dose of ¹⁴C-Asenapine [56 μCi] administered on day 10 of asenapine administration by placing an ethanolic solution containing the radioactive dose on a 10 mg tablet of unlabeled asenapine and administering it sublingually. This resulted in a total dose of 10.3 mg in six healthy male volunteers that included three smokers and three nonsmokers. Figure 6 shows the numbering of asenapine and location of the ¹⁴C label.

Figure 6 Asenapine Numbering and Location of ¹⁴C Label



* is the place of the [¹⁴C]-label in [¹⁴C]-asenapine maleate.

Plasma was sampled through 72 hours post dose. In addition feces and urine were to be collected until >90% of the total radioactivity was recovered; although this was not done, possibly due to partial loss of the collected sample, a technical issue, or inaccurate dosing.

Subjects were also phenotyped for CYP1A2, 2C19, 2D6, and 3A4 using the cocktail shown in Table 15.

Table 15 Phenotyping Cocktail – Study 25532

CYP P450	Substrate	Dose (mg)	Measurement	Matrix
1A2	Caffeine	100	Paraxanthine / caffeine ratio at 6 h	Plasma
2C19	Mephenytoin	100	4-OH S-Mephenytoin / S-Mephenytoin excreted over 8 h	Urine
2D6	Dextromethorphan	30	Dextrophan / dextromethorphan at 4 h	Plasma
3A4	Cortisol	Endogenous	6 β -OH Cortisol / Cortisol excreted over 8 h	Urine

Results for phenotyping are stated as being reported in report INT00003211, however this reviewer was unable to find any data on phenotype.

Subject Demographics

Table 16 shows the demographics of the enrolled subjects, Subjects 5 and 6 were withdrawn from the study due to opisthotonus on day 5. It's noteworthy that these two subjects had the lower weights and thus possibly higher concentrations. Although there were supposed to be 3 smokers and 3 non-smokers, the smoker who dropped out had nicotine metabolite exposures that were inconsistent with smoking.

Table 16 Demographics of Subjects in Mass Balance Study – Study 25532

Subject	Age	Gender	Race	Height (cm)	Weight (kg)	BMI (kg/m ²)	Smoker (Yes/No)	Serum Nicotine Metabolites (ng/mL)
1	40	Male	White	177	87.6	28.0	Yes	724.0
2	23	Male	White	179	90.1	28.1	No	<10.0
3	54	Male	White	176	82.1	26.5	No	<10.0
4	33	Male	White	180	80.1	24.7	Yes	424.0
5 ^a	23	Male	White	184	69.5	20.5	No	<10.0
6 ^a	21	Male	Asian	167	62.3	22.3	Yes	<10.0
N = 4^a	38 ± 13			178 ± 1.8	85.0 ± 4.7	26.8 ± 1.6		

a Dropped out due to severe opisthotonus on day 5

b Mean ± SD of study completers

5.4.2.3 Analytic Methodology

Initially a μ -Bondapak phenyl column was used (HPLC system 1) however the metabolite profile was not reproducible on a replacement column. Consequently, a new HPLC system was developed on a μ -Bondapak C18 column (HPLC system 2). This necessitated a change in the mobile phase gradient. The two HPLC systems used are shown in Table 17.

Table 17 Comparison of HPLC Systems Used for Metabolic Profiling of Mass Balance Study 25532

System	HPLC System 1	HPLC System 2
Guard-column	μ -Bondapak phenyl	μ -Bondapak C18
Column	μ -Bondapak phenyl (internal length: 300 mm; internal diameter: 7.8 mm)	μ -Bondapak C18 (internal length: 300 mm; internal diameter: 7.8 mm; particle size: 10 μ m)
Solvents	A. 0.1 mol·L ⁻¹ Ammonium acetate buffer, adjusted to pH=4.2 with acetic acid	A. 0.1 mol·L ⁻¹ Ammonium acetate buffer, adjusted to pH=4.2 with acetic acid
	B. Methanol/ Acetonitrile (1/3 v/v %)	B. Methanol/ Acetonitrile (1/3 v/v %)
Gradient	5% B isocratic during 5 minutes	10% B isocratic during 3 minutes
	5 to 35% B in 30 minutes (linear)	10 to 40% B in 17 minutes (linear)
	35 to 90% B in 20 minutes (linear)	40 to 90% B in 30 minutes (linear)
	90 to 100% B in 1 minutes (linear)	90 to 95% B in 1 minute (linear)
	100% B isocratic during 9 minutes	95% B isocratic during 8 minutes
	100% to 5% B in 5 minutes (linear)	95 to 10% B in 1 minute (linear)
Flow	2.0 mL/min	2.0 mL/min
Temperature	50°C	50°C
LS-Flow	3.5 mL/min	3.5 mL/min
LS Cell-volume	0.5 mL	0.5 mL

System 1 and system 2 employed different HPLC numbering systems.

Metabolite numbering, except for human metabolites, was generally performed based on the retention time for each separate matrix. For human metabolites numbering for HPLC system 2 for all matrices were based on the retention times for peaks from chromatograms from all matrices. Thus the retention time of metabolite U10 is comparable with the retention time of metabolite F10. In contrast HPLC System 1 utilized a different peak numbering system.

Multiple metabolites have been identified and associated with a single or even two overlapping peaks from HPLC system 2. The identification of multiple metabolites associated with these peaks was based on further characterizations of the pooled urine and feces peak components. To do this the sponsor subjected the effluent of the initial radiochromatography (HPLC system 2) to a second HPLC-UV chromatographic process (HPLC system 3) and collected fractions of the effluent of this second chromatographic process. Fractions of effluent representing separate peaks were recombined and the metabolite(s) contained in them were identified. Although it might be possible to further identify amounts associated with these individual fractions, time constraints prevent this. See Figure 7 for an example of the HPLC fraction chromatogram of urine peak 35 (aka PC2) showing two subpeaks, U35A and U35B.

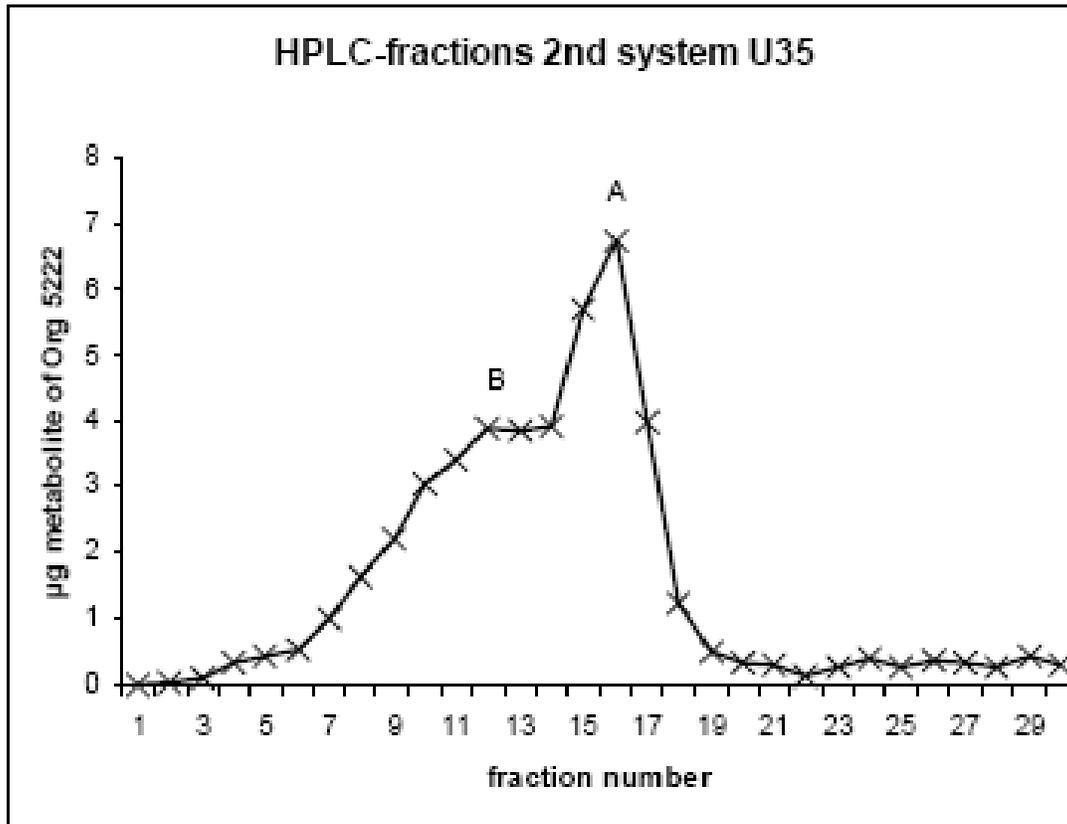
In addition, a fourth HPLC system was also utilized for radio-chromatograms, that included purification and identification of the subpeaks of HPLC system 2 but the description is confusing and will not be discussed further.

Retention times, numbering and identified metabolites associated with various peaks and HPLC systems are shown in Table 18.

Table 18 Peak Numbering Found in HPLC Chromatograms from Plasma, Urine and Feces Samples Collected after Sublingual Administration of [¹⁴C]-Asenapine – Study 25532

Nominal Description	HPLC System 2									HPLC System 1		
	Combined Peak #	Urine			Feces			Secondary Isolation (HPLC Systems 3 and 4)			Peak no.	Mean RT (minutes)
		Peak no.	Mean RT (minutes)	Relative RT	Peak no.	Mean RT (minutes)	Relative RT	Combined Peak #	Isolation codes	Mean RT (minutes)		
	PC1	U1	15.2	0.45								
N(2)-des-methyl asenapine 10-Methoxy 11-O-Glucuronide & N(2)-des-methyl asenapine 10-O-Glucuronide 11-Methoxy	PC2	U2	16.6	0.49				PC2	U35	16.6	1	24.5
	PC3	U3	17.6	0.52								
	PC4	U4	18.5	0.55								
	PC5	U5	19.3	0.57								
N(2)-des-methyl asenapine 10-methoxy 11-O-Sulfate & N(2)-des-methyl asenapine 10-O-Sulfate 11-Methoxy N-des-methyl asenapine 11-O glucuronide Asenapine-11-O-glucuronide Plus some other sulphates and glucuronides	PC6	U6	22.0	0.65				PC6	U80	22.0	4	32.1
	PC7	U7	22.7	0.68								
U8/9 contained some conjugated metabolites (sulphates and glucuronides)	PC8	U8	23.3	0.69								
	PC9	U9	23.6	0.70				PC8/9	U87	23.3/23.6	6/7	35.1/36.2
U10/11 Asenapine 11-O-Sulfate N-oxide asenapine sulphates and glucuronides F10/11 is identified as the 10, 11-dihydroxy-des-methyl asenapine and 10, 11-dihydroxy-asenapine.	PC10	U10	25.1	0.74	F10	25.1	0.75	PC10/11	U108	25.2/25.5	10	38.9
	PC11	U11	25.6	0.76	F11	25.6	0.76		P72	22.4		
U12/13 asenapine glucuronide	PC12	U12	26.8	0.80				PC12/13	F71b	24.9/25.6		
	PC13	U13	27.2	0.81	F13	27.2	0.81		U117	26.8/27.3	11	40.8
									P84 and P88	24.6/25.1/25.3		
	PC14				F14	28.4	0.85					
	PC15	U15	29.0	0.86	F15	29.0	0.86					
U16- N(2)-des-methyl asenapine glucuronide	PC16	U16	30.7	0.91	F16	30.7	0.91	PC16	U151	30.7	13	44.6
									P107 & P110	28.4/28.9		
	PC17				F17	31.4	0.93					
	PC18				F18	32.1	0.96					
F19 co-elutes with the N(2)-des-methyl of asenapine	PC19				F19	32.6	0.97	PC19	P116	29.7		
asenapine	PC20				F20	33.6	1.00	PC20	F127	33.6	15	47.5
									P115 & P120	29.7/30.6		
	PC21				F21	34.6	1.03					
11-hydroxy N-formyl asenapine	PC22				F22	35.1	1.04	PC22	F151c	35.1		
X-hydroxy N-formyl asenapine (the position of the hydroxyl group could not be assigned)	PC23				F23	36.2	1.08	PC23	F159c	36.2		

Figure 7 HPLC Fractions from HPLC System 3 associated with Urine Peak 35 (AKA PC2) from HPLC System 2 – Report 040218



5.4.2.4 Extent of Recovery of Radioactivity

Cumulative radioactivity recovery was >85% in 3 of the 4 subjects with approximately 40% of the dose recovered in feces and 50 – 60% of the dose recovered in urine. The low recovery of radioactivity in subject 3 was attributed by the sponsor as likely due to inadvertent loss of part of the urine sample. This is a reasonable possibility. Total individual and mean recoveries by route are show in Table 19, Figure 8, and Figure 9.

Table 19 Cumulative Radioactivity Recovery in Urine and Feces after Sublingual Administration of Asenapine 10 mg plus [¹⁴C]-Asenapine 0.3 mg – Study 25532

	Excreted Radioactivity (% of the Radioactive Dose)					
	Subject 1	Subject 2	Subject 3	Subject 4	Mean ± SD	Mean ± SD (excluding subject 3)
Urine	50.7	58.8	37.0	49.0	48.9 ± 9.0 37 - 59	52.8 ± 5.3
Feces	36.2	37.1	34.8	47.0	38.8 ± 5.6 35 - 47	40.1 ± 6.0
Total	86.9	95.9	71.8	96.0	87.7 ± 11.4 (72 – 96)	93.0 ± 5.2

Figure 8 Cumulative Radioactive Excretion Profile by Subject after Sublingual Administration of Asenapine 10 mg plus [¹⁴C]-Asenapine 0.3 mg – Study 25532

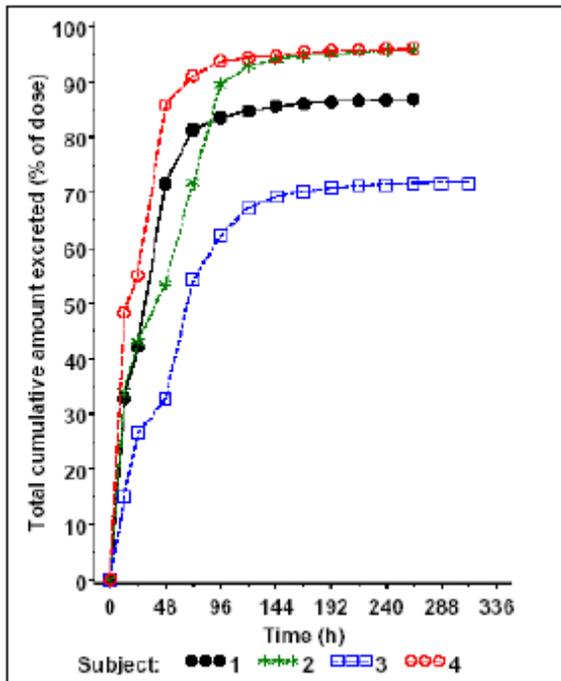
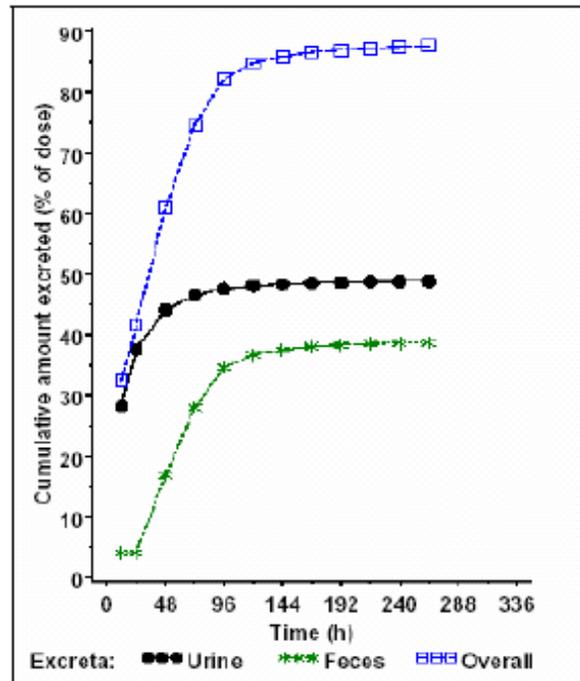


Figure 9 Cumulative Radioactive Excretion in Urine and Feces after Sublingual Administration of Asenapine 10 mg plus [¹⁴C]-Asenapine 0.3 mg – Study 25532



5.4.2.5 Plasma Metabolic Profiles

5.4.2.5.1 HPLC System 1

At first plasma samples at selected time points between 1.5 – 12 hours were analyzed per subject on HPLC system 1. These data were used to give quantitative data. Representative radiochromatograms and quantitative data are shown in Figure 10 and Table 20 respectively.

Figure 10 Radio-Chromatograms at 1.5 and 4 hours from Subjects 1 & 4 – Study 25532 / Report 040218

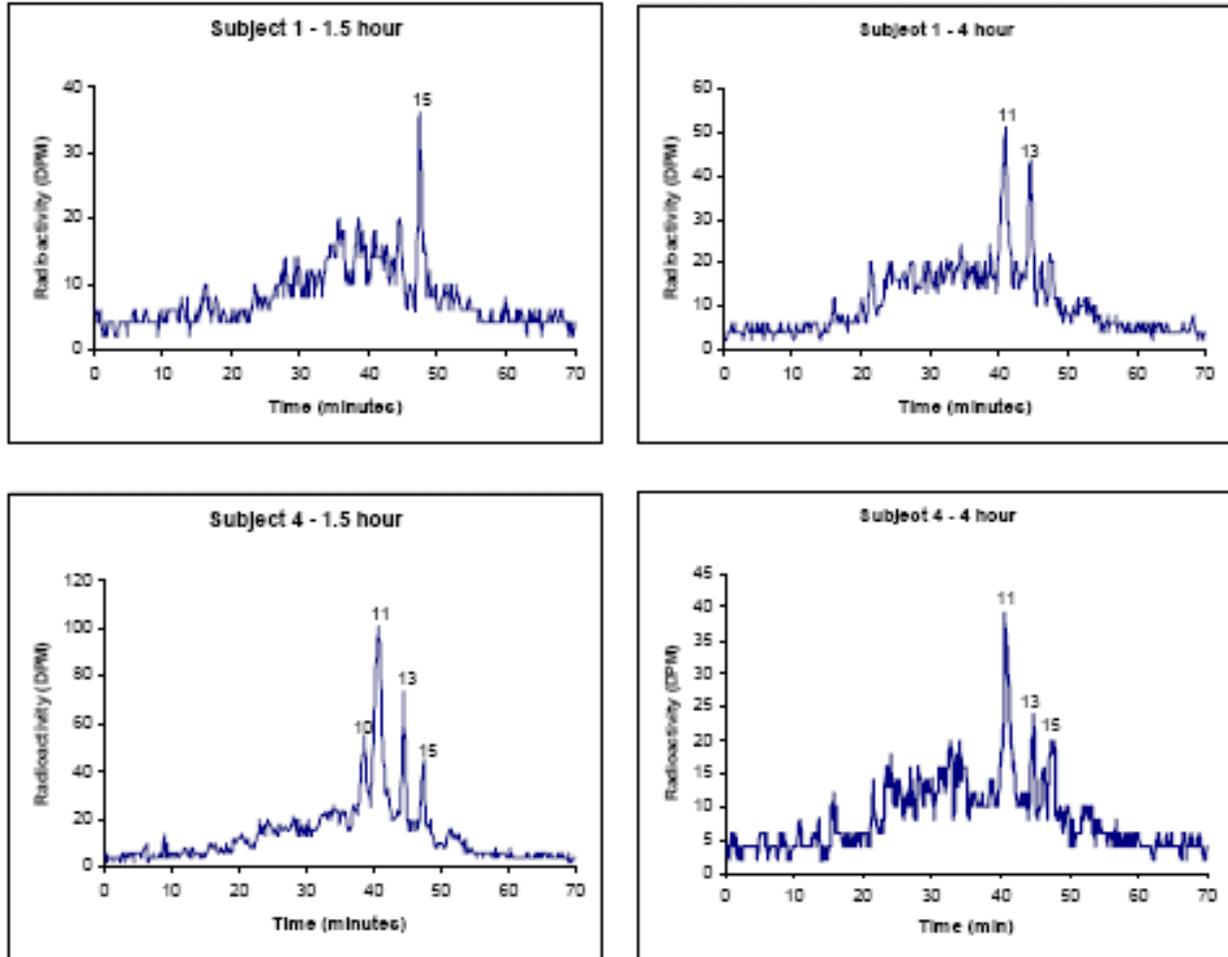


Table 20 Individual Plasma Concentrations by Time Point Detected by HPLC System 1 after Sublingual Administration of ¹⁴C-Asenapine – Study 25532 / Report 040218

Subject	Peak	Analyte Identity	RT	1.5 h	2.0 h	4.0 h	8.0 h	12.0 h
1	10	11-OH-Asenapine	38.7	—	—	—	—	—
	11	Asenapine-Glucuronide	40.8	—	—	6.3	3.5	—
	13	N-Desmethyl-Glucuronide	44.6	—	—	2.6	2.9	—
	15	Asenapine	47.5	2.2	2.2	—	—	—
2	10	11-OH-Asenapine	38.7	2.0	—	—	—	—
	11	Asenapine-Glucuronide	40.8	13.2	12.5	10.1	—	—
	13	N-Desmethyl-Glucuronide	44.6	1.9	—	—	—	—
	15	Asenapine	47.5	2.8	3.1	—	—	—
3	10	11-OH-Asenapine	38.7	—	—	—	—	—
	11	Asenapine-Glucuronide	40.8	7.6	10.7	15.9	10.5	3.4
	13	N-Desmethyl-Glucuronide	44.6	—	—	—	—	—
	15	Asenapine	47.5	3.8	—	—	—	—
4	10	11-OH-Asenapine	38.7	4.5	2.3	—	—	—
	11	Asenapine-Glucuronide	40.8	12.0	11.8	9.3	6.7	—
	13	N-Desmethyl-Glucuronide	44.6	3.8	3.0	3.3	—	—
	15	Asenapine	47.5	2.1	1.4	3.0	—	—

Figure 10 and Table 20 only show the three metabolites that the sponsor also measured by standard analytic methodologies, yet in the study reports the sponsor states that at least 9 different peaks could be identified using system 1. The sponsor then further explains that the resolution of the obtained metabolite signals of urine and feces samples obtained on HPLC system 1 was sub-optimal (see Figure 10), and the integration of the metabolite profiles was inconclusive (see Table 20).

5.4.2.5.2 LSC and Bioanalysis of Selected Metabolites

In addition to comparing radioactivity via HPLC system 1, the sponsor also compared the plasma concentrations of selected species determined by standard bioanalytic methods, (i.e. asenapine, desmethyl-asenapine, and asenapine N-oxide) to total plasma radioactivity as determined by scintillation counting.

Figure 11 shows the mean plasma concentration vs. time profile for asenapine, desmethyl-asenapine, asenapine-N-oxide, and total ¹⁴C in asenapine, ng-eq/mL. Since this study was conducted at steady-state the total radioactivity reflects the radioactivity for a single dose, whereas the concentrations of asenapine and the two metabolites can readily be seen to be superimposed on concentrations from prior dosing. Thus even though the relative exposures to asenapine and the metabolites are at best only a few % of the exposure to all species just based on the relative concentrations, if corrected for superpositioning the relative exposures would be even lower and the amount of unidentified species would account for nearly all of the circulating radioactivity. In addition, asenapine was administered at a dose of 10 mg, whereas the radioactive dose was less than 0.3 mg, yet the peak asenapine concentration is around 10 ng/mL, which is what we expect from a 10 mg dose. Thus it appears that the relative exposures for asenapine the metabolites and the radioactivity were not corrected for the disparate doses.

Figure 11 Mean Plasma concentration-versus-time curves – Study 25532

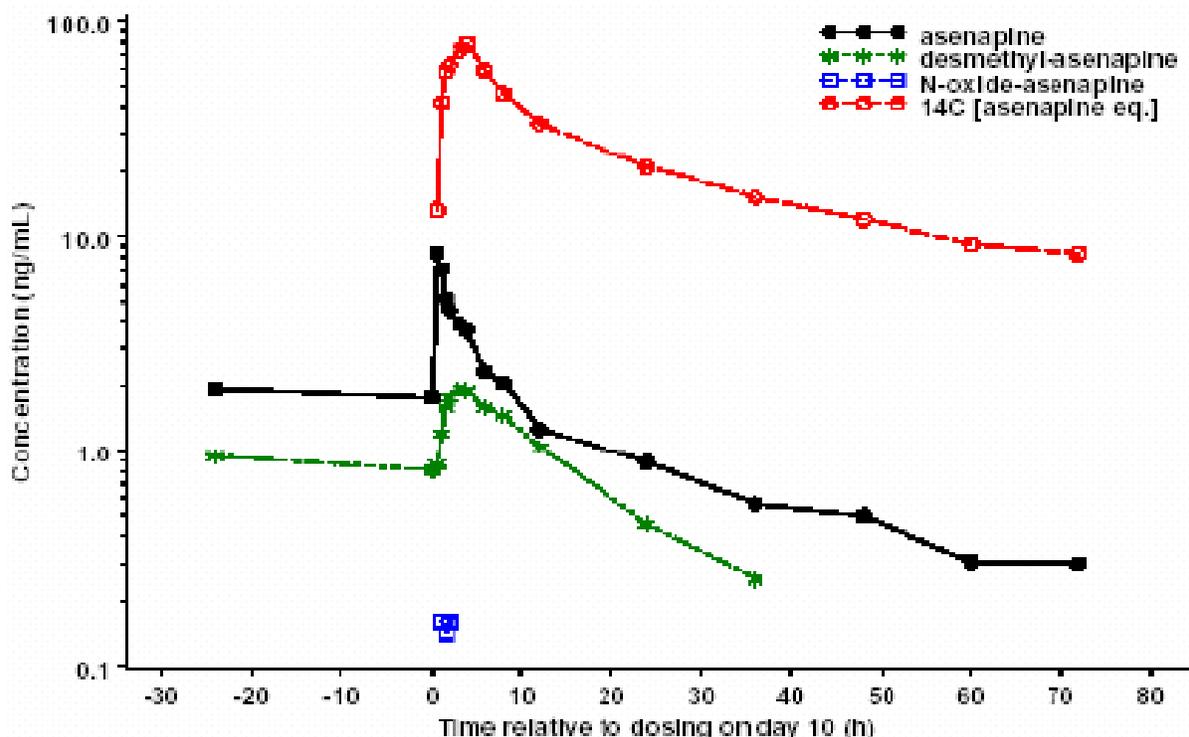


Table 21 shows the concentration vs. time data for total radioactivity both in terms of raw data and dose normalized, and the raw data for asenapine, desmethyl-asenapine, and asenapine N-oxide. When dose normalized radioactive C_{max} is compared to the C_{max} of asenapine the total radioactivity is 223 – 552 fold higher, (i.e. 3145/14.1 and 3008/5.44).

In addition when appropriate dose normalized AUCs are compared the unidentified radioactivity is clearly even larger with 99.9% of the circulating radioactivity unidentified. The pharm/tox reviewer was advised of this a few days after the midcycle meeting held at the end of January 2008.

Table 21 Plasma Concentration vs. Time Data for Total Radioactivity, Asenapine, Desmethyl-Asenapine, and Asenapine N-Oxide – Study 25532

Day	Normalized Dose	Subject	10										11		12		13
			0	0.5	1	1.5	2	3	4	6	8	12	24	36	48	60	72
¹⁴ C [asenapine equivalents] (ng/mL)*	(0.3 mg)	1	0	6.67	13.7	23.6	39.8	65.7	69.7	60.7	46.9	36.1	22.9	16.2	10.9	9.01	7.02
		2	0	19.6	53.8	64.7	64.2	61.7	64.7	43.7	31	27	16.2	13	10.2	7.27	8.36
		3	0	15.1	45.2	75.2	77.7	84.6	91.6	77.2	62.2	40.9	24.6	18.1	16.2	13.5	11.3
		4	0	11.7	55.7	69.2	68.7	77.2	87.6	55.3	44.9	30.5	20	13.3	10.7	7.02	6.67
Dose Normalized ¹⁴ C [asenapine equivalents] (ng/mL)* (DN to 10.3 mg)		1	0	229	470	810	1366	2256	2393	2084	1610	1239	786	556	374	309	241
		2	0	673	1847	2221	2204	2118	2221	1500	1064	927	556	446	350	250	287
		3	0	518	1552	2582	2668	2905	3145	2651	2136	1404	845	621	556	464	388
		4	0	402	1912	2376	2359	2651	3008	1899	1542	1047	687	457	367	241	229
Asenapine (ng/mL) 10.3 mg		1	1.29	7.16	7.24	4.49	4.35	3.48	3.37	2.14	1.77	1.09	0.629	0.398	0.365	0.173	0.246
		2	1.24	6.82	6.07	4.5	3.55	2.99	2.67	1.61	1.39	0.881	0.657	0.374	0.348	0.234	0.187
		3	2.55	14.1	9.5	6.92	5.39	4.77	4.49	3.15	3.01	1.9	1.33	1.06	0.853	0.617	0.524
		4	2.06	5.23	5.44	4.71	4.54	4.3	4	2.48	2.14	1.21	0.922	0.425	0.424	0.197	0.246
Desmethyl- asenapine (ng/mL)		1	0.435	0.459	0.567	0.639	0.859	1.37	1.58	1.24	1.14	0.787	0.304	0.144	0	0	0
		2	0.363	0.412	1.01	1.43	1.51	1.34	1.28	1.39	1.08	0.811	0.305	0.207	0	0	0
		3	1.66	1.75	1.97	2.65	3.05	3.15	2.75	2.31	2.26	1.58	0.784	0.398	0.287	0.204	0.122
		4	0.782	0.842	1.3	1.71	1.72	1.95	2.05	1.49	1.42	1.01	0.434	0.27	0	0	0
Asenapine N-oxide (ng/mL)		1	0	0	0.137	0	0.135	0	0	0	0	0	0	0	0	0	0
		2	0	0.247	0.217	0.12	0.171	0.133	0	0	0.117	0	0	0	0	0	0
		3	0	0.256	0.233	0.189	0.191	0	0.174	0	0	0	0	0	0	0	0
		4	0	0	0	0.205	0.129	0.175	0.174	0	0	0	0	0	0	0	0

Table 22 Plasma Exposures to Asenapine and Selected Metabolites Relative to Total ¹⁴C Radioactivity after Asenapine 10 mg and 0.3 mg ¹⁴C-Asenapine at Steady-State - Study 25532

Dose		10.3 mg			0.3 mg	10.3 mg	
Metric	Subject	Asenapine	Desmethyl – Asenapine	Asenapine N–oxide	¹⁴ C [asenapine equivalents]	Dose Normalized ¹⁴ C [asenapine equivalents]	% extrap
AUC_τ^a (ng/mL x hr ⁻¹)	1	33.3	12.8	0.2	1523.2	52297	11.5
	2	27.8	13.6	0.9	1282.6	44036	25.6
	3	50.6	27.7	0.7	1952.8	67046	16.5
	4	35.7	17.7	0.6	1470.0	50470	8.5
Fraction of ¹⁴C (%)	1	2.2	0.8	0.01	–	–	–
	2	2.2	1.1	0.07	–	–	–
	3	2.6	1.4	0.04	–	–	–
	4	2.4	1.2	0.04	–	–	–
	Mean ^b	2.3	1.1	0.04	–	–	–
Fraction of Dose Normalized ¹⁴C (%)	1	0.06	0.02	0.000	–	–	–
	2	0.06	0.03	0.002	–	–	–
	3	0.08	0.04	0.001	–	–	–
	4	0.07	0.04	0.001	–	–	–
	Mean ^c	0.067	0.032	0.001	–	–	–

a AUC_∞ for ¹⁴C. N.B. AUC_∞ used because it's a single dose.

b Mean = 3.44 (i.e. minimum without dose normalization 96.6% unidentified)

c Mean = 0.102 (i.e. 99.9% unidentified)

Pharmacokinetic metrics as reported by the sponsor are shown in Table 23. Total ¹⁴C is elimination rate limited however what's most interesting is that the elimination of desmethyl-asenapine appears to be more rapid than asenapine which should not be. The reason for this is unclear.

Table 23 Reported Pharmacokinetic Metrics of Selected Species - Study 25532

Metric (unit)	¹⁴ C [asenapine equivalents]	Asenapine	Desmethyl-asenapine	Asenapine N-Oxide
Tmax (h)	4.00 (1.50-4.00)	0.75 (0.50-1.00)	3.50 (2.00-4.00)	0.75 (0.50-1.50)
Cmax (ng/mL)	78.4 (13.2)	8.40 (3.88)	2.07 (0.757)	0.211 (0.0543)
AUC ₀₋₁₂ (ng /mL x hr ⁻¹)	n.a.	36.9 (9.72)	17.9 (6.87)	n.c.
AUC _{tlast} (ng /mL x hr ⁻¹)	1557 (284)	n.a.	n.a.	n.a.
AUC _∞ (ng /mL x hr ⁻¹)	2020 (467)	n.a.	n.a.	n.a.
Cl _{app} (L/h)	n.a.	293 (68.9)	n.a.	n.a.
V _{z,app} (L)	n.a.	11371 (2096)	n.a.	n.a.
t _{1/2} (h)	39.3 (7.55)	27.5 (4.97)	12.9 (4.46)	n.c.

Presented are median (minimum-maximum) for T_{max}; arithmetic mean (SD) for other PK parameters.

#: n=4; n.a.: Not applicable; n.c.: Not calculated.

Source Appendix BI, Table 5-3. Study Report 25532

5.4.2.5.3 HPLC System 2

Later the plasma from the 1 hour sample and from the remaining plasma from all of the plasma samples from 1.5 – 12 hours from all four subjects was pooled. Both pooled plasma samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively (i.e. the sponsor does not report the volumes) and therefore these chromatograms were only evaluated by the sponsor in a qualitative way.

In spite of this it should still be possible to infer approximate exposures to various metabolites since the samples are pooled over time.

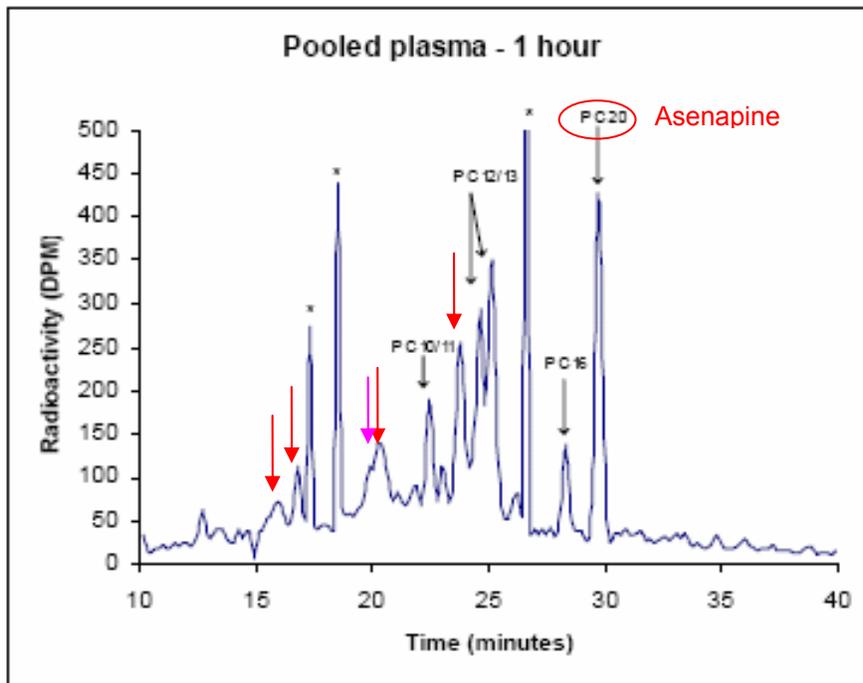
Figure 12 shows the pooled plasma chromatograms from the 1 hour sample and the combined 1.5 – 12 hour samples. The sponsor only labels asenapine and 4 metabolites as being of interest, (i.e. peaks labeled PC#), it's clear that the areas under the peaks identified by this reviewer with red arrows are nearly as great the peak area for asenapine in the pooled 1.5 to 12 hour sample.

Examination of the scale used for the peak heights used for the two different chromatograms reveal that the area under the smaller peaks in the 1.5 to 12 hour sample may be as great as the areas under peaks that appear visually taller in the 1 hour sample. In addition, since asenapine is declining yet radioactivity in plasma continues past 72 hours post dose the relative exposures to these metabolites may be even higher yet.

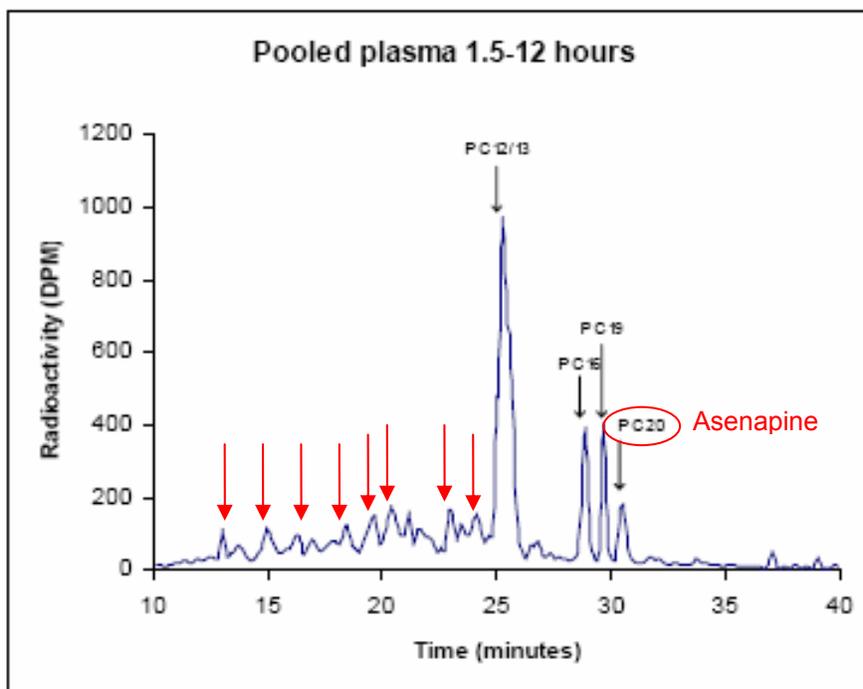
Although the sponsor claims that peaks identified in the 1 hour plasma sample with asterixes are not related to asenapine this seems suspect as they are so tall and the mode of detection is radioactivity. Consequently they should not only be due to the ^{14}C that was incorporated into asenapine. It's possible that their lack of detection in later samples may be secondary to their being formed by CYP2D6, which appears to be mechanistically inactivated by N-desmethyl-asenapine, and their subsequent rapid elimination.

In conclusion it appears that there may be a dozen or more unidentified metabolites circulating in plasma for which the plasma exposure is greater than 10% of the exposure to asenapine. Consequently, a large number of unidentified metabolites may still need to be qualified. The pharm/tox reviewer was also advised of this a few days after the midcycle meeting held at the end of January 2008.

Figure 12 Representative HPLC Metabolite Profiles (HPLC system 2) of Pooled Plasma Samples of Male Human Volunteers after Sublingual Asenapine plus [¹⁴C]-Asenapine – Study Report 40218



* These spikes are based on LC-MS analysis not related to asenapine.



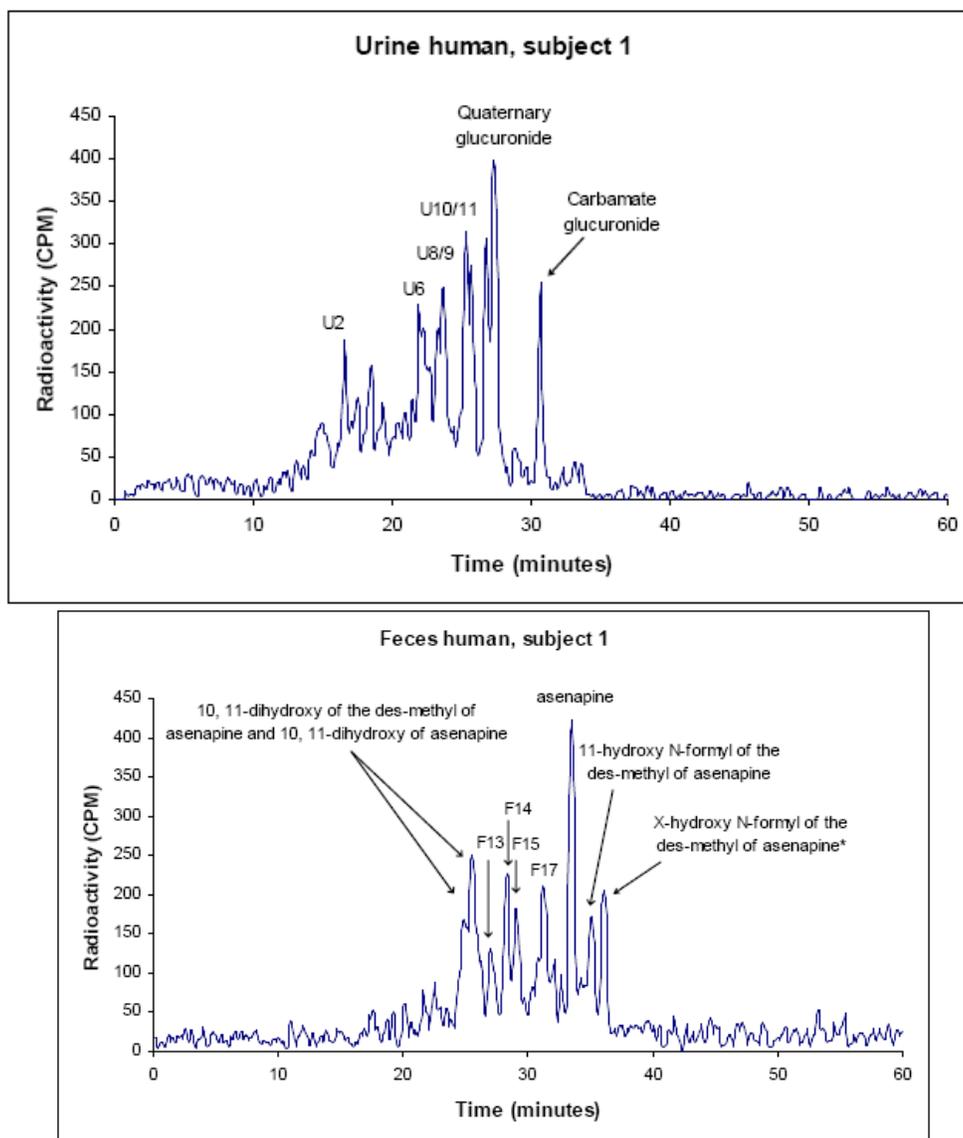
Peak PC10/11 contains at least the sulfate of the 11-hydroxy of asenapine
 Peak PC12/13 are identified as the quaternary glucuronide of asenapine
 Peak PC16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine
 Peak PC19 is identified as the N(2)-des-methyl of asenapine
 Peak PC20 is identified as asenapine

5.4.2.6 Recovery in Urine and Feces, Metabolic Scheme, & Mass Balance

5.4.2.6.1 Metabolites Identified in Urine and Feces

Figure 13 shows 'representative' HPLC system 2 metabolite profiles with separate urine and feces numbering of pooled urine and feces samples collected after sublingual administration of [¹⁴C]-Asenapine to a healthy male volunteer in study 25532. Figure 14 on the following page shows 'representative' chromatograms of urine metabolites with HPLC system 2 for all subjects. The collection interval for these urine samples were not described, thus the sponsor's description as 'representative'. Yet it's clear that more than 20 potential peaks are visible yet the peak for asenapine (PC20) is not identifiable.

Figure 13 Representative HPLC Metabolite Profiles (HPLC system 2) of Urine and Feces Samples Collected after Sublingual Administration of [¹⁴C]-Asenapine to a Healthy Male Volunteer



U2 is identified as the methoxy and glucuronide of the 10, 11-dihydroxy of the N-des-methyl of asenapine in which the position of the methoxy and glucuronide is 10, 11 and the reverse.

U6 is identified as the methoxy and sulphate of the 10, 11-dihydroxy of the N-des-methyl of asenapine in which the position of the methoxy and sulphate is 10, 11 or the reverse, the glucuronide of the 11-hydroxy of N-des-methyl of asenapine, the glucuronide of the 11-hydroxy of asenapine plus some other conjugated metabolites (sulphates and glucuronides).

U8/9 contained some conjugated metabolites (sulphates and glucuronides)

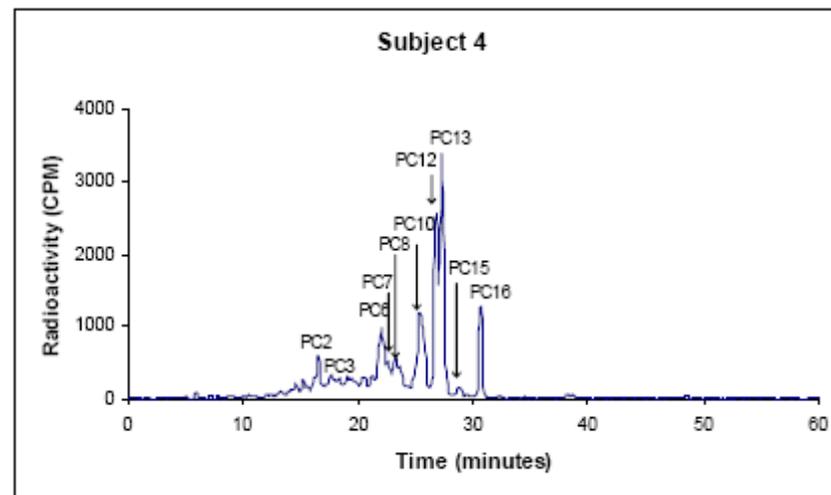
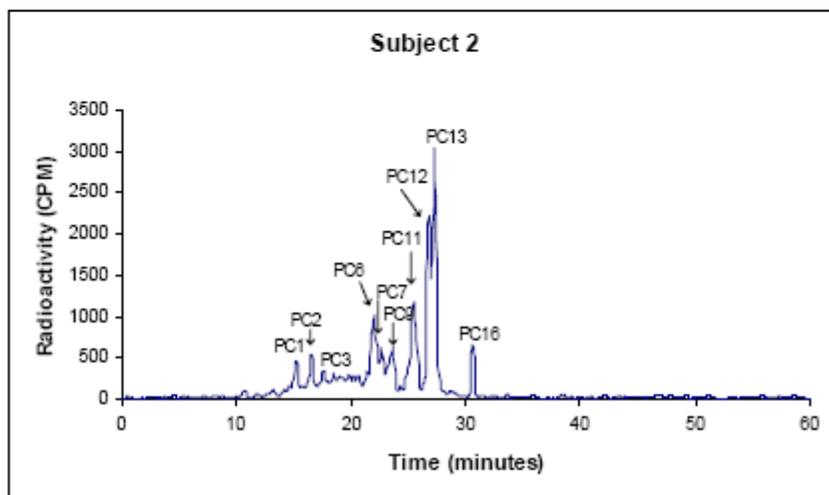
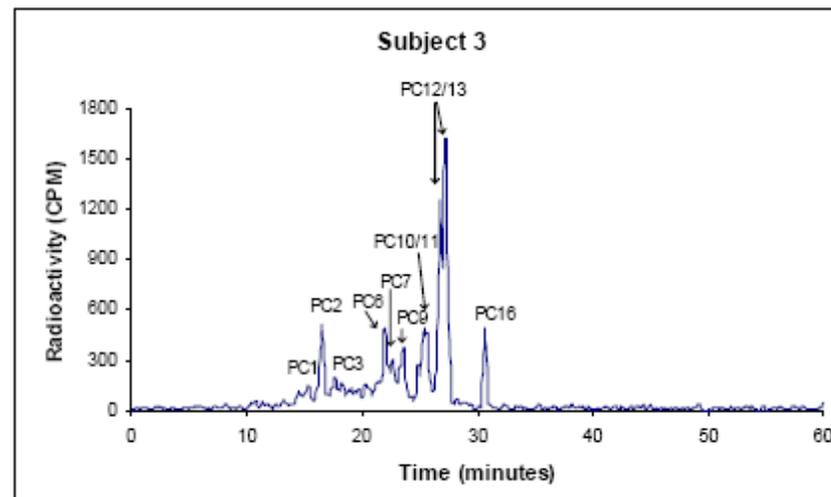
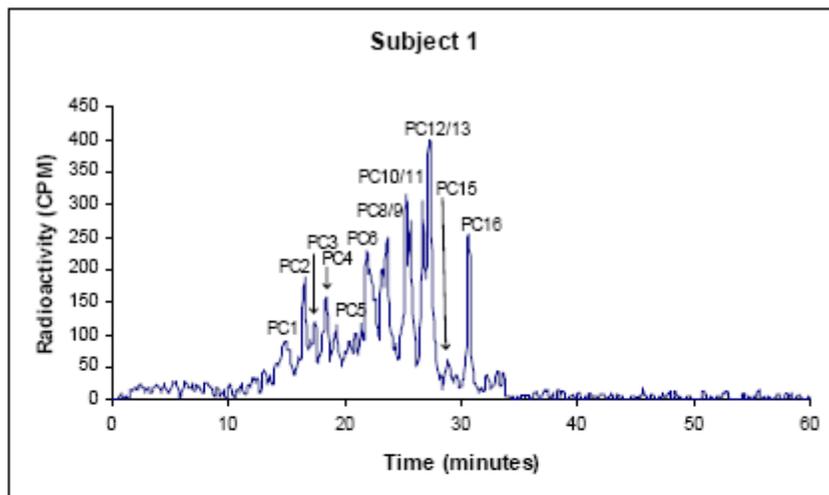
U10/11 is identified as the sulphate of the 11-hydroxy of asenapine plus some other conjugated metabolites (sulphates and glucuronides) of most probably the N-oxide of asenapine.

U12/13 is identified as the quaternary glucuronide of asenapine.

U16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine.

* the position of the hydroxyl group could not be assigned but it might be the 6-hydroxy

Figure 14 Representative HPLC Metabolite Profiles (HPLC System 2) of Pooled Urine Samples after Sublingual Administration of Radiolabeled and Unlabeled Asenapine – Study 25532



PC2 is identified as the methoxy and glucuronide of the 10, 11-dihydroxy of the N(2)-des-methyl of asenapine in which the position of the methoxy and glucuronide is 10, 11 and the reverse.

PC6 is identified as the methoxy and sulfate of the 10, 11-dihydroxy of the N(2)-des-methyl of asenapine in which the position of the methoxy and sulfate is 10, 11 or the reverse, the glucuronide of the 11-hydroxy of N(2)-des-methyl of asenapine, the glucuronide of the 11-hydroxy of asenapine plus some other conjugated metabolites (sulfates and glucuronides).

PC8/9 contained some conjugated metabolites (sulfates and glucuronides)

PC10/11 is identified as the sulfate of the 11-hydroxy of asenapine plus some other conjugated metabolites (sulfates and glucuronides) of most probably the N(2)-oxide of asenapine.

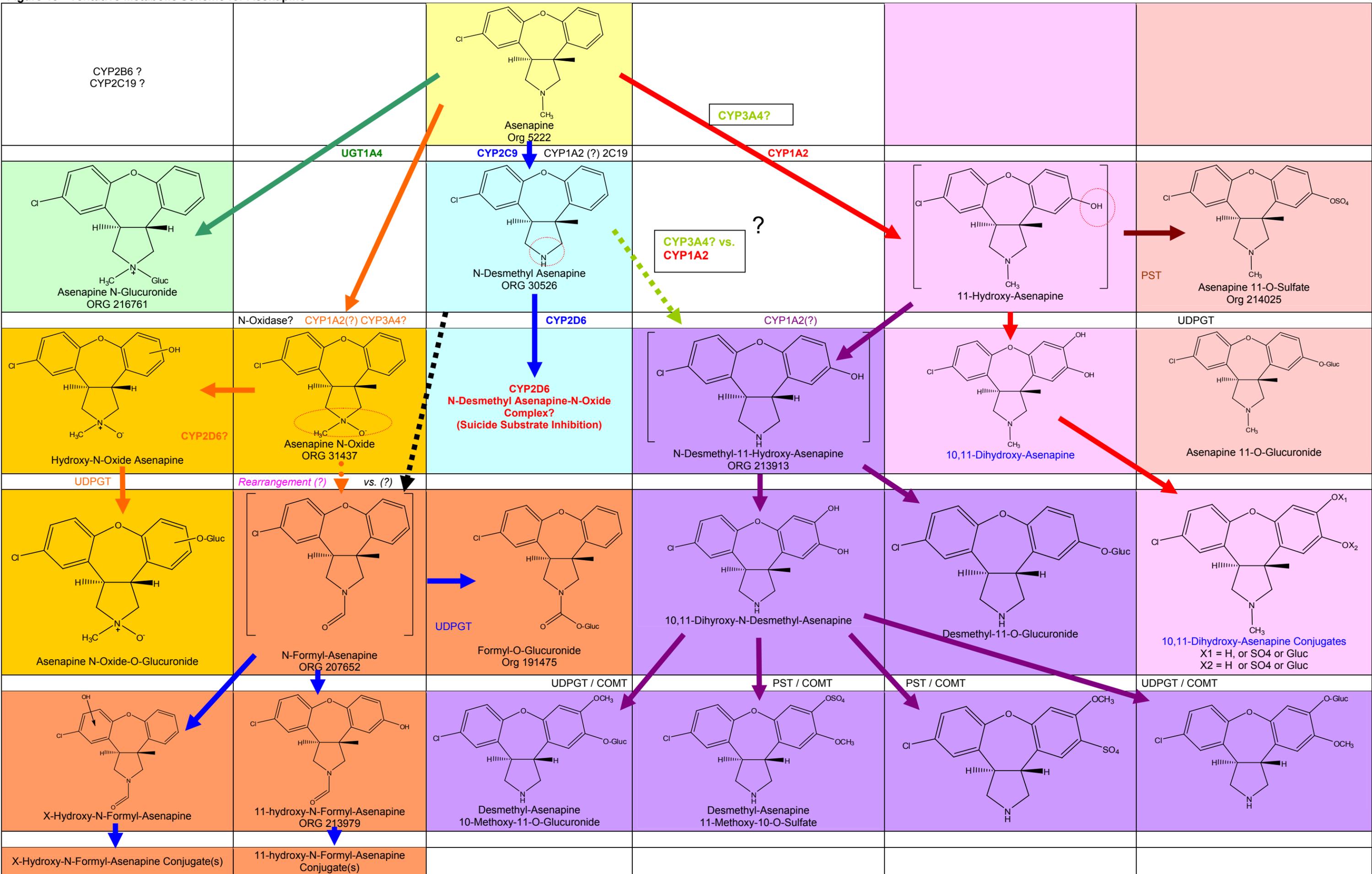
PC12/13 is identified as the quaternary glucuronide of asenapine.

PC16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine.

5.4.2.6.2 Metabolic Scheme (Tentative)

Figure 15 on the next page shows a tentative metabolic scheme. This scheme is based on the sponsor's more limited proposed scheme with the addition of metabolites only identified nominally by the sponsor, and with the addition of metabolites that can be inferred based on the available data. The scheme is only tentative as the data provided by the sponsor on certain secondary, tertiary and even lower level pathways cannot be identified with certainty. More importantly the enzymes or specific isozymes involved frequently cannot be identified. Consequently, pathways for which the enzymes or isozymes are relatively certain have been identified with bolded text.

Figure 15 Tentative Metabolic Scheme for Asenapine



5.4.2.6.3 Mass Balance

Table 25 on the following page shows the recovery of the radioactive dose by identified peak and by patient in both urine and feces, i.e. the reported mass balance.

Table 24 below summarizes the recovery of the radioactive dose reported in Table 25 and compares it to that reported by the sponsor. At least part of the discrepancy may be due to the radioactive peaks shown in Figure 12 that the sponsor claims was not associated with asenapine or any metabolites.

Table 24 % of Radioactive Dose Recovered in Urine and Feces as Determined from Individual Peaks and as Reported by the Sponsor

Reference	Description	Urine	Feces	Urine and Feces
Table 25	Tally from Mass Balance Data provided by Sponsor	43% 33% - 52%	32% 30 - 40%	75% 59% - 83%
Table 19	Recovery of Radioactivity as Reported by Sponsor	48.9% 37% - 59%	38.8% 35% - 47%	87.7% (72% - 96%)

Table 26 attempts to figure out relative contributions to the elimination of asenapine from each of the four primary metabolic pathways and shows only one possibility.

When the fraction of the dose that was not recovered, not accounted for, or not identified is totaled the fate of 37% - 56% (average 45%) of the dose is unknown.

Since multiple metabolites were identified for each peak, (see Table 25), and since the metabolic scheme is uncertain, (see Figure 15), except for direct glucuronidation by UGT1A4 which accounts for 12% - 21% of the dose and elimination of unchanged asenapine which accounts for 5% - 16% of the dose, the relative contribution of the 3 primary oxidative pathways cannot be definitively assigned. Thus the primary elimination pathways and enzymes have not been identified for 64.5% - 82.8% of the dose.

Table 25 Mass Balance Recovery of the Radioactive Dose by Identified Peak (HPLC System 2) for each Subject in both Urine and Feces – Study 25532

Peak No.	RT (min)	% of Radioactive Dose Recovered in Urine				% of Radioactive Dose Recovered in Feces				Nominal Description	% of Radioactive Dose Recovered in Urine & Feces			
		Subj 1	Subj 2	Subj 3	Subj 4	Subj 1	Subj 2	Subj 3	Subj 4		Subj 1	Subj 2	Subj 3	Subj 4
PC1	15.2	2.71	2.29	1.19							2.71	2.29	1.19	0
PC2	16.6	2.51	2.7	2.8	2.61					N(2)-des-methyl asenapine 10-Methoxy 11-O-Glucuronide & N(2)-des-methyl asenapine 10-O-Glucuronide 11-Methoxy	2.51	2.7	2.8	2.61
PC3	17.6	1.53	1.93	1.14	1.67						1.53	1.93	1.14	1.67
PC4	18.5	2.85									2.85	0	0	0
PC5	19.3	2.35									2.35	0	0	0
PC6/7	22	6.17	6.01	2.76	3.95					N(2)-des-methyl asenapine 10-methoxy 11-O-Sulfate & N(2)-des-methyl asenapine 10-O-Sulfate 11-Methoxy N-des-methyl asenapine 11-O glucuronide Asenapine-11-O-glucuronide Plus some other sulfates and glucuronides	6.17	6.01	2.76	3.95
PC7	22.7		2.35	1.56	1.86						0	2.35	1.56	1.86
PC8	23.3	2			3.1					U8/9 contained some conjugated metabolites (sulphates and glucuronides)	2	0	0	3.1
PC9	23.6	3.92	4.34	2.83							3.92	4.34	2.83	0
PC10	25.1	4.53		1.27	6.9	2.83	3.33	2.35	2.95	U10/11 Asenapine 11-O-Sulfate N-oxide asenapine sulphates and glucuronides	7.36	3.33	3.62	9.85
PC11	25.6	3.24	8.44	3.62		4.5	6.77	4.46	2.8	F10/11 10, 11-dihydroxy-des-methyl asenapine and 10, 11-dihydroxy-asenapine.	7.74	15.21	8.08	2.8
PC12	26.8	3.88	9.36	5.99	7.43					asenapine glucuronide	3.88	9.36	5.99	7.43
PC13	27.2	6.34	11.97	7.51	9.79	2.17			2.12	asenapine glucuronide	8.51	11.97	7.51	11.91
PC14	28.4					2.87	1.42	2.32	2.5		2.87	1.42	2.32	2.5
PC15	29	1.12			0.73	2.43	3.12	1.85	4.29		3.55	3.12	1.85	5.02
PC16	30.7	3.13	2.42	2.02	3.16			0.77		U16- N(2)-des-methyl asenapine glucuronide	3.13	2.42	2.79	3.16
PC17						3.79	4.05	2.6	2.81		3.79	4.05	2.6	2.81
PC18						1.13					1.13	0	0	0
PC19						0.92	1.65			N-desmethyl-asenapine	0.92	1.65	0	0
PC20						4.79	5.97	7.62	16.2	Asenapine	4.79	5.97	7.62	16.2
PC21							1.17	1.1	1.59		0	1.17	1.1	1.59
PC22						1.97	1.44	1.51	2.31	11-hydroxy N formyl N-desmethyl	1.97	1.44	1.51	2.31
PC23						2.7	1.88	1.71	2.82	X-hydroxy N-formyl of N-desmethyl	2.7	1.88	1.71	2.82
Cumulative Recovery (% of ¹⁴C Dose)		46.3	51.8	32.7	41.2	30.1	30.8	26.3	40.4		76.4	82.6	59.0	81.6

Table 26 One Possibility for Relative Contributions by Primary Pathways to Mass Balance

Peak No.	Description	Subj 1	Subj 2	Subj 4	Subj 4
11 Hydroxylaton (CYP1A2)					
PC2	N(2)-des-methyl asenapine 10-Methoxy 11-O-Glucuronide & N(2)-des-methyl asenapine 10-O-Glucuronide 11-Methoxy	2.51	2.7	2.8	2.61
PC6	N(2)-des-methyl asenapine 10-methoxy 11-O-Sulfate & N(2)-des-methyl asenapine 10-O-Sulfate 11-Methoxy N-des-methyl asenapine 11-O glucuronide Asenapine-11-O-glucuronide Plus some other sulphates and glucuronides	6.17	6.01	2.76	3.95
PC10	Asenapine 11-O-Sulfate	7.36	3.33	3.62	9.85
PC11	N-oxide asenapine sulfates and glucuronides 10, 11-dihydroxy-des-methyl asenapine and 10, 11-dihydroxy-asenapine.	7.74	15.21	8.08	2.8
Subtotal		23.78	27.25	17.26	19.21
N-Demethylation ?					
PC22	11-hydroxy N formyl N-desmethyl asenapine	1.97	1.44	1.51	2.31
PC23	X-hydroxy N-formyl of N-desmethyl asenapine	2.7	1.88	1.71	2.82
PC19	N-desmethyl-asenapine	0.92	1.65	0	0
PC16	N(2)-des-methyl asenapine glucuronide	3.13	2.42	2.79	3.16
Subtotal	N.B. it's uncertain if formyl metabolites should be included under N-Demethylation or not. Or alternatively under N-oxidation or even another pathway.	8.72	7.39	6.01	8.29
quaternary glucuronide of asenapine UGT1A4					
PC12	asenapine. glucuronide	3.88	9.36	5.99	7.43
PC13	asenapine. glucuronide	8.51	11.97	7.51	11.91
Subtotal		12.39	21.33	13.5	19.34
Unidentified					
PC1		2.71	2.29	1.19	0
PC3		1.53	1.93	1.14	1.67
PC4		2.85	0	0	0
PC5		2.35	0	0	0
PC7		0	2.35	1.56	1.86
PC14		2.87	1.42	2.32	2.5
PC15		3.55	3.12	1.85	5.02
PC17		3.79	4.05	2.6	2.81
PC18		1.13	0	0	0
PC21		0	1.17	1.1	1.59
Subtotal		20.78	16.33	11.76	15.45
Unidentified Sulfate and Glucuronide Conjugates					
PC8	some conjugated metabolites (sulfates and glucuronides)	2	0	0	3.1
PC9	some conjugated metabolites (sulfates and glucuronides)	3.92	4.34	2.83	0
Subtotal		5.92	4.34	2.83	3.1
PC20	Asenapine	4.79	5.97	7.62	16.2
Total Recovery from Individual Peaks		76.38	82.61	58.98	81.59
	<i>Identified</i>	<i>49.68</i>	<i>61.94</i>	<i>44.39</i>	<i>63.04</i>
	Unidentified	26.7	20.67	14.59	18.55
	Not Accounted For in report of Urine and Feces Recovery	23.62	17.39	41.02	18.41
Total Recovery per Sponsor		86.9	95.9	71.8	96.0
	Not Recovered	13.1	4.1	28.2	4.0
Difference between amount reported as not recovered by sponsor and amount not accountable for in report of urine and feces recovery		10.52	13.29	12.82	14.41
Unidentified, Unaccounted, and Not Recovered (Average)		50.32	38.06	55.61	36.96
		(45.2%)			

5.4.3 In Vitro Drug Metabolism Studies

5.4.3.1 Hepatocytes

Metabolism in isolated human hepatocytes will be discussed first as the intact cells provides the best information on the overall metabolic profile as they include cytosolic enzymes in addition to microsomal enzymes. However it should be remembered that a hepatocyte system lacks the anatomical structure found *in vivo* and thus may not be accurate in terms of relative abundance of each metabolite or the importance of various metabolic pathways.

5.4.3.1.1 Study 5067 (1997) - AKA NCL Study

Study 5067 conducted in 1997 incubated [³H]-Asenapine labeled at the 11 position, (see Figure 16), at a concentration of 149 ng/mL (521.4 nMol/L) for 3 hours with isolated human hepatocytes from a 41 yo female.

Results are shown in Table 27. Recoveries were reported for both the cell medium as well as the cell extract, unfortunately the relative amounts in the cell extract compared with the cell medium were not reported so only tentative conclusions may be drawn. The following tentative conclusions are made based upon the relative retention times:

Peach Table Cells – greater amount found in cell medium and also eluting earlier, thereby indicating greater hydrophylicity and possible active secretion.

Yellow Table Cells - approximately equal amounts found in cell medium and cell extract possibly indicating passive diffusion.

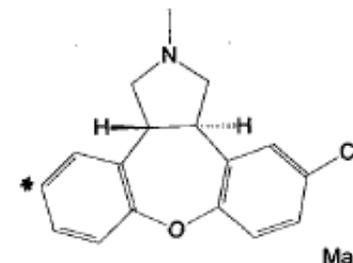
Light Blue Table Cells - greater proportion found in cell extract indicating possible binding to cellular components or greater lipophilicity.

Table 27 Percent Radioactive Recovery by Peak after Asenapine Incubation with Human Hepatocytes at 521 nMol – Study 5067 (1997)

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13 & H14	H15	Asenapine	H16
	Unknown												N-Oxides	Desmethyl Asenapine		Unknown
Cell Medium	37.7	9.3	3.2	12.5			2.8	6.9	11.9	1.1			9.1	4.0	1.6	
Cell Extract	3.1					2.1	3.9	8.2	12.0			3.9	10.4	46.7	9.6	

Metabolite H1 is highly polar and accounts for the majority of the recovery in the cell media. In addition 80% of the radioactivity in the cell media was volatile suggesting that much of the radioactivity was tritiated water. Taken together these facts suggest that the majority of asenapine's metabolism in this system is via is 11-oxidation and that H1 is likely the 11-O-sulfate.

Figure 16 Position of Asenapine ³H Radiolabel - Study 5067



5.4.3.1.2 Study NL0060905 (2006)

Study NL0060905 conducted in 2006 incubated [¹⁴C]-Asenapine at concentrations of 4.7 nMol/mL (μM) and 19.5 nMol/mL (μM) in a final ethanol concentration of 2% (v/v) performed in duplicate with isolated human male hepatocytes.

Results are shown in Table 28. Unfortunately only total recoveries were reported even though the sponsor stated that recoveries were determined in both the cell medium as well as the cell extract. Where feasible, recoveries that can be attributed to a single primary pathway are combined to show the relative importance of that primary pathway. This reveals that over 50% of asenapine's metabolism in this system proceeds via N-desmethylation.

Table 28 Fractional Recovery after Asenapine Incubation with Human Hepatocytes - Study NL0060905 (2006)

Peak		Total recovery	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15	H16	H17		
m/z							384.1	464.2	290.1	450.2			274.1	288.1	318.1	304.1	302.1				
Code #													30526	5222		34137					
Nominal Structure							O-SO4	N-Gluc	OH-N-Des	N-Des-Gluc ^c			N-Des	As	N-formyl OH	N-oxide	N-formyl				
B	4.7 nMol/mL (μM)	Total	88.5	— ^a	—	5.17	3.76 ^b	27.19	4.03	2.51	6.15	19.27	2.29	21.29	4.89	5.35	—	—	—	—	
		Media																			
		extract																			
Combined							31.2	2.5					52.0	4.9	5.35						
A	19.5 nMol/mL (μM)	Total	83.5	—	—	1.81	1.31	13.07	1.85	2.47	2.55	19.2	1.53	13.63	31.1	2.4	1.32	1.88	4.81	1.11	
		Media																			
		extract																			
Combined							15.0	2.5					42.7	31.1	7.2	3.1					

a – not detected

b - observed in only 1 duplicate

c –structure not identified by sponsor

It should be noted that the sponsor did not identify the structure of metabolite H9, however from the molecular weight it is readily apparent that it is the glucuronide conjugate of N-desmethyl-asenapine. By not identifying this structure, if this reviewer had not realized that the N-formyl metabolites proceed via N-desmethylation the relative contribution of N-desmethylation would have been capped at half of what the results truly show. Consequently the clinical importance of inhibition of this pathway would not have been as apparent.

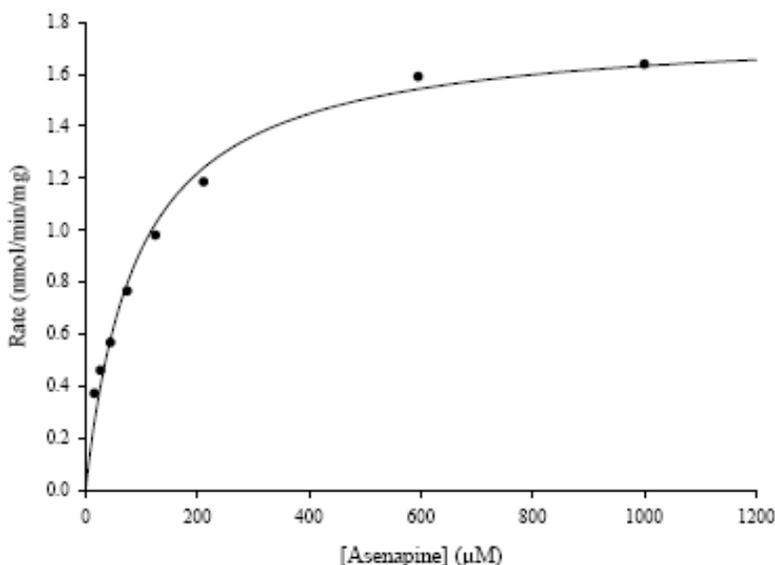
5.4.3.2 N-Glucuronication

The Uridine Glucuronosyl Transferase isozymes (UGT) involved in the N-glucuronidation of asenapine were identified in study DM2006-005222-013. Glucuronidation of metabolites was not examined.

Incubations were first conducted with pooled human liver microsomes (HLM-13) to determine apparent intrinsic enzyme kinetic parameters, followed by incubations with the recombinant UGT enzymes (UGT1A1, 1A3, 1A4, 1A6, 1A8, 1A9, 1A10, 2B4, 2B7, and 2B15). Incubation times were 1 hour, and the duration of incubation and the protein concentration used were established in preliminary experiments that assessed the linearity of the relationship with the reaction velocity. The formation of asenapine N-glucuronide was determined by mass spectrometry.

Data from incubations with pooled human hepatic microsomes were fit to a Michaelis-Menten model resulting in a K_m of 92.6 μM and V_{max} of 1.8 $\text{nMol} / \text{min} / \text{mg}$, (see Figure 17). Since asenapine's *in vivo* concentrations peak between 10 – 70 nMol/L glucuronidation should be a linear *in vivo*,

Figure 17 Mean Asenapine N-Glucuronide Formation Rate vs. Concentration in Pooled Human Hepatic Microsomes – Study DM2006-005222-013



After the apparent intrinsic kinetic parameters in pooled microsomes were determined, various recombinant UGT isozymes were incubated under nonlinear conditions with asenapine at a concentration equal to the apparent intrinsic K_m , (i.e. 92 μM).

Based on these experiments UGT1A4 was identified as the isozyme with the greatest intrinsic affinity to glucuronidate asenapine, (see Table 29).

Table 29 Formation Rate of Asenapine N-Glucuronide by Recombinant UGT Isozymes at the Apparent K_m (92 μM) – Study DM2006-005222-013

UGT Isozyme	1A1	1A3	1A4	1A6	1A8	1A9	1A10	2B4	2B7	2B15
Formation Rate ^a ($\text{nmol} / \text{min} / \text{mg}$)	<LLOQ	<LLOQ	0.49	<LLOQ						

a LLOQ = 0.03 $\text{nmol}/\text{min}/\text{mg}$

UGT1A1 glucuronidates bilirubin and is also known as bilirubin-UGT-1 (BUGT1).

Despite high sequence identity, UGT1A3 and UGT1A4 differ in terms of substrate selectivity. UGT1A3 glucuronidates planar phenols such as 1-naphthol (1-NP) and 4-methylumbelliferone (4-MU). Whereas UGT1A4 converts the tertiary amines, such as lamotrigine (LTG) and trifluoperazine (TFP), to a quaternary ammonium glucuronide. Thus the finding that UGT1A4 glucuronidates asenapine is not surprising.

5.4.3.3 Microsomal Oxidative Metabolism

In vitro studies were conducted examining the microsomal oxidative metabolism of asenapine. Studies utilized the following test systems:

- a) Human Liver Microsomes
- b) Supersomes (i.e. microsomes from P450 isozyme specific cDNAh expressed in intact insect cells)

There were typically at least two study reports for each test system, an initial study conducted by Organon during their initial development, and a later study conducted by Pfizer within a few years of submission.

Unfortunately almost all of the studies were conducted at asenapine concentrations ~ 1000 fold higher than *in vivo* concentrations (2 – 28 nMol). Therefore results are somewhat suspect.

5.4.3.3.1 Human Liver Microsomes

The following three studies were conducted with human liver microsomes:

- 1) Study 2874 (1991)
- 2) NL0060848 (2005)
- 3) INT00003054 (2006)

5.4.3.3.1.1 Human Liver Microsomes – Study 2874 (1991)

Study 2874 examined the fractional recovery of radioactivity after incubation of 25 µM of ³H-Asenapine in human liver microsomes from two Dutch males. Table 30 shows that recovery as metabolites is primarily as the N-Desmethyl. Three other metabolites including the diastereomeric N-oxide and 2 unidentified metabolites are recovered at lower fractions.

Table 30 Fractional Recoveries of Extracted Radioactivity after Incubation of ³H-Asenapine 25 µM with Human Liver Microsomes for 30 Minutes – Study 2874

% of Extracted Radioactivity				
N-Oxide (Diastereomeric)	M2	M3	Desmethyl-Asenapine	Asenapine
5.8	8.3	4.5	12.7	68.9

5.4.3.3.1.2 Human Liver Microsomes – Study HLM NL0060848 (2005)

5.4.3.3.1.2.1 NADPH Dependence

In study NL0060848 (2005) male human liver microsomes (microsomal protein concentration: 500 µg/mL) were incubated for 15 minutes at 37°C with [¹⁴C]-asenapine at 2 and 20 µmol/L in the presence and the absence of NADPH.

Table 31 shows that at lower asenapine concentrations of 2 µM biotransformation is NADPH dependent, indicating that only P450 is involved in oxidation of asenapine at clinical concentrations which are much lower. At higher concentrations of 20 µM asenapine turnover is not entirely NADPH dependent, likely indicating the involvement of FMO, in addition the turnover is lower than at 2 µM, indicating the possibility

of a mechanism based inhibitor. Based on the structure of asenapine and the likely involvement of FMO there is a good likelihood that this is an N-oxide metabolite.

Table 31 % Biotransformation of Asenapine in Human Liver Microsomes 500 mcg/ml – Study NL0060848 (2005)

	2 µmol/L [¹⁴ C]-asenapine			20 µmol/L [¹⁴ C]-asenapine		
	Sample-1	Sample-2	Mean	Sample-1	Sample-2	Mean
Control^a	0.00	--	--	5.06	--	--
(-) NADPH	0.00	0.00	0.00	5.48	6.12	5.80
(+) NADPH	17.50	24.96	21.23	9.65	11.31	10.48

5.4.3.3.1.2.2 Inhibition by Isozyme Specific Inhibitors

Table 32 shows the degree of inhibition of asenapine biotransformation by CYP450 isozyme specific inhibitors in human liver microsomes. As expected the degree of inhibition is less at the higher asenapine concentrations as the $I/K_i : C/K_m$ ratio is smaller at the higher asenapine concentration. The results show that 3A4, 1A2, and likely 2D6 are involved in the metabolism of asenapine and 2D6 might cause autoinhibition at higher concentrations, (also possibly 2C19 but this is less certain). Plus inhibition of 3A4, 1A2, and 2D6 might occur *in vivo* but the importance of these can only be determined from *in vivo* data since the specific metabolites and relative importance of the pathways need to be considered.

Table 32 % Inhibition of Asenapine Biotransformation by CYP450 Isozyme Specific Inhibitors in Human Liver Microsomes - NL0060848 (2005)

Asenapine (μmol/L)	1.8	20.5	2.4	24.3	2.4	24.3	2.4	24.3	2.4	24.3	0.2	2	1.8	22.7
Isozyme	1A2		2B6		2B6		2C19		2C19		2D6		3A4	
Inhibitor (μM)	Furafylline		MPEP		Orphenadrine		Benzylrivanol		Tranlycypromine		Quinidine		Ketoconazole	
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.1											1.84	2.66	55.76	3.23
0.2			10.04	3.23										
0.5							-9.17	1.32			17.62	2.91	59.53	5.08
1	11.51	2.39	15.16	-0.97			11.09	-4.71	11.29	12.66	19.93	0.15	77.37	13.26
2			10.34	7.30										
2.5					1.87	4.55								
5	45.83	10.90					6.98	-8.45	2.70	16.24			77.23	25.20
10	15.69	12.70	14.22	4.26			0.12	-10.02	4.60	17.03			86.14	36.08
11											24.32	2.96		
12.5					6.94	4.73								
20			14.08	4.44										
50	40.63	25.68			6.54	5.14	-12.92	-18.78	11.18	21.40				
53											31.71	7.72		
100	100.0	30.29												
125					11.96	6.69								
250									27.27	24.39				
500					7.29	6.28								

5.4.3.3.1.3 Human Liver Microsomes – Study INT00003054 (2006)

Study INT00003054 examined the fractional HPLC peak recoveries of radioactivity after Incubation of ¹⁴C-Asenapine at ~ 5 and ~20 nMol/L with human liver microsomes at a protein concentration of 500 mcg/mL for 30 minutes.

Two sets of experiments were performed each using a different batch of microsomes. An initial set where the final concentration of ethanol used to dilute asenapine was 5% and a second set at a lower final ethanol concentration of 1%. The second set of experiments were conducted as ethanol interfered with the metabolism of asenapine and resulted in no turnover at the higher asenapine concentration.

The mechanism for alcohol's inhibition could be either nonspecific or specific inhibition of 2E1, 3A4, or alcohol and aldehyde dehydrogenase.

Similar to study 2874 (1971) the metabolites recovered included the N-desmethyl, the N-oxide and two other unidentified metabolites, (see Table 33).

Table 33 Fractional Recoveries of Radioactivity after Incubation of ¹⁴C-Asenapine at ~ 5 and ~20 nMol/L with Human Liver Microsomes - Study INT00003054 (2006)

		EtOH	kBq	nMol/L	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14
											DesMe	Asenapine		N-Ox				
A	1	5%	10.5	5.5				2.5			1.5	94.5		1.5				
	2	1%	10.1	5.3			2.3	5.0			5.2	81.7		5.9				
B	1	5%	42.4	22.3								100						
	2	1%	35.8	18.8				10.5			10.9	63.8	6.0	8.8				

5.4.3.3.2 Supersomes

5.4.3.3.2.1 Supersome Study NL0010293 (1998)

5.4.3.3.2.1.1 Initial Formation Rates

The initial formation rates of asenapine N-oxide and desmethyl-asenapine from [³H]-Asenapine by cDNAh P450 isozymes expressed in insect cells (i.e. Supersomes) was examined in study NL0010293.

[³H]-Asenapine labeled in two positions as shown in Figure 18 was incubated with CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP2C9, CYP2C19 and CYP3A4 supersomes at a microsomal protein concentration of 250 µg/mL for 15 min at 37 °C at concentrations of 2 and 20 µM.

Results are shown in Table 34. From this data it appears that CYP1A2 is involved in the formation of the reactive N-Oxide as well as is the primary isozyme responsible for formation of the N-Desmethyl metabolite, although CYP2C19, which is polymorphic, and CYP3A4 may be involved. It should be noted that the actual importance of these isozymes will also depend on their relative abundance *in vivo*. Consequently, CYP3A4 may be more important than CYP2C19.

Figure 18 ³H Radiolabeling of Asenapine Used in Study NL0010293 (1998)

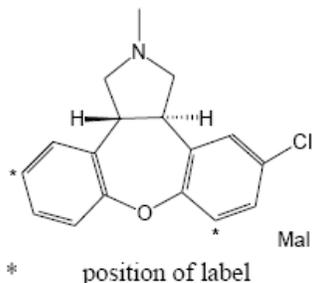


Table 34 Initial Formation Rates of Asenapine N-Oxide and Desmethyl-Asenapine by Supersomes - Study NL0010293 (1998)

Supersomes	Formation Rates ^a (pMol/ nMol P450 x min ⁻¹)			
	Asenapine - N(2)-Oxide		N(2)-Desmethyl Asenapine	
[³ H]-Asenapine Conc.	2 µM	20 µM	2 µM	20 µM
CYP1A2	*	*	376.91	1277.17
CYP2A6	—	—	—	—
CYP2C9	—	—	—	123.73
CYP2C19	—	—	85.77	725.44
CYP2D6	—	—	—	181.30
CYP2E1	—	—	—	—
CYP3A4	—	*	10.52	155.82

^a Data are presented as mean values of duplicate incubations

— Below limit of detection

* Showed activity.

According to the sponsor, 'It was not possible to quantify the formation of the N(2)-oxide metabolite of Org 5222, because in the HPLC metabolite profiles of the higher substrate concentration an impurity was present at a detectable level, which eluted at the retention time of the N(2)-oxide metabolite of Org 5222. However the activity of CYP1A2 towards the N(2)-oxidation was higher as compared with CYP3A4 activity.'

5.4.3.3.2.1.2 Enzyme Kinetic Parameters

Enzyme kinetic parameters for the formation of the N-oxide and the N-desmethyl metabolites were also determined for each of these isozymes, and the results are shown in Table 35. This data tends to confirm the previous conclusions.

Table 35 Enzyme Kinetic Parameters for the Formation of Asenapine N(2)-oxide and N(2)-Desmethyl Asenapine by CYP1A2, CYP2C19 and CYP3A4 Supersomes - Study NL0010293 (1998)^a

Supersome Isozyme	Enzyme Kinetic Parameter	N(2)-oxide	N(2)-Desmethyl Asenapine
CYP1A2	Vmax (pMol / min / nMol P450)	942 ± 47	1556 ± 251
	Km (nMol/mL) (μM)	0.7 ± 0.2	16.6 ± 8.4
	Clint (L/hr x μMol ⁻¹)	83.3	5.62
CYP2C19	Vmax	— ^b	6052 ± 6 42
	Km	—	99.1 ± 14.7
	Clint (L/hr x μMol ⁻¹)	—	3.66
CYP3A4	Vmax	572 ± 67	5735 ± 1156
	Km	77.0 ± 27.9	453.5 ± 166.0
	Clint (L/hr x μMol ⁻¹)	0.44	0.78

a Values are presented as mean ± standard error (SE) of the fit.

b not determined

5.4.3.3.2.1.3 Correlation of Asenapine Metabolite Formation with Isozyme Activity

Spearman Rank correlations between the formation of the asenapine metabolites N-oxide asenapine and N-desmethyl asenapine and the metabolism of cytochrome P450 enzyme selective substrates also tend to confirm the rank order of activity of these isozymes toward the formation of the N-oxide and N-desmethyl metabolite, (see Table 36).

Table 36 Spearman Rank Correlations between the Formation of Asenapine N-oxide asenapine and N-Desmethyl asenapine and the Metabolism of Cytochrome P450 Isozyme Selective Substrates - Study NL0010293 (1998)

Cytochrome P450	Substrate	Reaction	Asenapine N(2)-Oxide		N(2)-Desmethyl Asenapine	
			2 μ M	20 μ M	2 μ M	20 μ M
CYP1A2	Phenacetin	O-DeEthyl	0.78**	0.71*	0.92***	0.79**
CYP2A6	Coumarin	7-OH	-0.23	0.07	-0.37	0.09
CYP2C	S-mephenytoin	4-OH	0.28	0.59	0.45	0.56
CYP2D	Dextromethorphan	O-DeMethyl	-0.32	-0.07	-0.22	0.12
CYP2E	Chlorzoxazone	6-OH	-0.23	-0.20	-0.23	-0.33
CYP3A	Testosterone	6 β -OH	0.41	0.45	0.48	0.53

Statistical significance: *** p < 0.001; ** p < 0.01; * p < 0.05

5.4.3.3.2.1.4 Effect of Isozyme Selective Inhibitors on Metabolite Formation

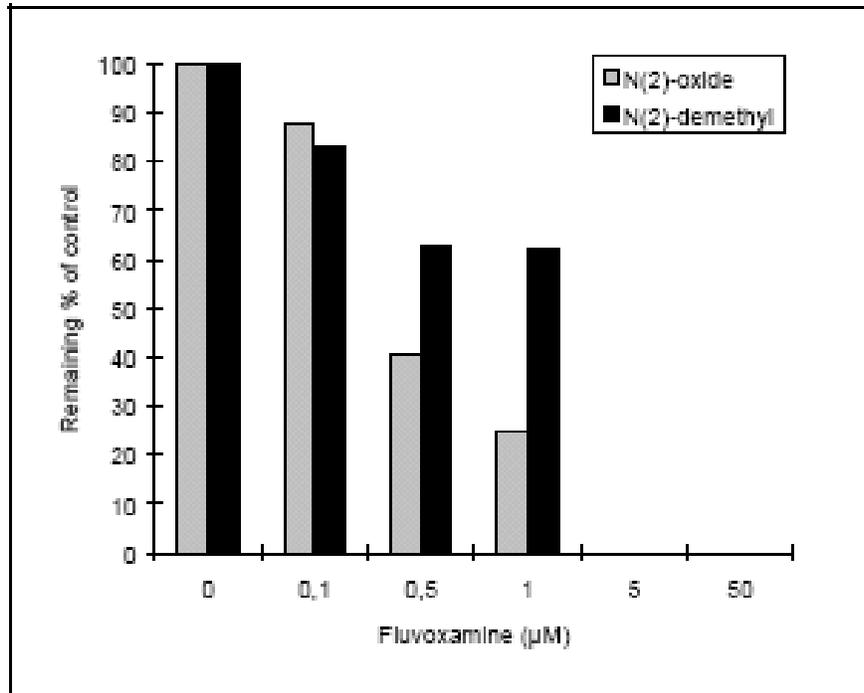
Microsomal incubations with 2 μ M and 20 μ M of [³H]-asenapine were performed with five different inhibitor concentrations, (0.1, 0.5, 1, 5, 50 μ M), of fluvoxamine and ketoconazole, selective inhibitors for CYP1A2 and CYP3A, respectively.

The sponsor's results are shown in Figure 19 and Figure 20. The asenapine concentrations shown in the figures appear to be transposed, as there is less inhibition at lower asenapine concentrations. If we assume that the concentrations are transposed, then the results would be consistent with the other experiments in supersomes which would not be surprising and all the results using the same experimental system should be consistent.

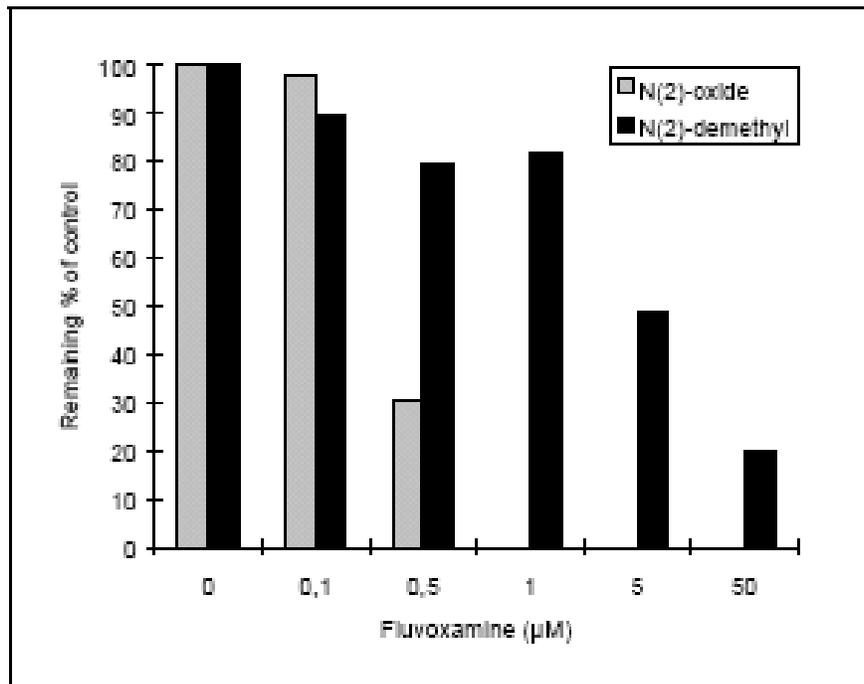
This should be remembered in assessing the weight of evidence for *in vitro* data showing the specific isozymes involved.

Figure 19 Inhibition of N(2)-Oxide and N(2)-Desmethyl Asenapine Formation by the CYP1A2 Selective Inhibitor Fluvoxamine – Study NL0010293 (1998)^a

• 2 nmol·mL⁻¹ Org 5222



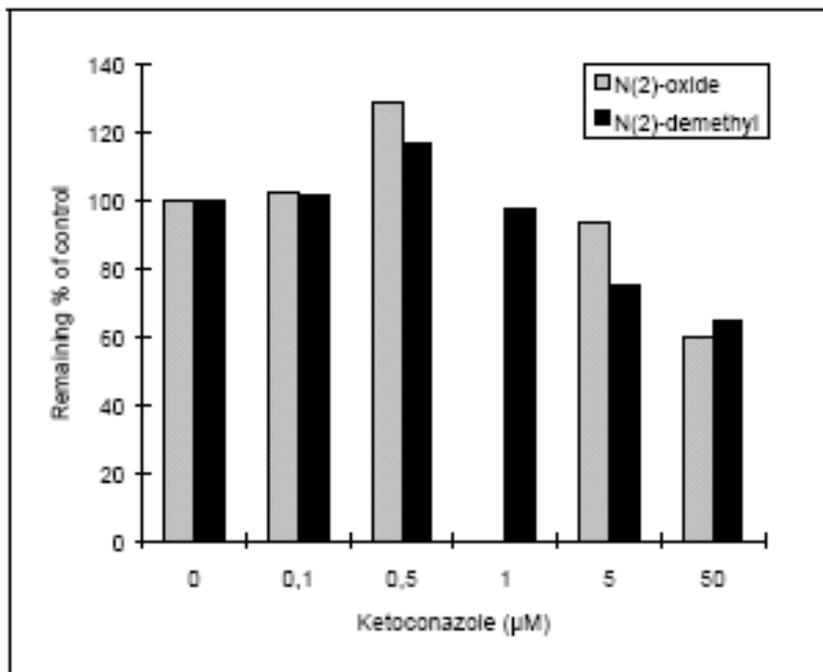
• 20 nmol·mL⁻¹ Org 5222



a Asenapine concentrations 2 and 20 μM (nMol/mL)

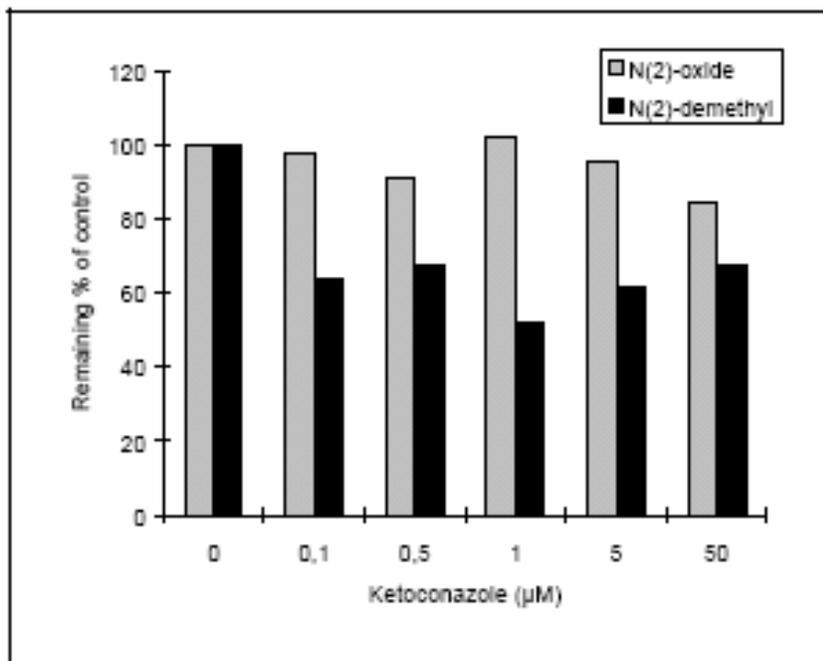
Figure 20 Inhibition of N(2)-Oxide and N(2)-Desmethyl Asenapine Formation by the CYP3A Selective Inhibitor Ketoconazole – Study NL0010293 (1998)

• 2 nmol·mL⁻¹ Org 5222



* No reliable data were obtained for the N(2)-oxidation at 1 μM ketoconazole.

• 20 nmol·mL⁻¹ Org 5222



a Asenapine concentrations 2 and 20 μM (nMol/mL)

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 [¹⁴C]-asenapine, approximately 2 and 20 µMol/L.

For CYP2D6 supersomes, [³H]-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			
CYP1A2		Control ^b	10 pMol	25 pMol	100 pMol
	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 μ M

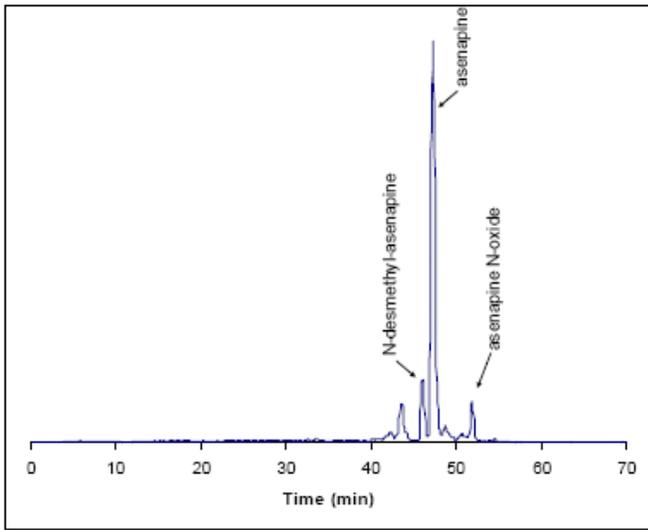


Figure 23 CYP2B6 Supersomes & Asenapine 20 μ M

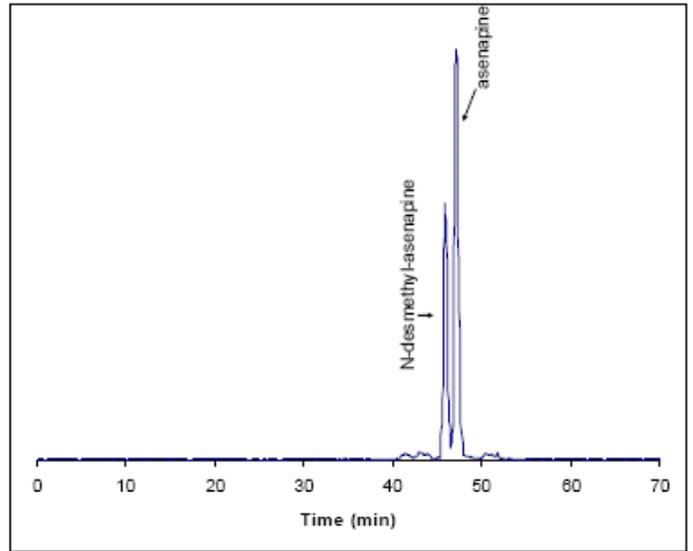


Figure 22 CYP3A4 Supersomes & Asenapine 20 μ M

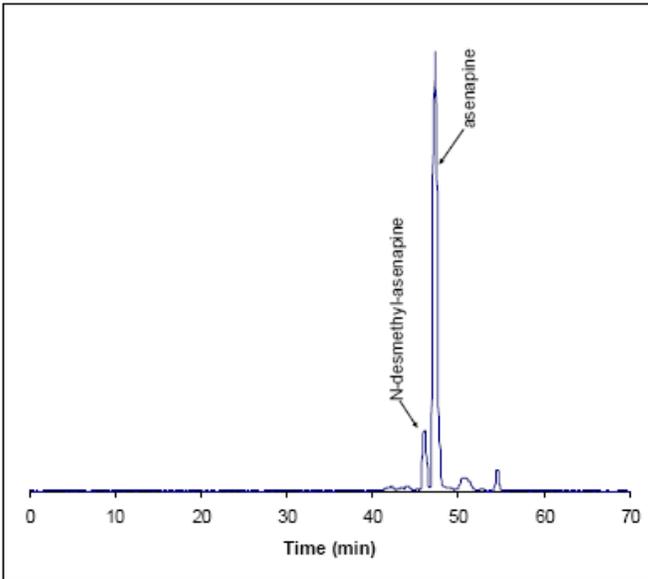


Figure 24 CYP2C19 Supersomes & Asenapine 20 μ M

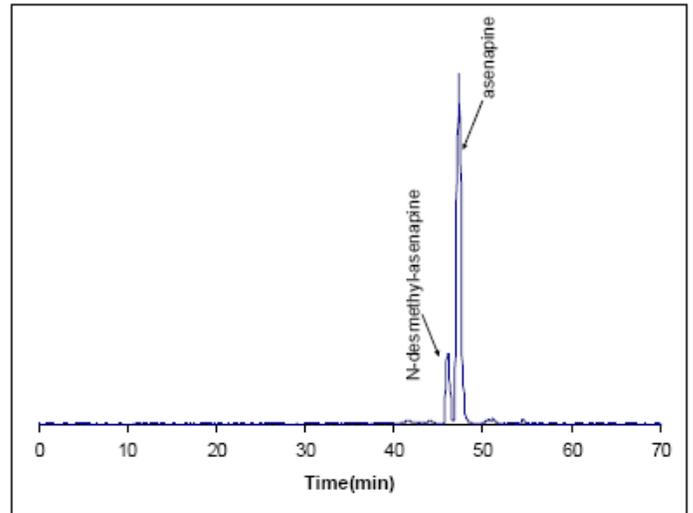
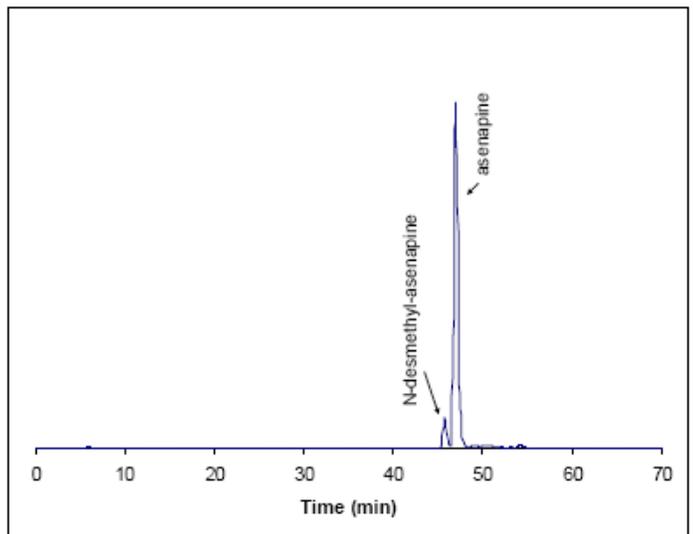


Figure 25 CYP2D6 Supersomes & Asenapine 2 μ M



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 [¹⁴C]-asenapine or [³H]-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.

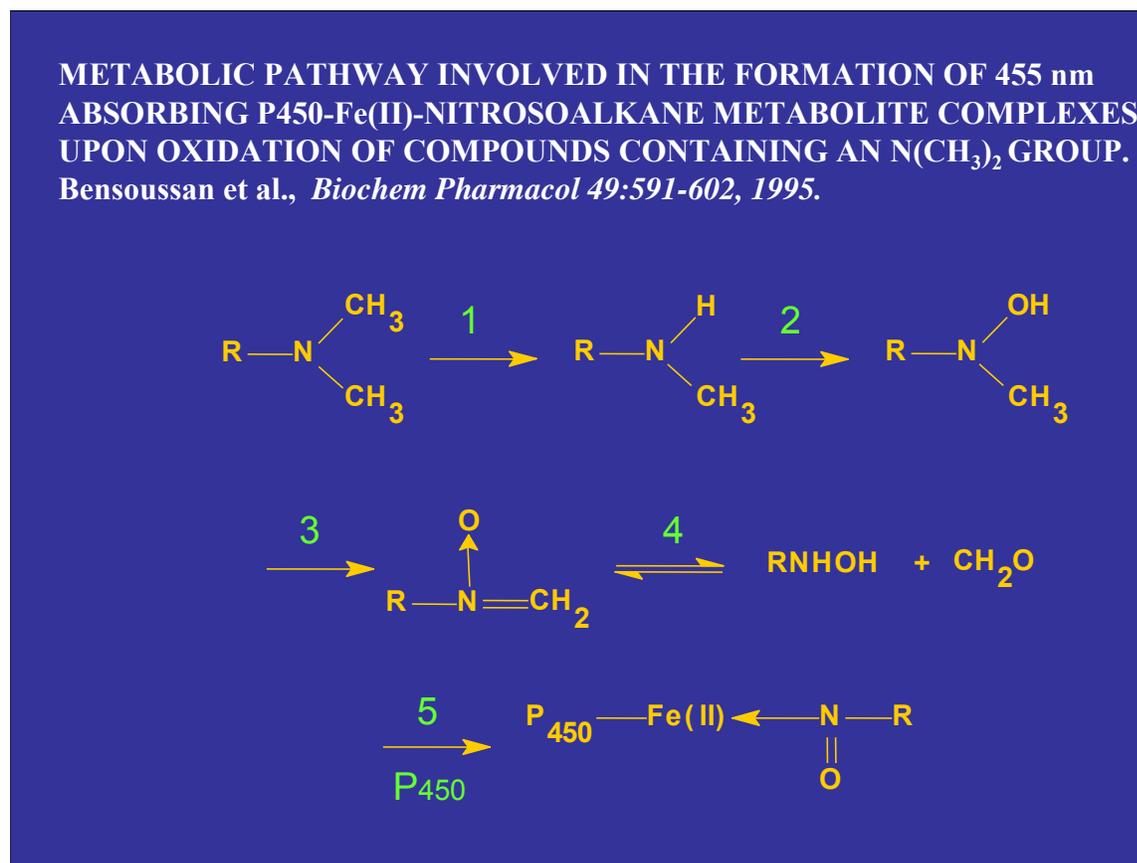
5.4.3.5 *In Vitro* Inhibition by Asenapine and Metabolites

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 K_i 's in the range of 6 – 85 nMol/L, which are at or somewhat above therapeutic concentrations. However, more important than the K_i 's 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 1999⁴ 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

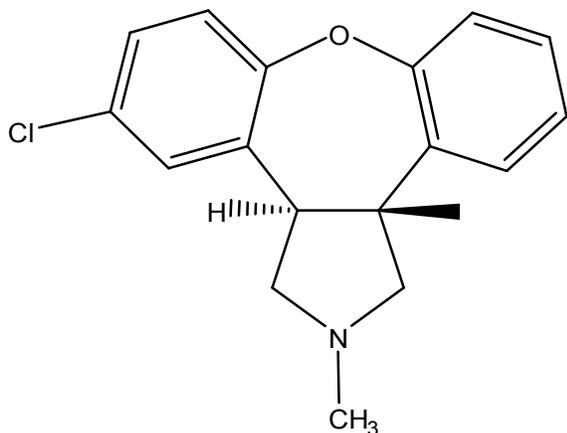
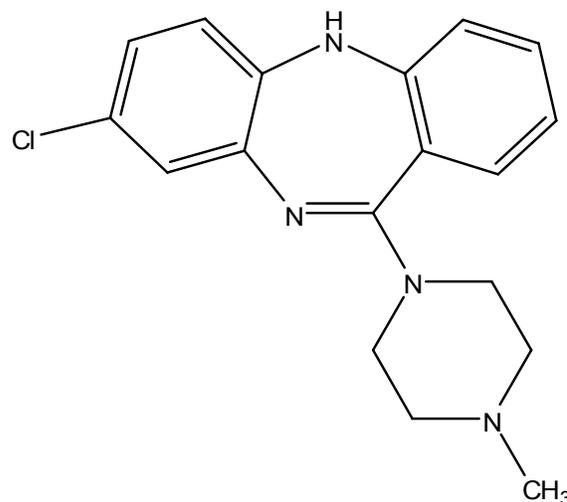


Figure 28 Structure of Clozapine



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 V_{max} . 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	6β-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 6β-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 IC₅₀ 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 IC₅₀ was calculated by interpolation using the following formula:

$$IC_{50} = (50\% \text{ Inhibition} - \% \text{ Inhibition at First Incubate concentration} < IC_{50}) / (\% \text{ Inhibition at First Incubate Concentration} > IC_{50} - \% \text{ Inhibition at First Incubate concentration}) \times (\text{Conc at First Conc} > IC_{50} - \text{Conc at First Conc} < IC_{50}) / (\% \text{ Inhibition} + \text{Conc at First Conc} < IC_{50})$$

An example follows:

Figure 29 Example of IC50 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 :

$$((50-33.8)/(55.8-33.8) \times (62.5-31.3)) + 31.3 \text{ nmol}\cdot\text{L}^{-1} = 54.27 \text{ nmol}\cdot\text{L}^{-1}$$

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)		91.4	Mixed-competitive ?
			3A4 (b)		125.59	?
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		No inhibition	
			2C8		No inhibition	
			2C9		No inhibition	
2C19	No inhibition					
3A4 (1)	No inhibition					
3A4 (2)	No inhibition					
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	<i>Competitive</i>	3.08	165.9	2.06	119.3	Passes
			1.5	7.92 a	196.7 b	<i>Non-Competitive</i>	4.63	185.7	8.90	134.1	Fails
			3	6.56 a	156.6 b	<i>Mixed Competitive</i>	3.09	165.9	2.06	121.3	Passes
						Uncompetitive	5.37	189.7	7.41 3916	141.2	Fails
	2D6	Asenapine	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
			0	0.72	7.03	<i>Competitive</i>	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
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
						<i>Uncompetitive</i>	43.97	0.39	25.16	88.4	Passes
3A4		Asenapine	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
			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	<i>Mixed Competitive</i>	30.25	1.69	91.40 125.59	0.21	Passes
						Uncompetitive	36.98	1.76	86.44	1.3	Passes
NL0048836	2D6	Asenapine	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
			0	0.83	521.17	<i>Competitive</i>	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
	2D6	Org 30526 N-Desmethyl-Asenapine	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	1.41	665.71	Competitive	0.79	535.21	19.35	1.05	Passes
			10	0.59		<i>Non-Competitive</i>	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

	1A2	Org 30526 N-Desmethyl- Asenapine	Org 30526 ($\mu\text{mol/L}$)	Km a ($\mu\text{mol/L}$)	Vmax b (units/pmol CYP1A2/min)	Model	Km ($\mu\text{mol/L}$)	Vmax (units/pmol CYP1A2/min)	Ki ($\mu\text{mol/L}$)	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 ($\mu\text{mol/L}$)	Km a ($\mu\text{mol/L}$)	Vmax b (units/pmol CYP2C8/min)	Model	Km ($\mu\text{mol/L}$)	Vmax (units/pmol CYP2C8/min)	Ki ($\mu\text{mol/L}$)	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 ($\mu\text{mol/L}$)	Km a ($\mu\text{mol/L}$)	Vmax b (units/pmol CYP2C9/min)	Model	Km ($\mu\text{mol/L}$)	Vmax (units/pmol CYP2C9/min)	Ki ($\mu\text{mol/L}$)	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 ($\mu\text{mol/L}$)	Km a ($\mu\text{mol/L}$)	Vmax b (units/pmol CYP2C19/min)	Model	Km ($\mu\text{mol/L}$)	Vmax (units/pmol CYP2C19/min)	Ki ($\mu\text{mol/L}$)	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 ($\mu\text{mol/L}$)	Km a ($\mu\text{mol/L}$)	Vmax b (units/pmol CYP3A4/min)	Model	Km ($\mu\text{mol/L}$)	Vmax (units/pmol CYP3A4/min)	Ki ($\mu\text{mol/L}$)	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 ($\mu\text{mol/L}$)	Vmax b (units/pmol CYP2D6/min)	Model	Km ($\mu\text{mol/L}$)	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

		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 $v = V_{max} * ([S] / (K_m + [S]))$

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 IC₅₀s 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 6 β -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 μM) and the estimated IC₅₀s are shown in Table 44.

Asenapine demonstrated marked inhibition of CYP2D6 and moderate inhibition of CYP1A2 activities with respective IC₅₀s 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 IC₅₀ Data for Asenapine in Human Liver Microsomes – Study DM2005-005222-009

Enzyme	Marker Substrate Activity	% of control at [I] = 30 μM	IC ₅₀ (μM) Mean \pm SE	IC ₅₀ (nM)
CYP1A2	Phenacetin O-Deethylase	6.9	0.61 \pm 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 \pm 0.001	44
CYP3A	Felodipine Oxidase	65	>30	
CYP3A	Midazolam 1'-Hydroxylase	120	>30	
CYP3A	Testosterone 6 β -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 6 β -Hydroxytestosterone Formation for Controls and Asenapine at 0 to 30 μ M in Human Hepatocytes; B) Fold Induction for CYP3A4 for Controls and Asenapine at 0 to 30 μ M in Human Hepatocytes - Study RR 764-04914

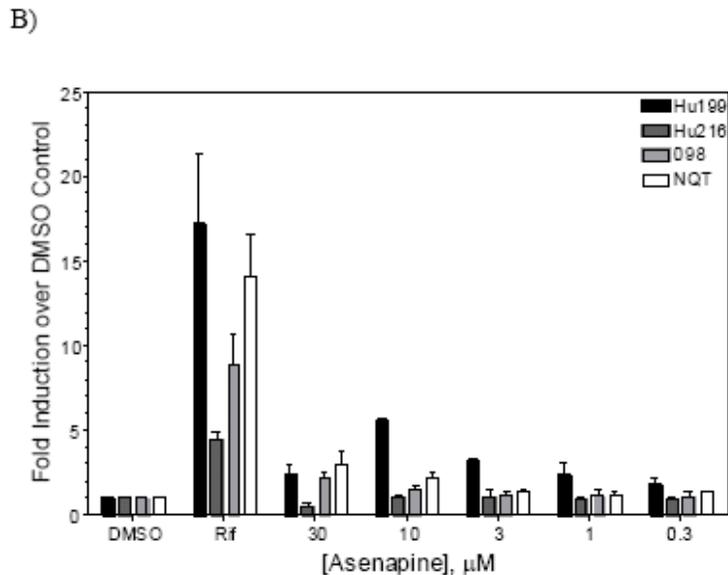
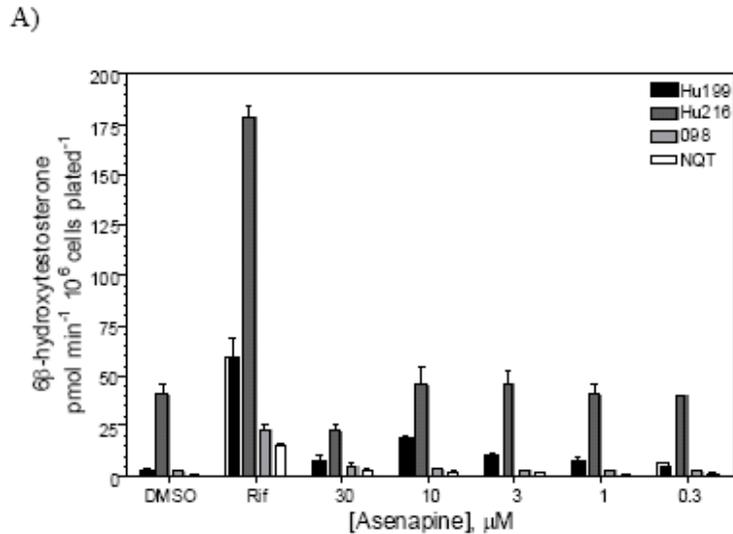


Figure 32 A) Rate of 6 β -Hydroxytestosterone Formation Normalized to Percent of Positive Control for Controls and Asenapine at 0 to 30 μ M in Human Hepatocytes; B) Mean Rate of 6 β -Hydroxytestosterone Formation Normalized to Percent of Positive Control and Relative Quantitation (RQ) Values of CYP3A4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

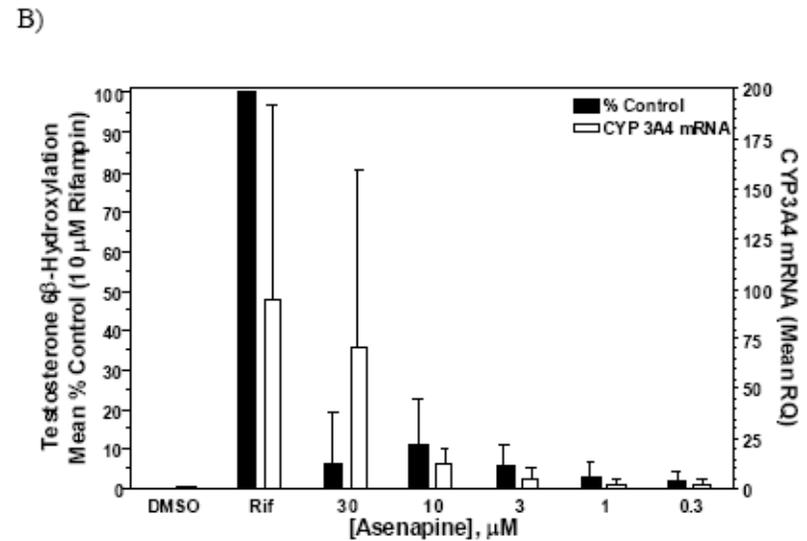
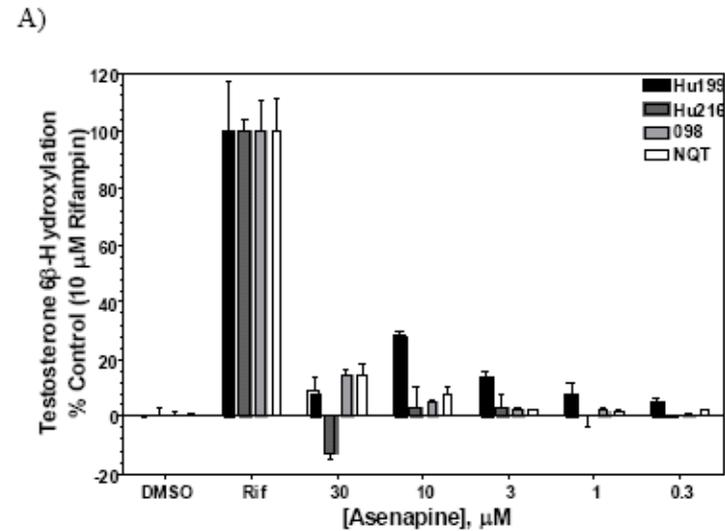
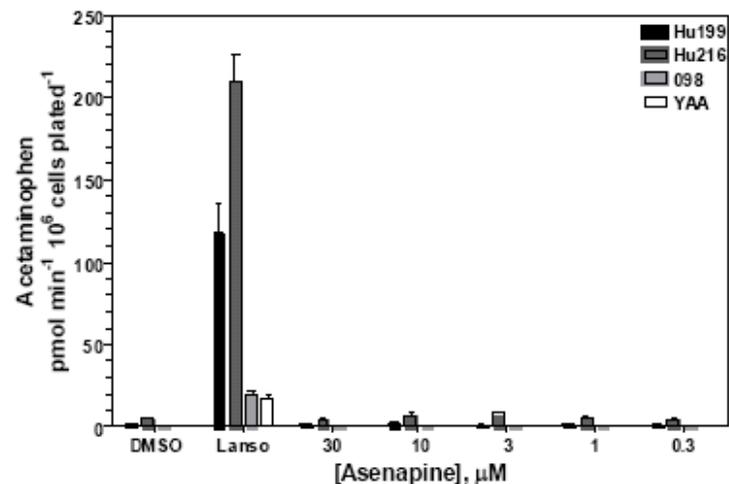


Figure 33 A) Rate of Acetaminophen Formation for Controls and Asenapine at 0 to 30 μM in Human Hepatocytes; B) Fold Induction for CYP1A2 for Controls and Asenapine at 0 to 30 μM in Human Hepatocytes

A)



B)

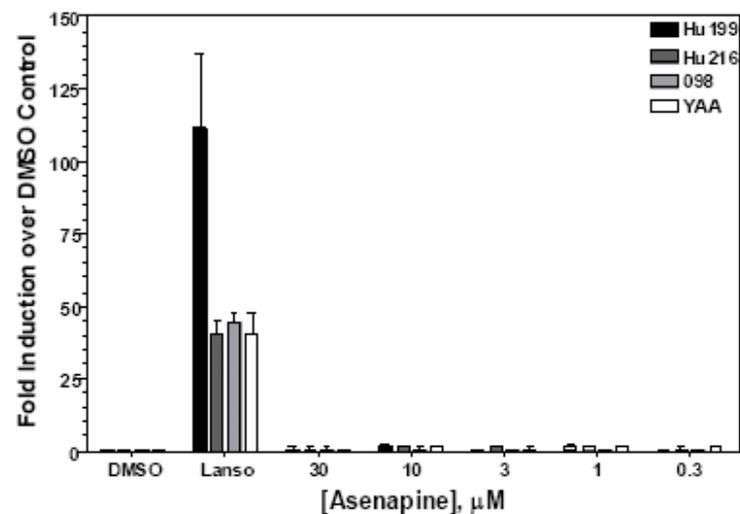
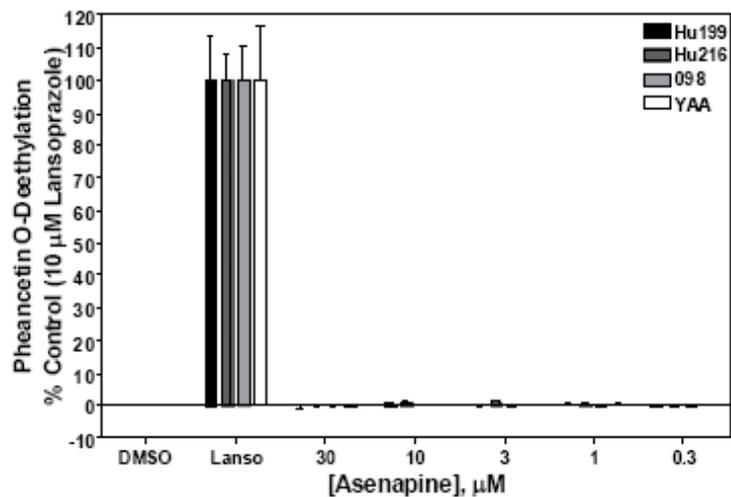


Figure 34 A) Rate of Acetaminophen Formation Normalized to Percent of Positive Control for Controls and Asenapine at 0 to 30 μM in Human Hepatocytes; B) Mean Rate of Acetaminophen Formation Normalized to Percent of Positive Control and

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

A)



B)

