CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-117

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	13 August 2009
From	Ellis F. Unger, M.D., Deputy Director, ODE-1
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	22-117
Applicant Name	Organon USA Inc.
Date of Submission	8/30/07 (original), 2/13/09 (response to CR)
PDUFA Goal Date	8/13/09
Proprietary Name / **Established (USAN) Name**	Saphris (asenapine)
Dosage Forms / Strength	5, 10-mg Sublingual Tablets
Proposed Indication(s)	1. Acute treatment of schizophrenia in adults 2. Acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Robert Levin
Statistical Review	George Kordzakhia, Yeh-Fong Chen
Pharmacology Toxicology Review	Elzbieta Chalecka-Franeszek
CMC Review/OBP Review	Chaggan Tele
Microbiology Review	N/A
Clinical Pharmacology Review	Ronald Kavanagh, Andre Jackson
DDMAC	N/A
DSI	Tejashri Purohit-Sheth
CDTL Review	Gwen Zornberg, Mitch Mathis
OSE/DEpi	N/A
OSE/DMEPA	Felecia Duffy
OSE/DRISK	N/A
Other	Suchitra Balakrishnan, QT Team Min Min, Carcinogenicity Team

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Concurrence
I concur with the asenapine summary review of Dr. Thomas Laughren, and recommend approval for asenapine sublingual tablets for the acute treatment of schizophrenia, as well as for the acute treatment of mania and mixed episodes in Bipolar I Disorder.

Background
Asenapine is an atypical "second generation" antipsychotic (combined serotonin and dopamine receptor antagonist), unique in that it is formulated as an immediate release sublingual tablet. The applicant seeks claims for: 1) acute treatment of schizophrenia; and 2) mania/mixed episodes in Bipolar I Disorder. They plan to market both 5- and 10-mg tablets for sublingual administration. The proposed doses are 5-mg bid for the treatment of schizophrenia and 10-mg bid for the treatment of mania/mixed episodes of Bipolar I Disorder (the dose can be reduced to 5-mg bid if the higher dose is poorly tolerated). The regulatory history has been well-documented by others. Briefly, the NDA was received 8/30/07, and a Complete Response action was taken on 1/13/09. The major concerns at that time were the need to review non-clinical histopathology data from a carcinogenicity study, and concerns regarding cases of anemia and thrombocytopenia. There were also questions as to whether the applicant had adequately characterized the circulating moieties in plasma.

The sponsor submitted a complete response to our action letter on 2/12/09, and the PDUFA date is 8/13/09.

Schering-Plough acquired asenapine in November, 2007 through its acquisition of Organon BioSciences, which developed the product. Asenapine is not approved in any other country; the dossier is currently under review in the European Union.

The Division's review was fairly straightforward, except that a number of concerns were raised by Dr. Ronald Kavanagh, the original biopharmaceutics (OCP) reviewer. These concerns have been well-addressed in the memoranda of Dr. Thomas Laughren, Director, Division of Psychiatry Products.

Chemistry

Impurity [redacted] had been an issue in FDA's complete response action. The applicant had set its specification at [redacted] and this exceeded the threshold for qualification. We had asked the sponsor to lower the specification limit to [redacted] or to qualify it adequately as a phase 4 commitment. In fact the applicant had conducted a non-GLP segment II rabbit study; however, we considered it inadequate, and were planning to request an embryofetal development study in rabbits as a phase 4 commitment. The applicant has recently conducted such a study and submitted it to the IND. Their conclusion is that the study is negative; we will be reviewing the data post-approval. The applicant has appropriately addressed other minor requests for CMC information included in our 1/13/09 action letter.

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Pharmacology

At the time the division took the Complete Response action, the lack of histopathology data for the low- and medium-dose groups in rat and mouse carcinogenicity studies was a major pharmacology/toxicology deficiency. The dose in the rat study exceeded the maximum tolerated dose (MTD), leading to excessive weight loss in the high-dose group, and rendering data from this group uninterpretable. In the mouse study, there was a large increase in the frequency of malignant lymphomas in high-dose females compared to the vehicle control

group, but not compared to an untreated control group. In our Complete Response, we requested histopathology slides from the lower dose groups to try to better understand these findings. The sponsor submitted the findings, and we reviewed them carefully.

The pharmacology/toxicology team does not believe that asenapine is a potent carcinogen. They point out that no increases in other tumor types were observed in female mice, and no tumors were observed in male mice or in rats of either sex. The team crafted language for the label, stating that lymphomas have a high and variable background incidence in mice, and that the clinical significance of the finding is unknown.

Biopharmaceutics

Initially there was concern that the applicant had not adequately determined the circulating moieties in plasma. After much discussion between OCP and the applicant, OCP agrees that approximately half of the circulating species have been identified in plasma, and that the metabolite data are acceptable for approval.

Evidence of Efficacy in Schizophrenia

The applicant performed four 6-week, double-blind, randomized, active- and placebo-controlled studies in adult subjects with acutely exacerbated schizophrenia (Table 1). The primary endpoint was change from baseline to endpoint on the Positive and Negative Syndrome Scale (PANSS) total score. The Clinical Global Impressions-Improvement Scale (CGI-I) was a key secondary endpoint. Three studies were fixed-dose; one allowed flexible dosing. Asenapine was dosed on a twice-daily (bid) basis. The primary analyses for all four studies used last observation carried forward (LOCF) for missing data, supported by mixed model repeated measures (MMRM). The results of the four studies are summarized in Table 1. Studies 41004 and 41023 were the two positive studies that constitute asenapine's evidence of efficacy for the schizophrenia indication, and they are emphasized in this memo. I also discuss study 41013, because it explored doses in a range lower than 5-mg bid.

Table 1: Efficacy Studies for Schizophrenia

		Treatment						
Study number	n/group (approx)	Asenapine 5-mg BID	Asenapine 10-mg BID	Olanzapine 15-mg QD	Risperidone 3-mg BID	Haloperidol 4-mg BID	placebo	% subjects retained
41004	60	-14.4*			-10.0		-4.6	43%
41021	100	-14.5	-13.4	-16.5*			-11.1	54%
[redacted]								
41023	110	-16.2*	-14.9			-15.4*	-10.7	63%

* p<0.05

Study 41021 compared asenapine 5-mg bid, asenapine 10-mg bid, olanzapine 15-mg qd, and placebo. Neither asenapine group was statistically superior to placebo; however, the olanzapine group was superior to placebo (p=0.017). Thus, this study appropriately demonstrated assay sensitivity, but was negative with respect to both the 5- and 10- mg doses of asenapine. The negative results of this study, for both dosage strengths of

asenapine, must be considered when weighing the overall persuasiveness of the evidence of efficacy for asenapine in schizophrenia.

Study 41022 was a 90-subject per arm comparison of a flexible dose of asenapine (5- to 10-mg bid) with olanzapine and placebo. Neither asenapine nor olanzapine were statistically superior to placebo. Thus, the study failed to establish assay sensitivity, and the results are difficult to interpret (results shown in gray highlight in Table 1).

Study 41004 was one of two studies providing evidence of efficacy for asenapine in the treatment of schizophrenia. It compared asenapine 5-mg bid, risperidone 3-mg bid, and placebo. This was a phase 2 study with only ~60 patients per group. The primary endpoint was change from baseline to endpoint on the PANSS total score. Subject retention was poor, with completion rates of only 47%, 45%, and 37% for the asenapine, risperidone, and placebo groups, respectively. Asenapine was statistically superior to placebo on the 1° endpoint (p=0.007); risperidone tended to be better than placebo (p=0.125). I have re-plotted the applicant's prespecified LOCF analysis, my analysis of the applicant's raw observed cases (OC) data (0000\m5\datasets\041004\listings\panss.xpt), and subject retention in Figure 1, top, middle, and bottom panels, respectively.

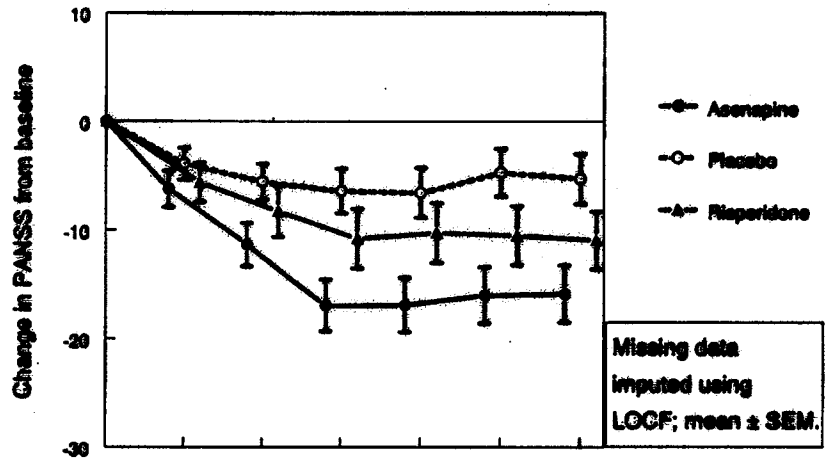
The results are compelling. It is noteworthy that the greatest separation between asenapine and placebo occurs at visit 3, at a time when retention is reasonable, i.e., approximately 3/4 of the subjects contributed data at this visit. The applicant performed a pair-wise comparison (ANOVA) between asenapine and placebo for the change in PANSS from baseline, including only observed cases, and the differences between asenapine and placebo reach statistical significance on visits 2 and 3 (Table 3.1.2.5 of Dr. Yeh-Fong Chen's statistical review, dated 4/17/08; Table 6.E.1.2, page F-265 of applicant's study report for 41004).

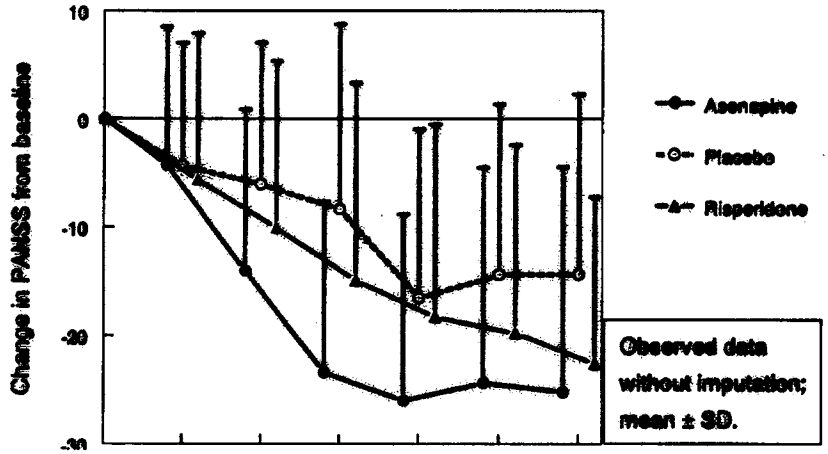
Dr. Chen found two subjects with no post-baseline results who had been included (inappropriately) in the applicant's LOCF analysis. Apparently, the applicant discovered the error, because the correct results are provided in the applicant's "NDA overview." Although the inclusion of these subjects does not importantly affect the overall study results, only the correct results would be appropriate for presentation in labeling.

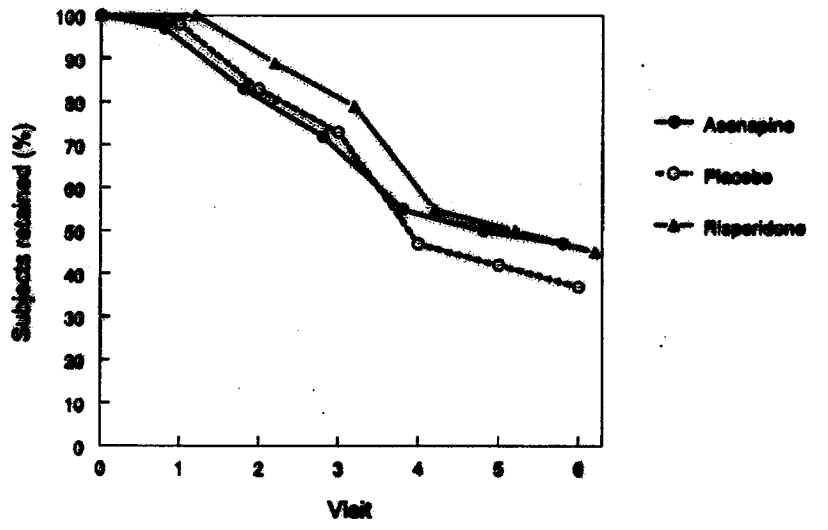
Drop-outs: Dr. Chen was troubled by the large number of dropouts, and, in particular, the proportionately larger fraction of dropouts for in the placebo group compared to the asenapine group. The differential drop-out rate suggests that data are not missing at random, which could confound the results. There was substantial discussion of this issue at the 7/30/09 Psychopharmacologic Drugs Advisory Committee Meeting. Most likely, subjects who drop out do so for either lack of efficacy or intolerable side effects. Dr. Laughren points out that study discontinuation can be construed as treatment failure, and a time to all-cause discontinuation endpoint was used in CATIE to assess the comparative efficacy of drugs of this class (N Engl J Med. 2005;353:1209-23). He also notes that this pattern of drop-outs is typical for an effective drug.

Related to this issue, Dr. Kavanagh plotted the total PANSS score by time (Clinical Pharmacology Review; figure 161, page 371). His interpretation was that "...all treatments result in the same final value, thus the greater change from placebo with asenapine is due to a higher initial baseline score in the asenapine group." His plot of the OC data with locally weighted scatterplot smoothing (LOESS) is reproduced in Figure 2, top, along with my plot of the data using conventional means and standard deviations (Figure 2, bottom).

Figure 1: Study 41004 - Change in PANSS by Visit: Top Panel – Last Observation Carried Forward; Middle Panel – No Imputation for Missing Data; Bottom Panel – Subjects Retained by Visit





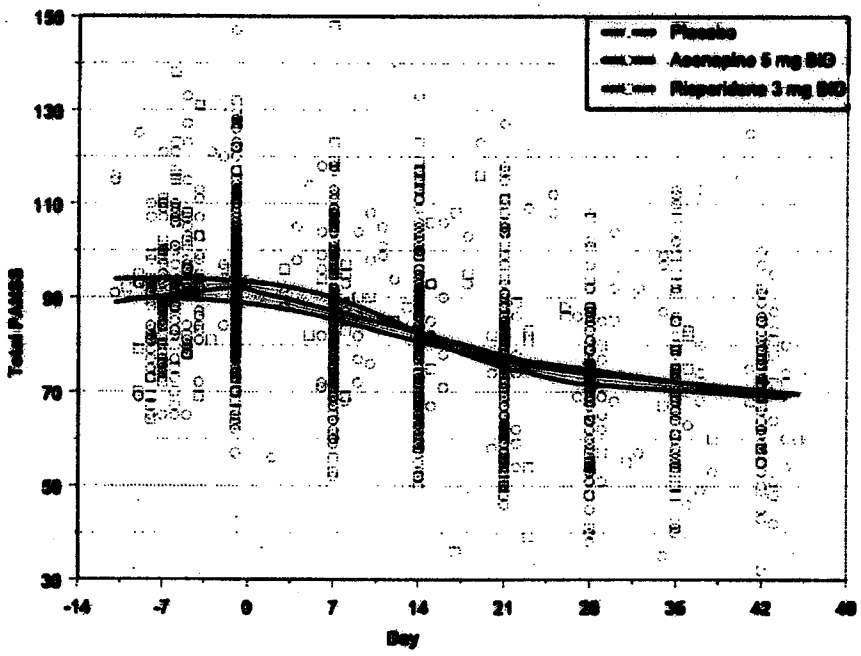


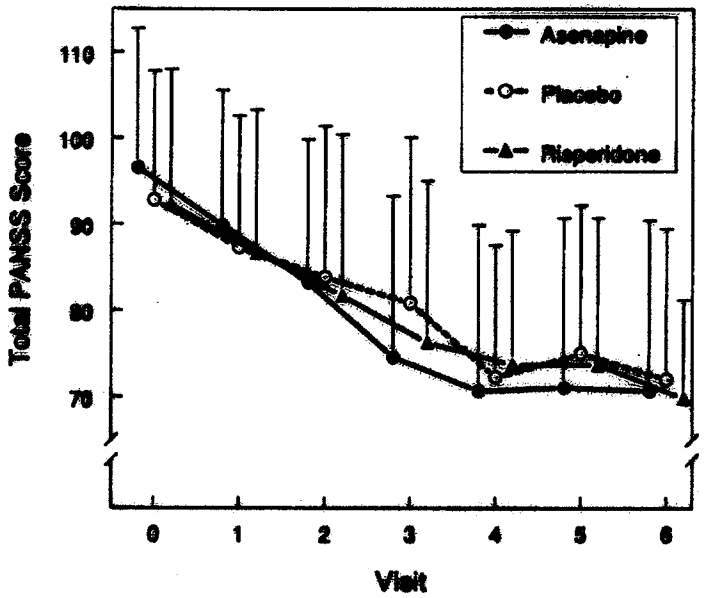
Recognizing that higher values represent more severe symptoms, subjects in the asenapine group had a mean total PANSS that trended slightly worse than placebo at baseline, and the mean for the asenapine group trended slightly better than placebo at the end of the study. Thus, the *change* in PANSS score, the 1° study endpoint, is statistically significant. Figure 2 also indirectly supports Dr. Laughren's view, in that patients with acute schizophrenia are extremely ill. Untreated, their symptoms can not be tolerated by patients, their families, or society at large. In essence, the degree of improvement shown in Figure 2 is *expected* and even *required*. When patients do not experience some reasonable rate of improvement on their assigned drug, or develop intolerable side effects, they will drop out of the study and seek a more effective treatment modality. In light of this, analyses of time-to-treatment failure, or some variation of that, seem appropriate for assessing efficacy of drugs in future clinical trials in schizophrenia.

The statistical reviewer made comments (#4 and #5, page 15 of review) that relate to a baseline imbalance in total PANSS scores between treatment groups, although the baseline scores do not appear to be importantly different. On page 9 of her review, the statistician notes: "...mean baseline total PANSS scores were similar among the three treatment groups (Org 5222, 96.48; risperidone 92.18; placebo, 92.43)." Thus, I find it difficult to interpret these points.

In sum, although study 41004 was is a small study with substantial rates of drop-out, it does support the efficacy of the 5-mg bid asenapine regimen. The LOCF analysis assumes that subjects who leave the study neither worsen nor improve. This approach has been used in similar registrational studies, and this seems to be an appropriate and conservative approach for missing data. As noted by Dr. Laughren, the pattern of drop-outs itself supports a conclusion of efficacy.

Figure 2: Study 41004 - Total PANSS Score by Time





Study 41023 was the second of two studies providing evidence of efficacy for asenapine in schizophrenia. It compared asenapine 5-mg bid, asenapine 10-mg bid, haloperidol 4-mg bid, and placebo. Approximately 110 subjects were enrolled in each group. Completion rates for

the 4 groups were approximately 65% for the two asenapine groups, 59% for the haloperidol group, and 57% for placebo. Asenapine 5-mg bid was statistically superior to placebo on the 1° endpoint (p=0.014). There was a positive trend for asenapine 10-mg bid, but the difference was not statistically significant (p=0.068). Haloperidol was superior to placebo (p=0.034). Results for the prospectively-defined 1° endpoint (Δ PANSS from baseline with LOCF methodology) are plotted in Figure 3 (top panel), along with OC results (middle panel), and subject percent retention (bottom panel). Although the results with the 10-mg bid dose are not statistically significantly different from placebo, there is a strong lean.

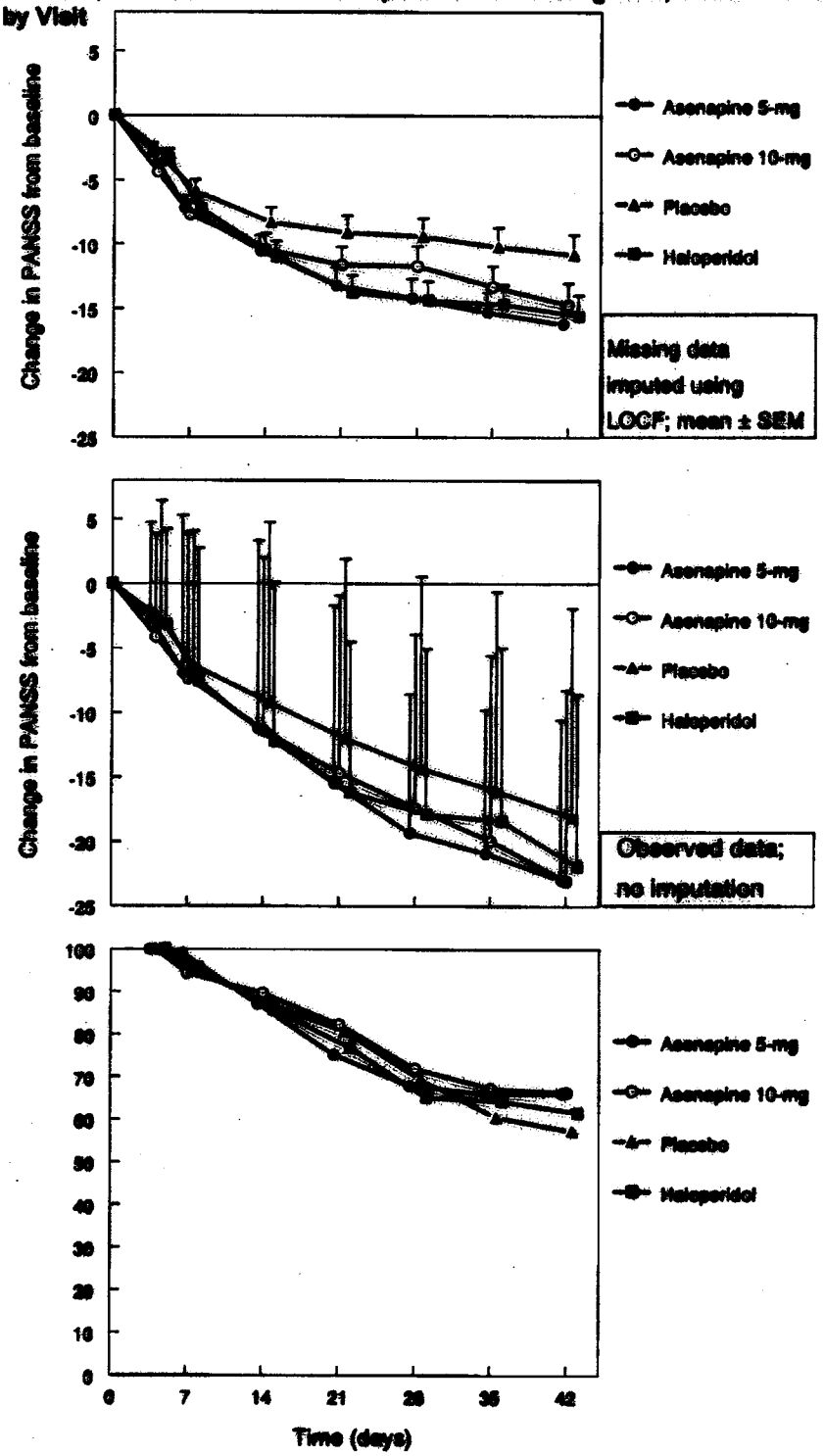
Dose-Response: Dr. Laughren notes that study 41023 could have provided information regarding a dose-response for asenapine; however, the higher dose appeared less efficacious than the lower dose, based on the point estimates. Dr. Laughren also notes that Dr. Zornberg, the Cross-Discipline Team Leader, initially argued in favor of permitting the sponsor's originally proposed labeling, recommending 5- to 10-mg bid. I agree with Dr. Laughren's more conservative approach of recommending the dose for which there is evidence of efficacy. (As noted by Dr. Laughren, Dr. Zornberg subsequently modified her view on this issue.) The label states that the recommended starting and target doses are 5-mg bid. It further states that there was no evidence of added benefit with higher doses in controlled studies, and that higher doses are associated with increases in certain adverse events.

Dr. Laughren has questioned whether it would be of value for the sponsor to explore a dose lower than 5-mg bid, because the applicant has not yet identified the lowest effective dose, and at least some adverse events appear to be dose-related. Study 41013 provided an additional opportunity for dose exploration.

Study 41013 was a dose-exploration study that evaluated asenapine doses of 1.6-mg and 2.4-mg bid against placebo, without an active comparator group. This was also a 6-week study, similar in design to the other efficacy studies, although it was conducted earlier in time, from 2000-2001, shortly before 41004. Approximately 60 subjects were enrolled in each group. Results are shown in Table 2. Differences from placebo were not statistically significant, but the 1.6-mg dose group showed a positive trend (p=0.13). Given that there was no active control group to demonstrate assay sensitivity, and given that other studies in the dossier have been uninterpretable or provided mixed results, study 41013 does not provide a compelling argument that doses <5-mg bid would be ineffective.

Some have cited the applicant's receptor occupancy studies as evidence that lower doses would be ineffective. These studies are, however, based upon relatively crude methods (^{11}C-raclopride PET imaging), conducted with small numbers of subjects using sub-therapeutic doses of asenapine. Specifically, studies 25510 and 25516 were conducted in 3 and 6 healthy male volunteers, respectively. In study 25510, the dose of asenapine was 0.1 mg. In study 25516, doses were titrated up to 0.3 mg bid over 3 days. Overall, these studies do not seem to make a persuasive case that doses lower than 5-mg bid would be ineffective.

Figure 3: Study 41623 - Change in PANSS by Visit: Top Panel – Last Observation Carried Forward; Middle Panel – No Imputation for Missing Data; Bottom Panel – Subjects Retained by Visit



I agree with Dr. Laughren's overall assessments of the magnitude of treatment effect and effects on subgroups. Efficacy analyses by subgroup were conducted on the combined data from the two studies where asenapine showed a treatment effect (studies 41004 and 41023, Statistical Review page 23, Tables 4.1.1, 4.1.2, and 4.1.3). The treatment effect appears to be consistent across subgroups of sex and race, but I would note that only 6 of 271 asenapine-treated subjects (2.2%) were age 65 or older; thus it is clear that efficacy data in elderly patients are sparse. This should be noted as a limitation in the label.

Table 2: Study 41013 Results

	asenapine		placebo
	1.6-mg	2.4-mg	
n (randomized)	58	61	64
n (baseline visit)	54	54	62
Mean ↑ PANSS	-8.7	-5.8	-3.7
SEM	2.0	2.2	2.1
n completed	20	17	18
% completed	37%	31%	29%
p-value	0.13	0.54	-

Overall Assessment of Efficacy in Schizophrenia

As discussed by Dr. Laughren, the support for asenapine's efficacy in schizophrenia is not overwhelming (Table 1). The evidence of effectiveness was established by two studies: in the smaller of the two (study 41004), asenapine was superior to placebo with a persuasive p-value; however, in the larger study (41923), which enrolled nearly twice as many subjects per group and retained them to a greater extent, only the lower dose (5-mg bid) was statistically superior to placebo. The fact that the higher dose (10-mg bid) never showed a statistical "win" against placebo detracts somewhat from the evidence of effectiveness. A third study (41022) failed to demonstrate assay sensitivity, and all seem to agree that it can be discounted. Most concerning was a fourth study (41021) where the active comparator (olanzapine) showed positive results, but neither asenapine dose beat placebo.

It is reasonable, however, to take some measure of reassurance from the studies in Bipolar I Disorder, which were more solidly positive (see below). Overall, although the negative studies and negative results on the higher dose are concerning, my view is that the evidence of efficacy is marginally sufficient for approval. These data were presented to the Psychopharmacologic Drugs Advisory Committee, and they voted that asenapine had been shown to be effective for the acute treatment of adult patients with schizophrenia.

We have reconsidered the utility of exploring a lower dose for schizophrenia, and decided that this would be worthwhile. We have reached agreement with the applicant on a post-marketing commitment to conduct a study to assess the efficacy of asenapine 2.5-mg bid against placebo, to include a 5-mg bid group and another active drug to establish assay sensitivity. Maintenance data are also needed, and the applicant has in fact conducted a maintenance study for asenapine in schizophrenia; they plan to submit the results in a supplement post-approval. We will also request deferred studies under PREA to assess asenapine's pharmacokinetics, safety, and efficacy for the treatment of patients with schizophrenia, aged 13 to 17 years. We are waiving the pediatric study requirements for patients younger than 13.

Evidence of Efficacy in Bipolar I Disorder

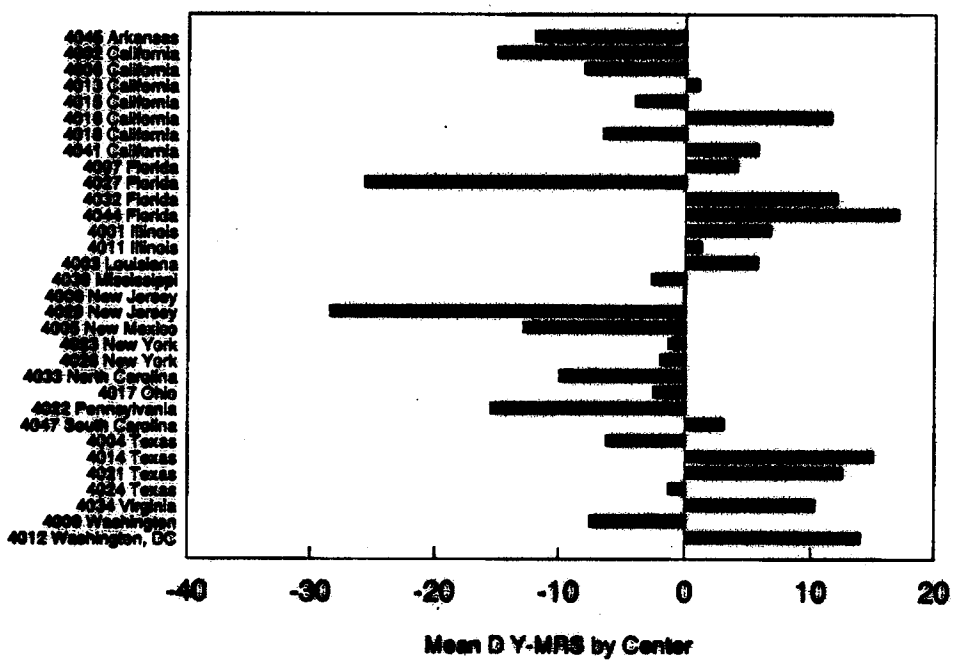
The applicant performed two 3-week, double-blind, randomized, flexible dose, placebo- and olanzapine-controlled studies of asenapine in adult patients with manic or mixed episodes of Bipolar I Disorder (studies A7501004 and A7501005). The doses used were 5- to 10-mg bid for asenapine and 5- to 20-mg qd for olanzapine. Subjects were randomized in a 2:2:1 ratio to asenapine, olanzapine, and placebo. Subjects randomized to asenapine were started on the 10-mg bid dose, but the dose could be reduced to 5-mg bid if desired (in fact, only ~10% of subjects were down-titrated; therefore, the studies essentially evaluated 10-mg bid). The 1° primary endpoint was change from baseline to endpoint in the Young Mania Rating Scale (YMRS) score, and the key 2° endpoint was Clinical Global Impression-Bipolar CGI-BP scale score on day 21. The 1° analysis was ANCOVA, with missing data imputed using LOCF.

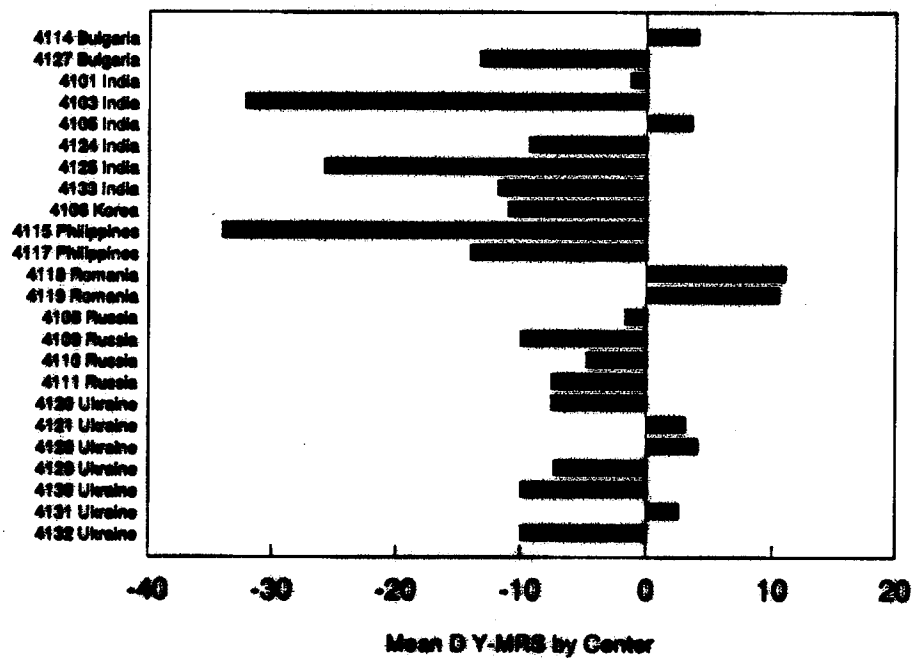
I have little to add to the analysis and commentary of Dr. Laughren and the review team. The results of both studies were positive. Approximately 200 subjects were enrolled in the active treatment groups in each study, and approximately 100 subjects were enrolled in each placebo group. Approximately 2/3 of subjects completed the studies. In both studies, both asenapine and olanzapine groups were statistically superior to placebo on the 1° as well as the key 2° endpoints. Dr. George Kordzakhia, the statistical reviewer for the bipolar indication, found that virtually none of asenapine's treatment effect in study A7501004 could be attributed to the U.S. sites. Surprisingly however, nearly 60% of asenapine-treated subjects were enrolled at domestic sites. Thus, the results were driven entirely by the 40% of study subjects enrolled outside the U.S.

Figure 4 shows the results by center; note that negative numbers indicate greater treatment effect. The figure does not indicate the numbers of subjects enrolled by site. In the U.S., the results are well-distributed around both sides of zero. The foreign sites are fairly consistently in favor of asenapine. (Two Romanian sites appeared least favorable for asenapine, but together enrolled only 4 subjects in the asenapine group and 2 in placebo.) Site 4115 in the Philippines showed the strongest treatment effect, but enrolled only 2 subjects. Two sites in India, both medical colleges, provided results that were strongly in favor of asenapine, and made the greatest overall impact. Together they contributed 6 subjects to the placebo group, and their Y-MRS scores *worsened* by a mean of approximately 5 units. They contributed 12 subjects to the asenapine group, and their Y-MRS scores *improved* by a mean of 29 units. With removal of the data from these two sites, the study no longer reaches statistical significance. Though this might seem concerning, this phenomenon would not seem unusual in a study of this size. Overall, the treatment effect seems consistent within the foreign sites, and I, like Dr. Laughren, am inclined to dismiss the lack of efficacy in the U.S. as an anomaly. Results for the other study (A7501005) were consistent across U.S. and non-U.S. sites. Development programs with disparate results at U.S. and non-U.S. sites are not unprecedented, unfortunately.

Dr. Kordzakhia also noted in his review that results were numerically in favor of asenapine and olanzapine across subgroups of sex and race, but, similar to the schizophrenia studies, there were too few subjects over the age of 65 to draw any conclusions. This would be appropriate information for labeling.

Figure 4: Study 7501004 – Results by Country and Site





Dr. Laughren commented on Dr. Kavanagh's exploratory analysis, wherein he separated the sample into quintiles based on symptom severity at screening or baseline. Based on this analysis, Dr. Kavanagh concluded that only the most severely affected patients experience a treatment benefit. I believe his analyses are reasonable; however, I strongly disagree with his interpretation and conclusions. For therapies for a number of diseases, there would seem to be a "ceiling" – a degree of symptom amelioration beyond which improvement would be unusual. Consider the treatment of ADHD, osteoporosis, or irritable bowel syndrome. One would not expect patients with mild symptoms to improve to the same extent as patients with severe ones. This situation seems similar. Thus, I do not believe that Dr. Kavanagh's analyses by quintile are unreasonable, but as Dr. Laughren has stated, it would be inappropriate to interpret them in such a way as to suggest that patients with mild symptoms are unlikely to derive benefit, and therefore should not be treated.

Overall Assessment of Efficacy in Manic or Mixed Episodes Associated with Bipolar I Disorder

The evidence of efficacy seems fairly compelling for short-term treatment for the mania/mixed episodes of Bipolar I Disorder indication. The data were presented to the Psychopharmacologic Drugs Advisory Committee, who voted overwhelmingly that asenapine's effectiveness had been demonstrated for this disorder. I, like Dr. Laughren, am inclined to overlook the negative results in the US sites in study A7501004 as an anomaly, because the overall data are so compelling.

There were no data in the dossier pertinent to asenapine's dose-response for the indication of mania/mixed episodes of Bipolar I Disorder. Ninety percent (90%) of subjects received 10-mg bid in the pivotal studies. The applicant has agreed to a post-marketing commitment to evaluate a fixed-dose of 5-mg asenapine bid for bipolar mania in an adequate and well-controlled trial.

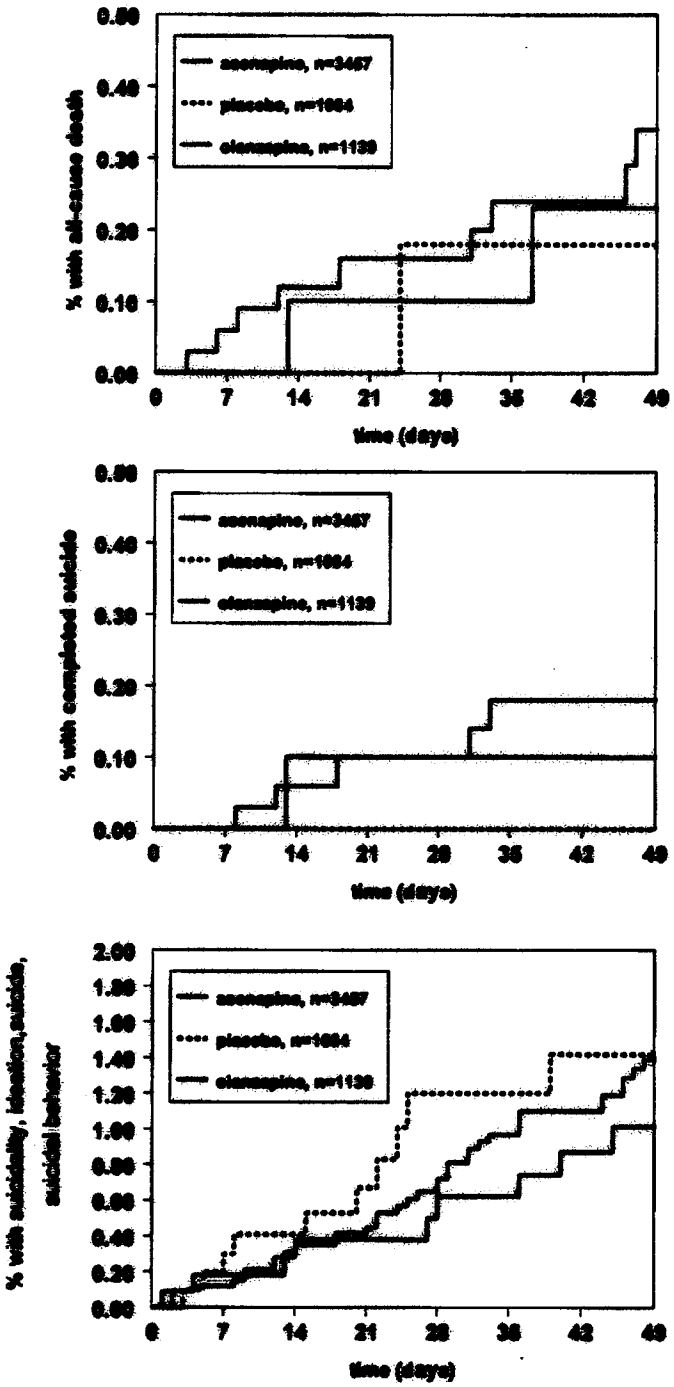
There were no data to address the longer-term efficacy of asenapine for the treatment of mania/mixed episodes. The applicant has also agreed to a post-marketing commitment to conduct an adequate and well-controlled long-term maintenance study to evaluate the efficacy and safety of asenapine in the treatment of adults with acute manic or mixed episodes associated with Bipolar I Disorder. We will also request deferred studies under PREA to assess asenapine's pharmacokinetics, safety, and efficacy for the treatment of patients with acute manic or mixed episodes associated with Bipolar I Disorder, aged 10 to 17 years.

Safety

Deaths and Suicides

Dr. Laughren and the review team have extensively discussed deaths and suicides in the asenapine development program. Dr. Levin filed a separate review focused on these topics. There were 12 suicides in the development program, including 8 on asenapine and 4 on olanzapine, with no suicides in subjects taking placebo, haloperidol, or risperidone. Adjusted for exposure, suicide rates were the same in the asenapine and olanzapine groups: 1.3 suicides per 100 patient-years. One concern noted in Dr. Laughren's memorandum was the *timing* of suicides, in that they tended to occur early after initiation of treatment with asenapine. Indeed, the patterns of all-cause mortality and completed suicides appear similar in the asenapine and olanzapine groups when considered using a time-to-event approach, although the numbers of events are small (Figure 5, top and middle panels).

Figure 8: Time to All-Cause Death (top), Completed Suicide (middle), and Suicidality (bottom)



The bottom panel of Figure 5 shows a time-to-first-event analysis of a composite of completed suicides, suicide attempts, suicidal ideation, or suicidal behavior. The data appear reassuring with respect to asenapine. Both asenapine and olanzapine trended better than placebo. I agree with Dr. Laughren, in that the standard suicidality warning language for antipsychotic drug labeling seems appropriate for asenapine.

Hematologic Effects

There is some confusion in the review documents regarding the numbers of subjects with various hematologic abnormalities. These numbers depend on whether or not investigators recorded laboratory abnormalities as adverse events, as well as the definitions used for the laboratory data. These are basically laboratory diagnoses, and it does not seem rational to assess these abnormalities on the basis of whether or not investigators happened to report them as adverse events or serious adverse events. The following analyses are based on my review of Cohort E from the SAS transport file in the original submission (0000\m5\datasets\scs\analysis\e lab-e-he.xpt). Apparently, no updated laboratory data files were submitted with the 120-day safety update.

Neutropenia

According to the review team, there were 4 subjects on asenapine identified by the sponsor as having "neutropenia," defined as having an ANC of < 1800 on at least 1 occasion. Overall, the team's analyses were a bit confusing; moreover, I could find no definitions of neutropenia in the applicant's study reports. For my analyses, I categorized subjects' neutropenia as mild, moderate, or severe on the basis of having a single absolute neutrophil count (ANC) within these ranges:

mild:	$1000 \leq ANC < 1500/\mu L$
moderate:	$500 \leq ANC < 1000/\mu L$
severe:	$ANC < 500/\mu L$

Of note, not all subjects in Cohort E had an absolute neutrophil count recorded in the dataset. Thus, the denominators I used are subjects in Cohort E with at least 1 ANC value reported.

Table 3: Neutropenia in Cohort E by Treatment Group and Severity

	N	severe n (%)	moderate n (%)	mild n (%)
asenapine	1410	1 (0.1%)	9 (0.6%)	31 (2.2%)
olanzapine	666	1 (0.2%)	2 (0.3%)	20 (3.3%)
placebo	704	(0%)	3 (0.4%)	22 (3.1%)
risperidone	120	(0%)	1 (0.8%)	3 (2.5%)
haldoperidol	114	(0%)	2 (1.8%)	4 (3.5%)

Although the numbers of cases are small, the data seem fairly reassuring. The percentages of subjects with mild and moderate neutropenia were similar in all 5 groups. There were only

two subjects with severe neutropenia – too few to draw any conclusions. Of note, for the subjects with severe neutropenia in the asenapine and olanzapine groups, the nadir occurred at 4 weeks.

Thrombocytopenia

The review team's discussion of numbers of subjects with thrombocytopenia also seemed confusing. Apparently, the sponsor had reported one case of thrombocytopenia. In the Cohort E laboratory data set, I found 4 subjects with thrombocytopenia, defined as a platelet count < 50,000/μL at any time.

Three (3) asenapine-treated subjects (0.2%) had thrombocytopenia. One olanzapine-treated subject had thrombocytopenia (0.2%). Another subject randomized to olanzapine had a platelet count of 8,000/μL prior to treatment. No subjects in the placebo or other active treatment groups had thrombocytopenia. Overall, these numbers do not seem concerning, and the label mentions thrombocytopenia in adverse reactions.

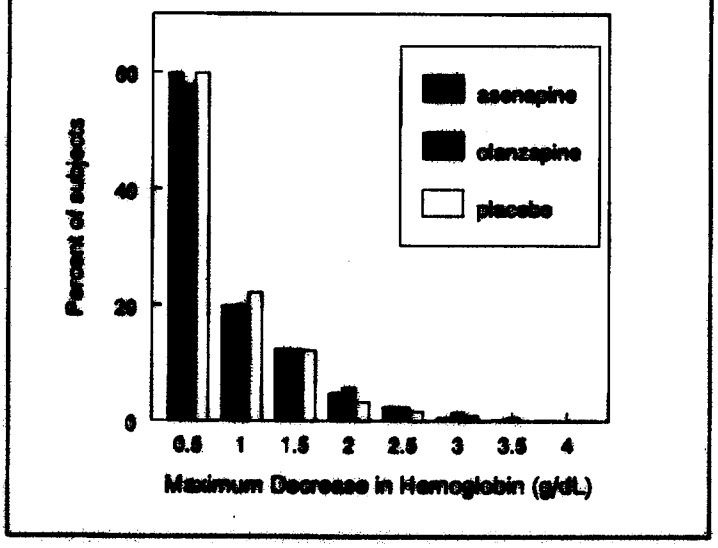
Anemia

Dr. Levin noted 5 cases of anemia in his original review; however, he revised this to a single case in his 6/27/08 addendum. Given that anemia is common in the general population, these numbers did not seem realistic to me. Of note, I could not find the applicant's definitions of "high" and "low" hemoglobin in the dossier. Based on my findings in the SAS transport files, their definition of "low" appears to have been selected to designate anemia of major clinical significance, with cutoffs of 10 g/dL for men and 8 g/dL for women.

I used World Health Organization definitions for my analyses of anemia: for males, hemoglobin <13 g/dL; for females, hemoglobin <12 g/dL. Subjects with baseline values below these cutoffs were not counted in my analyses of "new" anemia.

Based on these definitions, the percentages of subjects with new anemia were: 6.0% in asenapine (n=1392), 4.8% in placebo, and 8.1% in olanzapine. (Note: all subjects were included in the denominators of these calculations, including those with anemia at baseline.) An analysis of maximum decrease in hemoglobin values in 0.5 g/dL increments seems very reassuring (Figure 6).

Figure 6: Maximum Decrease in Hemoglobin Values by Treatment Group



Metabolic Effects

This drug class has known metabolic effects. There appeared to be slight changes in LDL cholesterol in the asenapine group compared to placebo (Figure 7), but the

change was less than that observed with the olanzapine group.

Figure 7: Change in LDL Cholesterol by Quintile

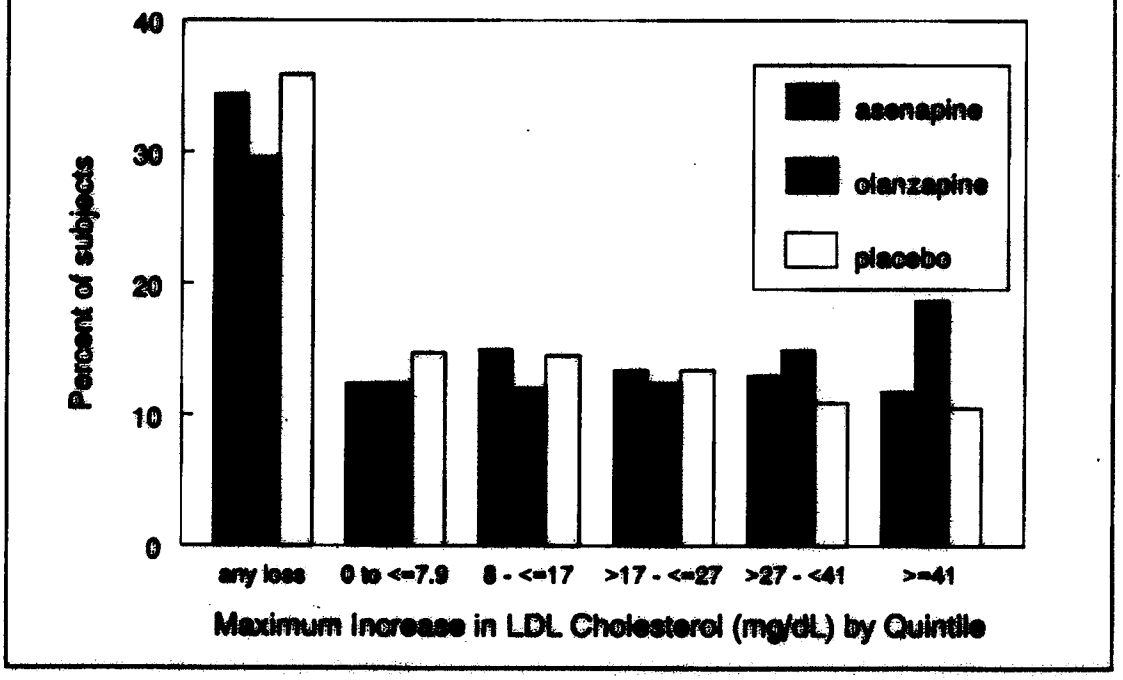
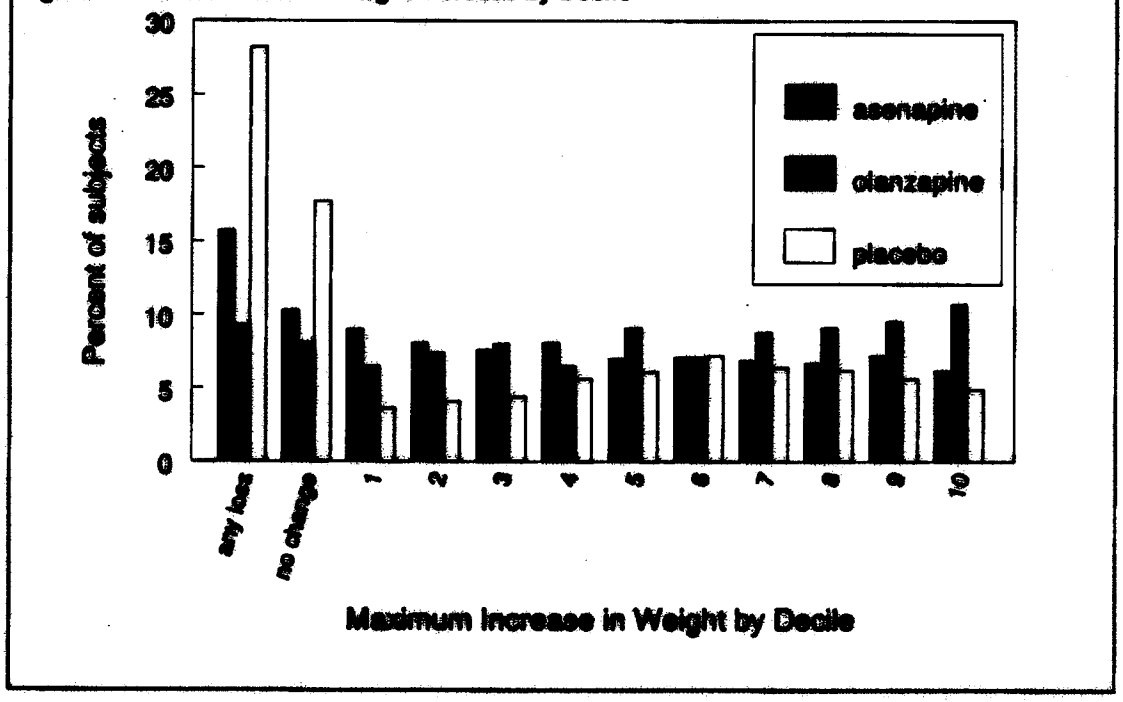


Figure 8: Maximum Rate of Weight Increase by Decile



Weight Gain

As noted by the review team, in the schizophrenic studies there was a mean weight gain of approximately 1.1 kg in the asenapine group, versus a 0.1 kg gain in placebo. Approximately 5% of asenapine-treated patients experienced a weight gain criterion of > 7% of body weight versus 2.0% for placebo. Increases in weight were very similar in subjects in the bipolar studies.

Figure 8 shows the maximum weight gain for all subjects in Cohort E. Given the relatively brief duration of the studies, and given that maximum weights were achieved at various times after initiation of treatment, a *rate* of weight gain was calculated for each subject, as Δweight/Δtime X 30 days, and divided into deciles, with cutoffs of 0.34, 0.64, 0.98, 1.4, 1.87, 2.43, 3.40, 4.76, and 7.50 kg/30 days. There appears to be moderate weight gain in the asenapine group compared with placebo, but substantially less weight gain than with olanzapine.

Other Effects

I have nothing add to Dr. Laughren's discussion of QTc increases, hyperprolactinemia, or transaminase increases.

Concerns Raised by Dr. Kavanagh

Dr. Laughren addressed at length the concerns raised in the four review documents filed by Dr. Kavanagh, and I agree with his conclusions. I will note that Dr. Kavanagh's area of expertise is clinical pharmacology. He is not a medical doctor, and I believe that many of his interpretations and conclusions indicate a lack of clinical judgment – not surprising given his area of training. In general, in my view, his conclusions often seem illogical, distorted, and/or mostly unsupported by the data (see Dr. Laughren's memorandum of 8/1/08).

Conclusions

I concur with the conclusions and recommendations of Dr. Laughren. Asenapine (Saphris) should be approved, as labeled, for the acute treatment of schizophrenia in adults, as well as for the acute treatment of manic or mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults.

The approval letter includes the agreed upon labeling, required pediatric assessments, and post-marketing commitments to perform a long-term maintenance study in adults with acute manic or mixed episodes associated with Bipolar I Disorder, and to evaluate the safety and efficacy of lower asenapine doses in both schizophrenia and manic or mixed episodes associated with Bipolar I Disorder.

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/s/

ELLIS F UNGER
09/13/2009