5.5.8.2 Phase II and Phase III Efficacy Studies

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

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

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

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

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

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

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

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

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

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

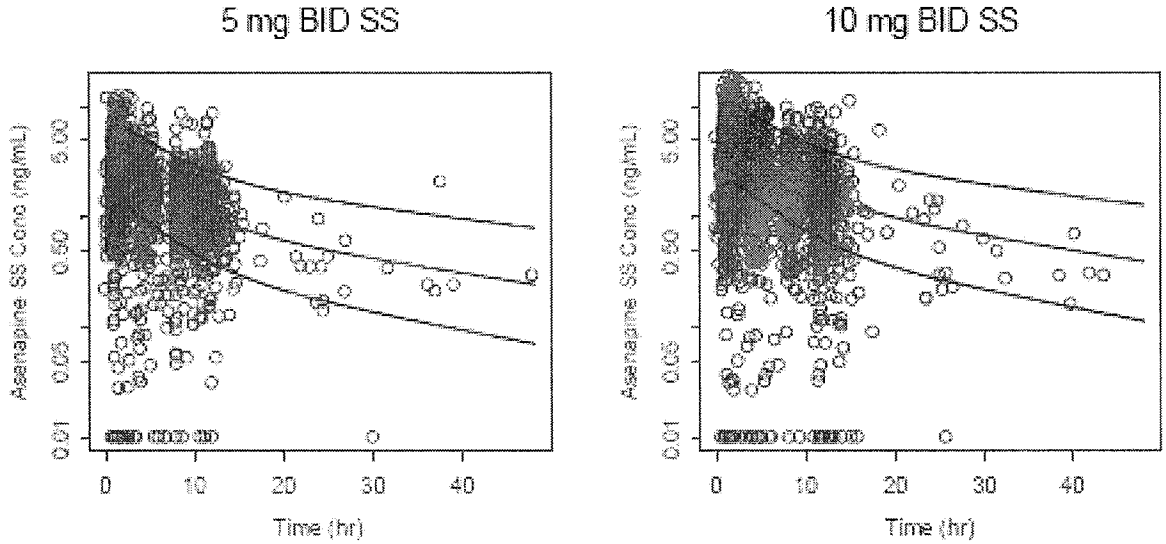
Study # (Phase)	SD / MD	Study Title	Subject Population	Treatment	Analytic Method	LLOQ (ng/mL)	PK Sampling Times
041004 (2b)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine, risperidone and placebo in acute exascerbation of schizophrenia	Acute Schizophrenia	Day 1: 1 mg BID Day 2: 2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

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

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

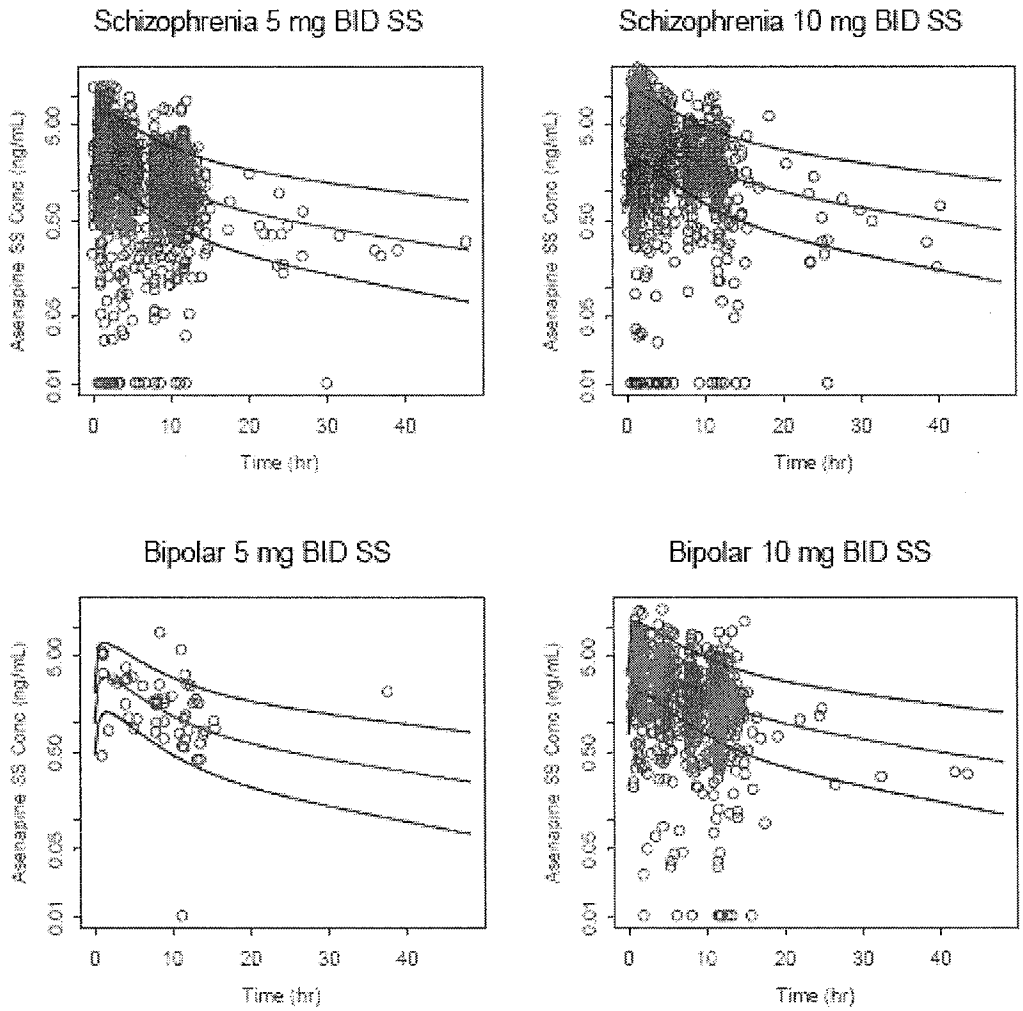
a Based on data at screening

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



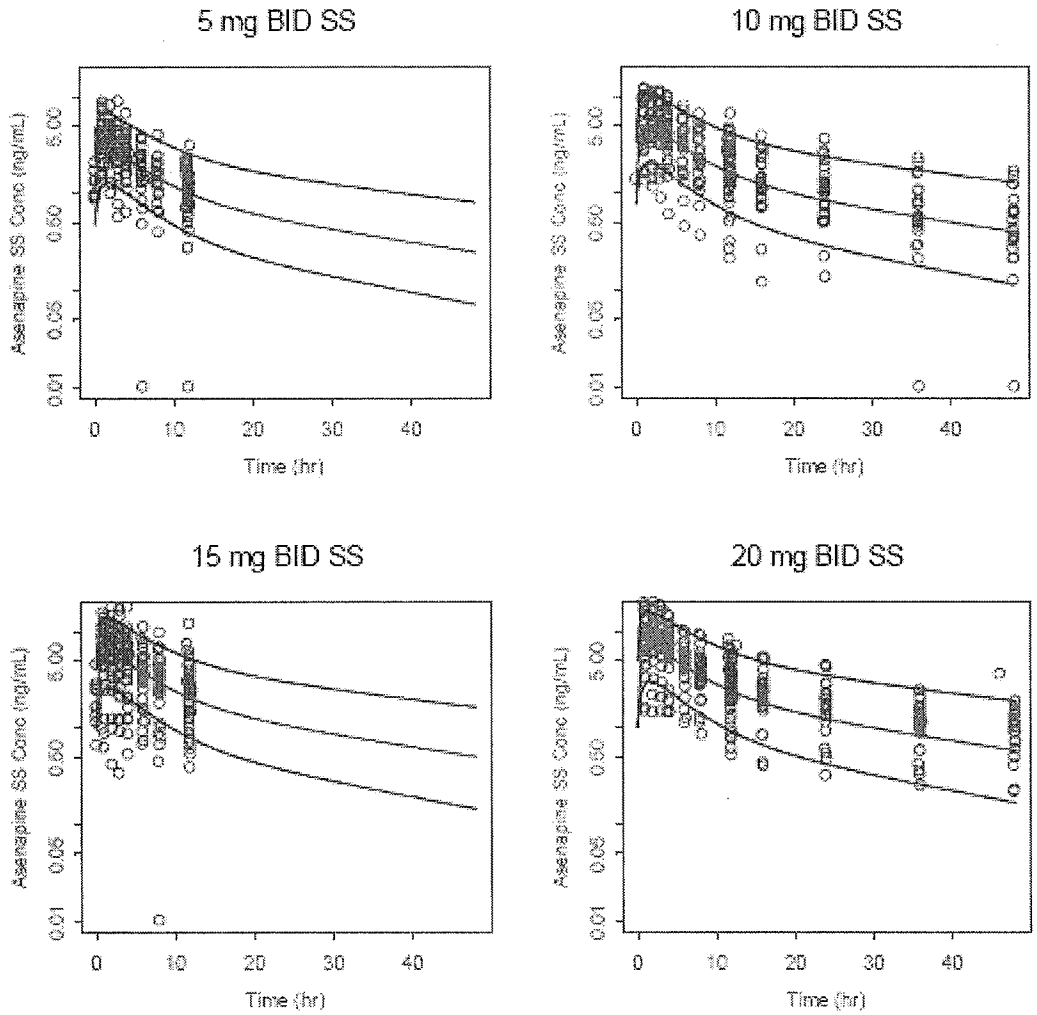
Grey circles represent the observed asenapine concentrations; red lines represent the 95th and 5th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

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



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

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

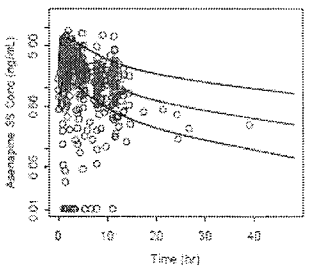


Grey circles represent the observed asenapine concentrations; red lines represent the 95th and 5th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

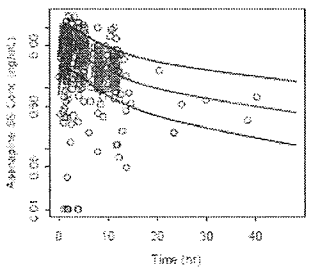
Figure 132 **Observed Asenapine Concentrations from Individual Phase 2/3 Studies Overlaid on Unconditional 90% Prediction Interval by Indication, Study, and Dose**

Phase II / III Efficacy Studies in Schizophrenia

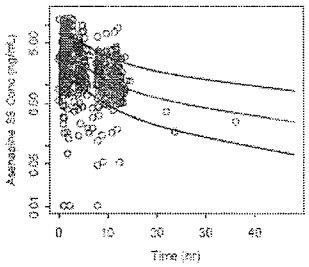
041-021 5 mg BID SS



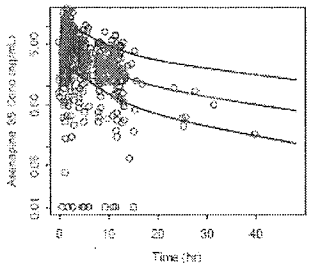
041-021 10 mg BID SS



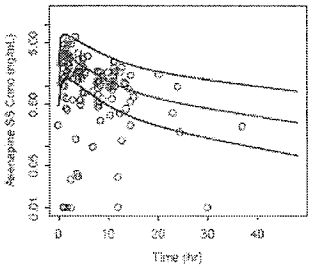
041-023 5 mg BID SS



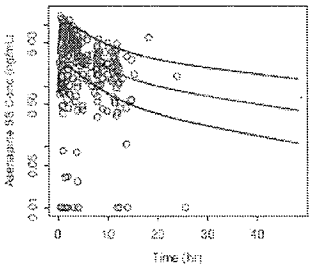
041-023 10 mg BID SS



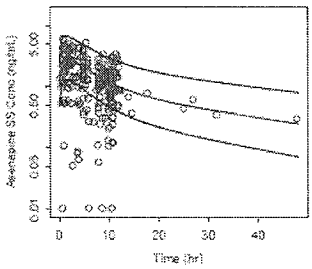
041-022 5 mg BID SS



041-022 10 mg BID SS

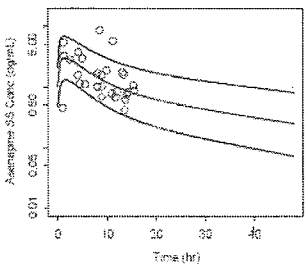


041-004 5 mg BID SS

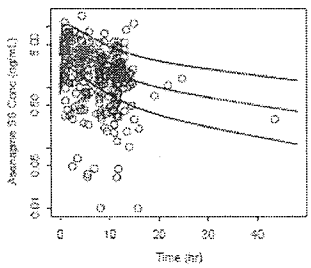


Phase II / III Efficacy Studies in Acute Mania

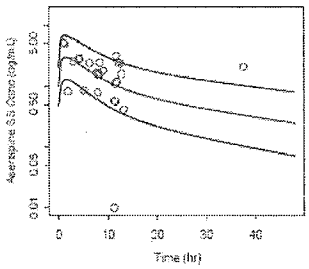
A7501004 5 mg BID SS



A7501004 10 mg BID SS



A7501005 5 mg BID SS



A7501005 10 mg BID SS

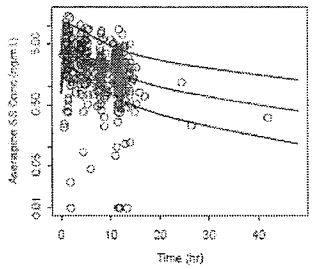


Table 153 shows the percent of the observations above and below the predicted median, 5th, and 95th, percentiles for the phase II / III studies. It's clear that the model overpredicts however, the large percent of concentrations that are below the 5th percentile and are even zero suggests that this may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

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

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

5.6 Pharmacodynamics

5.6.1 PK/PD

5.6.1.1 Biomarker - PET Studies

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

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

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

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

5.6.1.1.1 Oral Administration

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

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

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

5.6.1.1.2 Sublingual Administration

5.6.1.1.2.1 PET Study 25510

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

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

Table 154 PET Scans Employed in Study 25510

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

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

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

Receptor	Radioligand	ORG 5222 (K_i in nM)
D_1	[3H]SCH 23390	4
D_2	[3H]spiperone	3.1
D_3	[3H]NPA	0.6
α_1	[3H]prazosin	0.6
α_2	[3H]rauwolscine	7.9
5-HT_{1A}	[3H]8-OH-DPAT	10
5-HT_{1B}	[3H]5-HT (rat)	40
5-HT_{1D}	[3H]5-HT (calf)	79
5-HT_{2A}	[3H]ketanserin	0.06
5-HT_{2C}	[3H]5-HT (pig)	0.08
H_1	[3H]mepyramine	7.9
ACh/m	[3H]QNB	5000

From de Boer et al. 1993

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

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

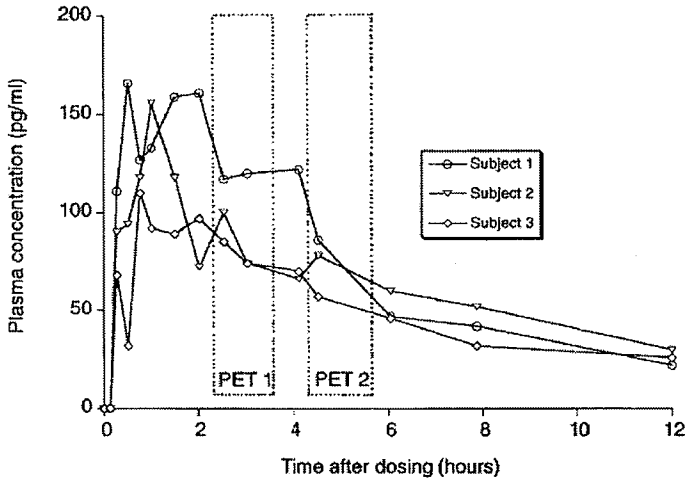


Figure 135 Radionuclide Receptor Binding to $5HT_{2A}$ in the Frontal Cortex and Cerebellum in the Presence and Absence of Asenapine 100 mcg – Study 25510

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

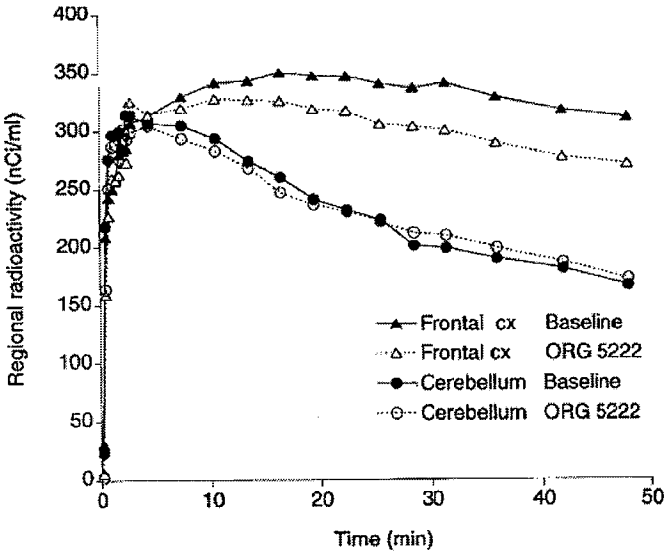


Figure 136 Radionuclide Receptor Binding to D_2 in the Putamen and Cerebellum in the Presence and Absence of Asenapine 100 mcg – Study 25510

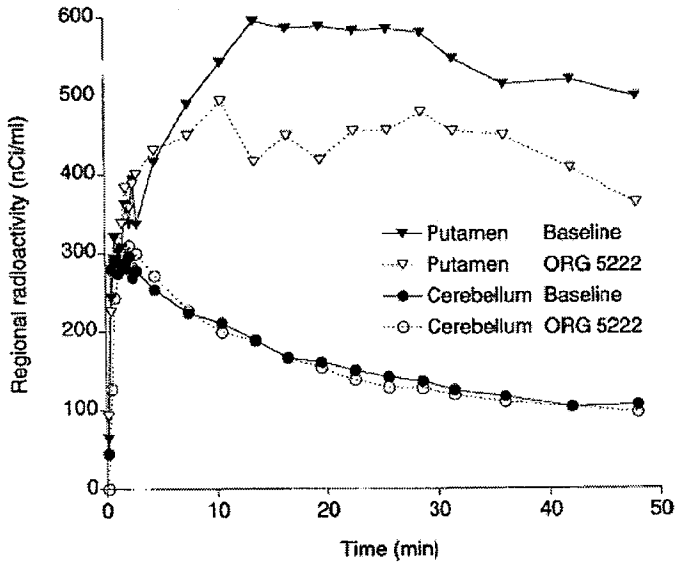


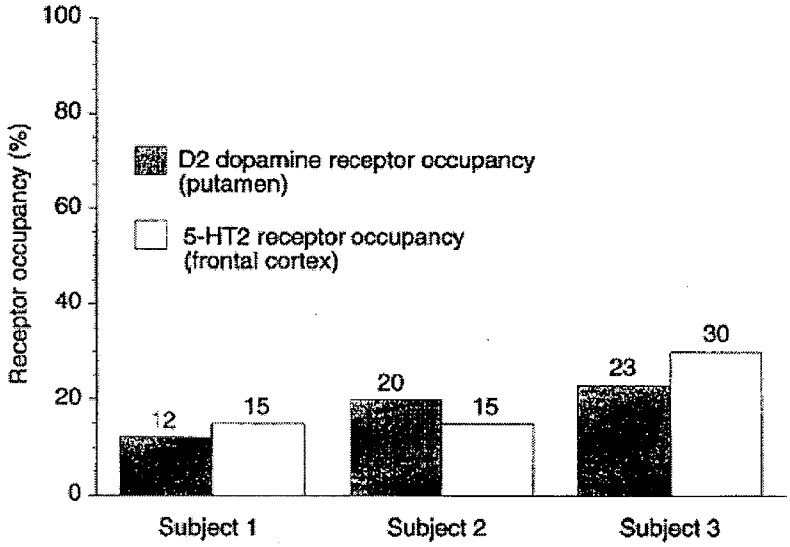
Figure 137 and Figure 138 show the actual pharmacokinetic metrics and the sponsor's calculated % binding to D_2 and $5HT_{2A}$ associated with these metrics in these 3 subjects.

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

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

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

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



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

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

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

a Reviewer's estimate based on simple Bmax model.

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

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

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

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

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

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

5.6.1.1.2.2 PET Study 25516

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

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

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

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

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

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

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

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

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

5.6.1.2 PK / PD Modeling and Simulation

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

According to the report:

'The revised objectives of Aim 1 were:

- Predict mean week 6 Last Observation Carried Forward (LOCF) PANSS change from placebo for the ongoing study (041-013)[1], and the uncertainty around these predictions (including uncertainty and variability).
- The underlying predicted mean LOCF PANSS true dose response curve for Org5222 and the uncertainty around that prediction.
- Simulations giving the predicted likelihood of the treatments in study 041-013 being significantly different from placebo.
- An evaluation of the effect of dropout on the LOCF predictions.
- Predicted doses of Org5222 corresponding to clinically used doses of atypical antipsychotics.'

To achieve this Pharsight did the following:

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

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

The following pharmacokinetic data was used per the report:

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

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

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

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

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

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

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

5.6.1.2.2 Fit of D2 Occupancy vs. Plasma Concentrations

The sponsor fit the following models to the data:

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

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

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

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

* SE of logs

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

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

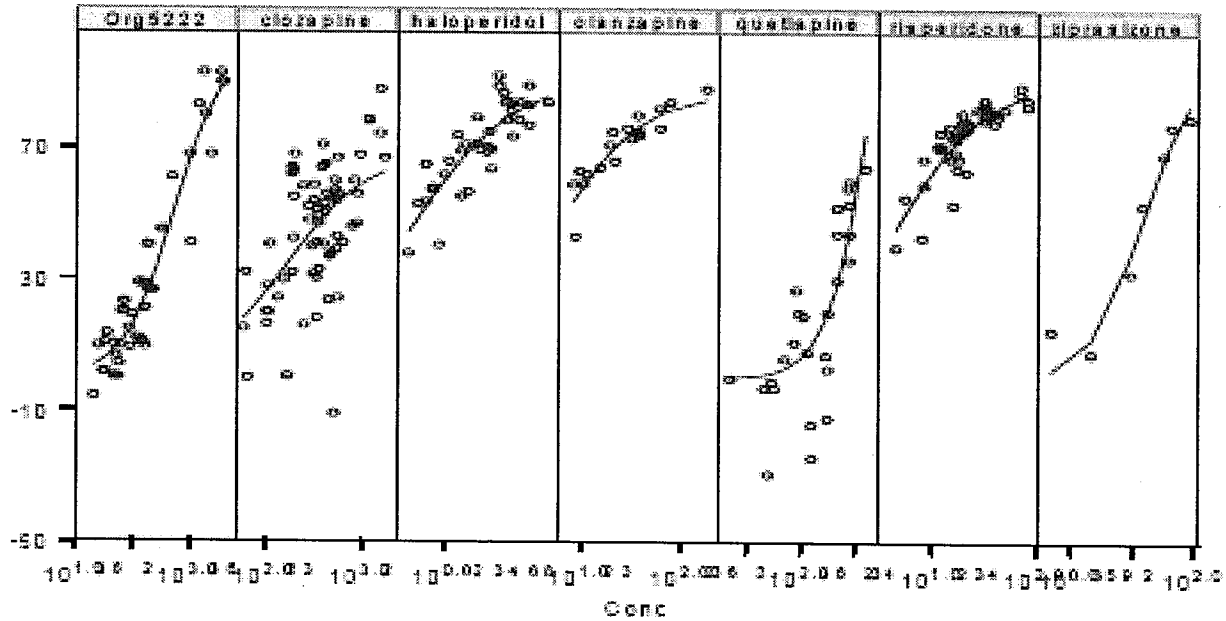
*SE of logs

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

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

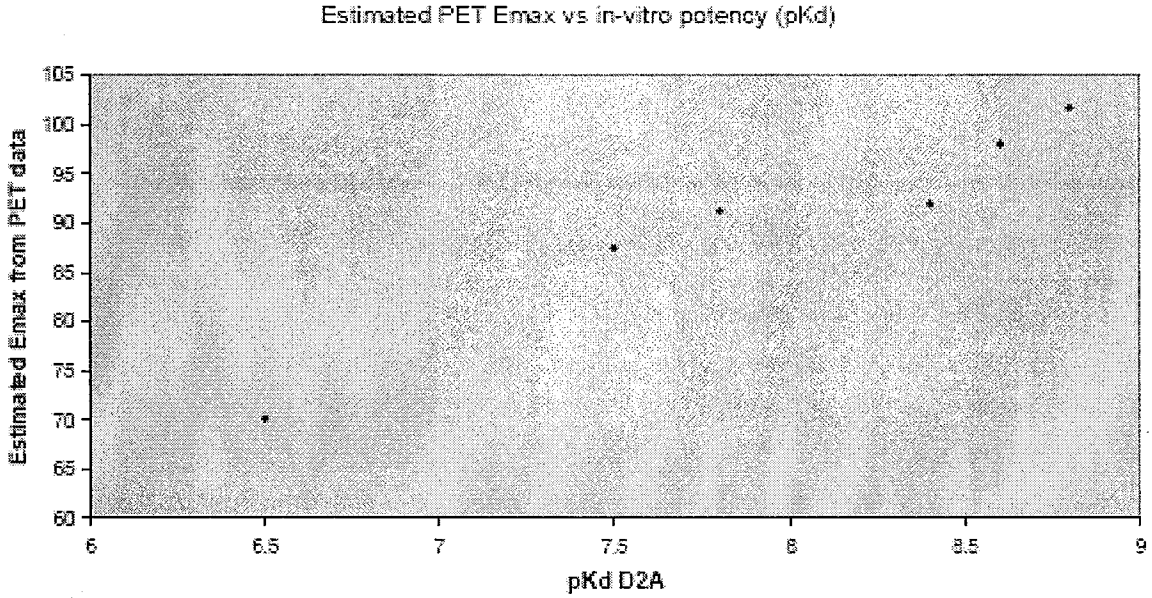
The sponsor's fits of individual Emax models to data for the various drugs is shown in Figure 139.

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



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

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



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

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

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

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

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

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

*Corrected for molecular weight and plasma protein binding.

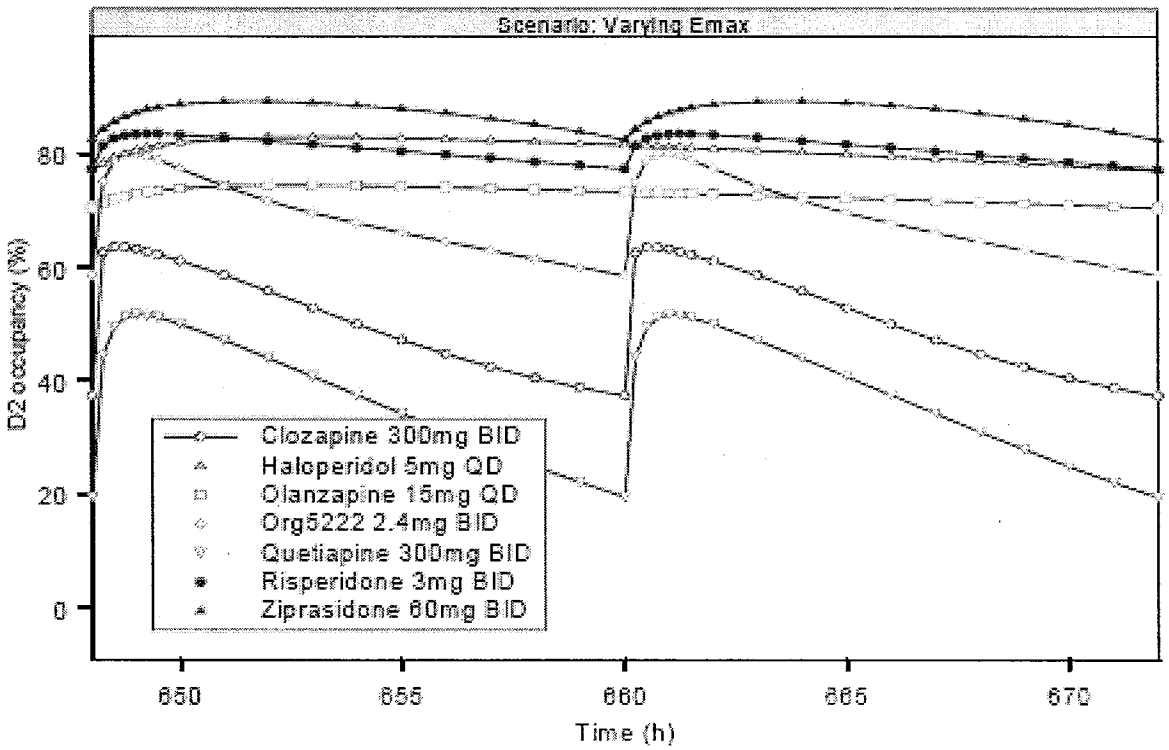
The sponsor to an extent came to a similar conclusion as shown by the following and excluded clozapine and quetiapine data from further analysis.

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

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

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

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



5.6.1.2.3.1 Convariate Analysis

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

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

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

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

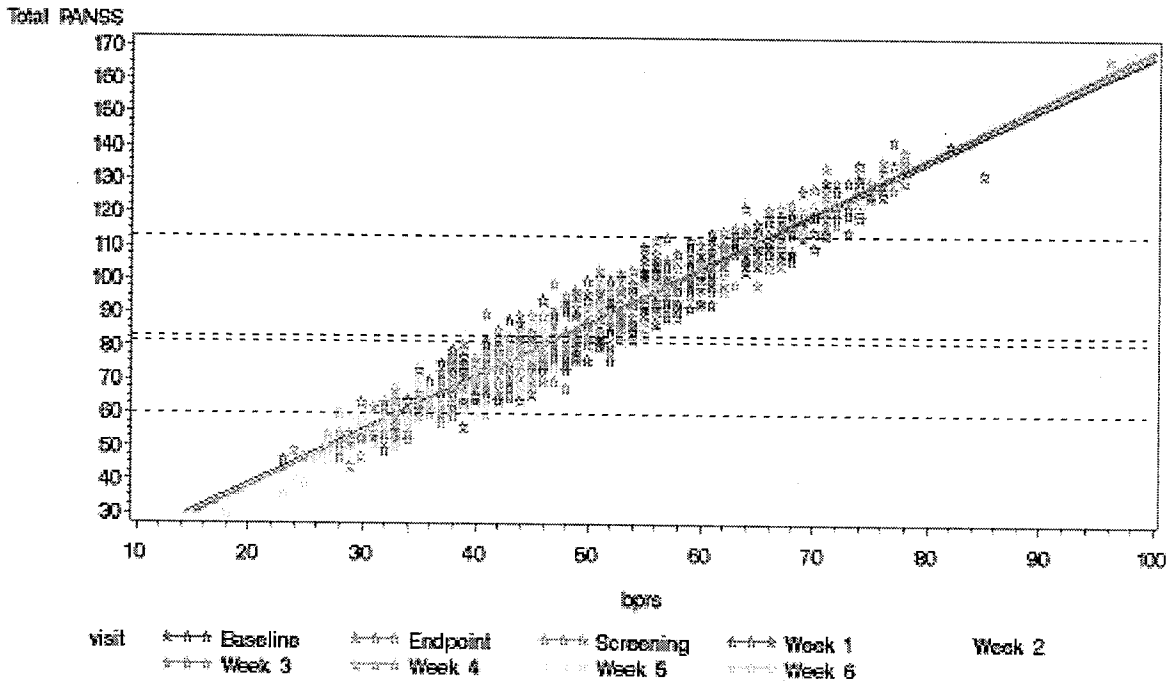
In the analysis looking at time of dropout, there was no evidence that any subgroup were significantly more likely to stay in or withdraw from the study. This result must be taken with caution, as subtle effects may be difficult to detect with this relatively small sample size.'

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

5.6.1.2.4 Conversion of BPRS Scores to PANSS Scores

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

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



5.6.1.2.5 Pharmacodynamic Link Model of PANSS vs. D2 Occupancy

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

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

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

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

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

Where:

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

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

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

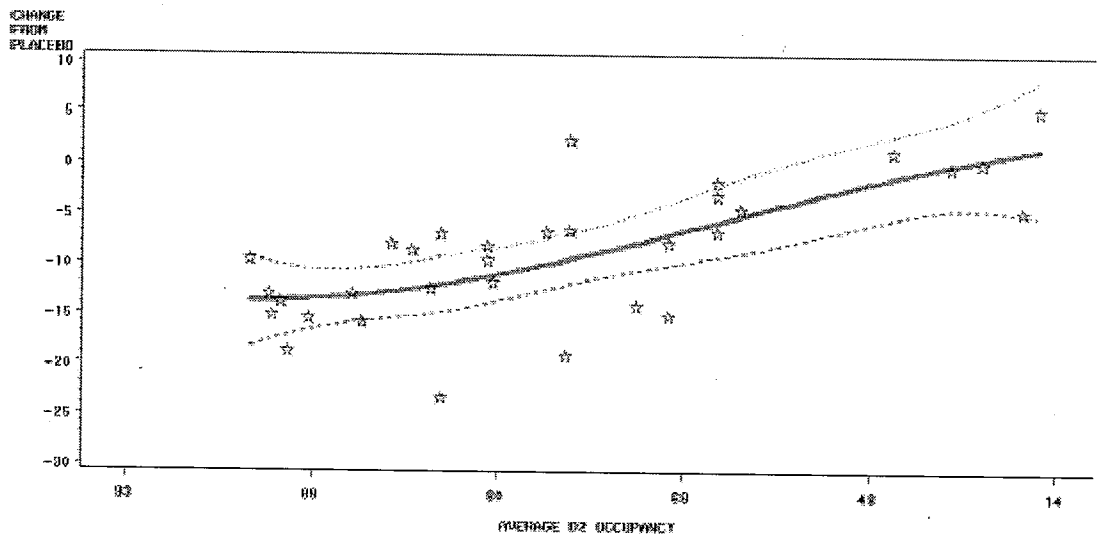
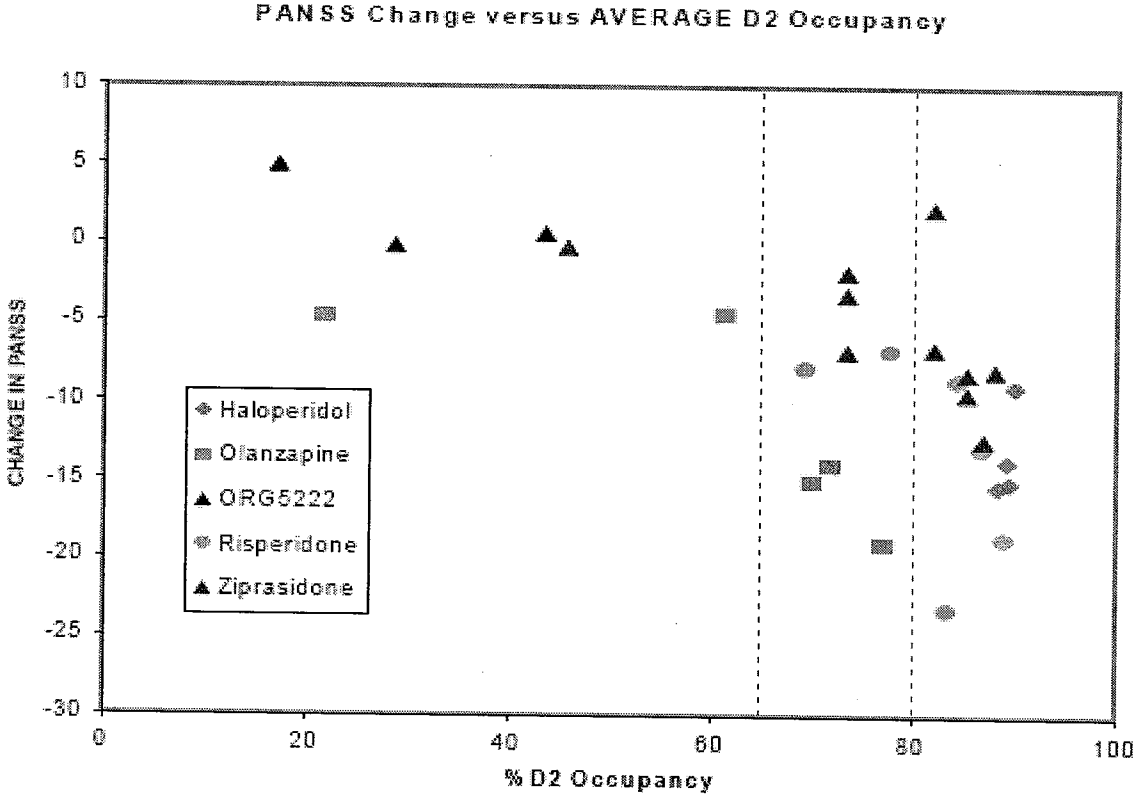


Figure 141 shows the sponsor's plot for Change in PANSS vs. predicted mean D2 occupancy. Interpretaion of this graph must be done cautiously, as we don't know for which data points the PANSS scores were estimated based on BPRS and thereby may introduce excessive variability. Also the D2 occupancy is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

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



5.6.1.2.6 Exploration of Other Potential Co-Factors

5.6.1.2.6.1 U-Shaped Dose Response

This was allowed initially but then rejected.

5.6.1.2.6.2 Mixed Effect Model of Drop-outs on LOCF

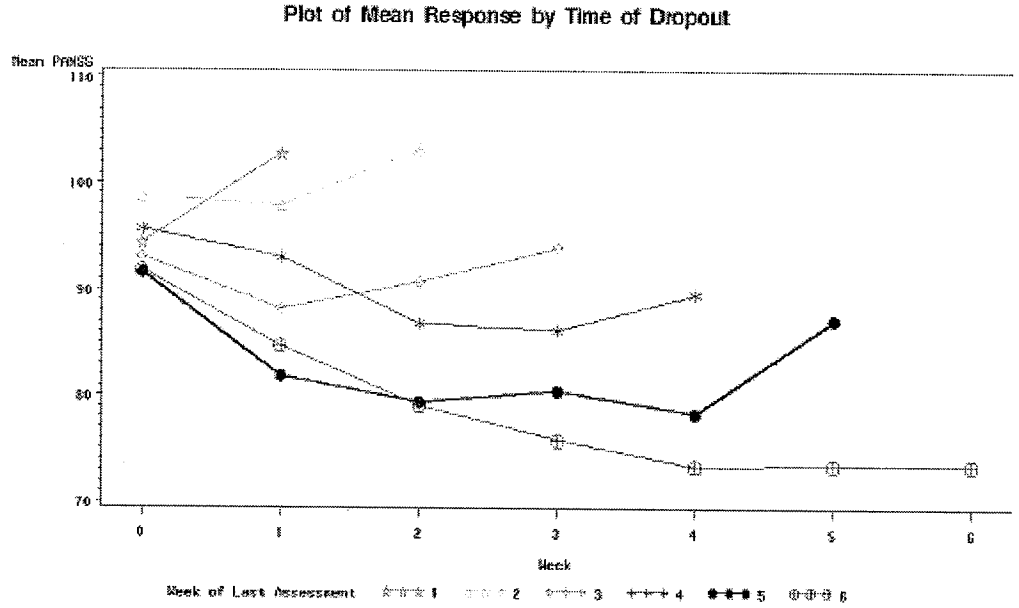
This was explored but eventually dropped from the model. The lack of a relationship may have been due to evaluating the effect on LOCF rather than OC, due to an inadequate model, or other reasons. The sponsor's discussion follows:

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

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

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

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



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

5.6.1.2.7 Modeling and Simulation

In summary the final model included:

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

5.6.1.2.7.1 Simulation of Study 041-013

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

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

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

1) Fit the model of Response versus Effect.

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

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

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

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

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

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

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

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

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

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

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

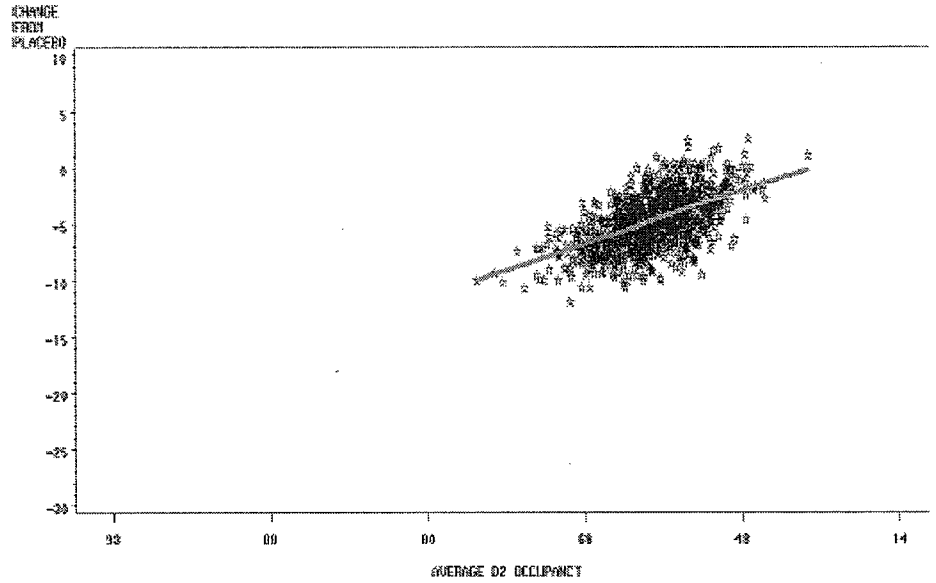


Figure 147 Sponsor's Figure 12 Distribution across 1000 simulated replicates showing predicted mean LOCF PANSS change from placebo after administration of 1.6 and 2.4mg Org5222 b.i.d to 60 subjects. Distribution incorporates model uncertainty and interindividual variability.

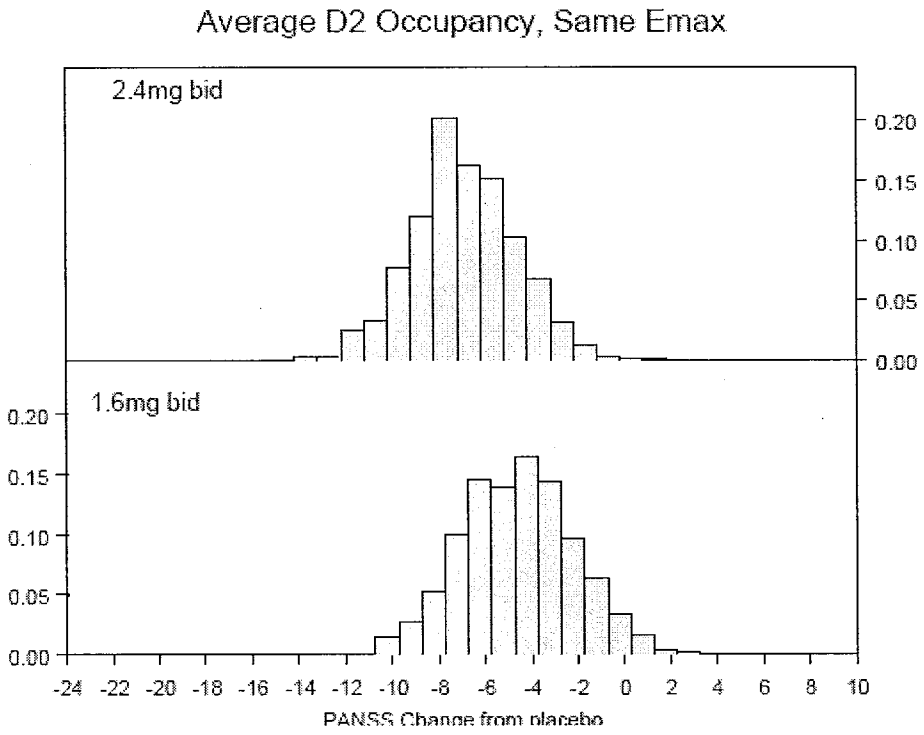


Table 164 Sponsor's Predicted mean PANSS LOCF change from placebo at 6 weeks for Org5222 given at the doses of 1.6 and 2.4mg in study 041-013 for 4 different simulation scenarios.

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

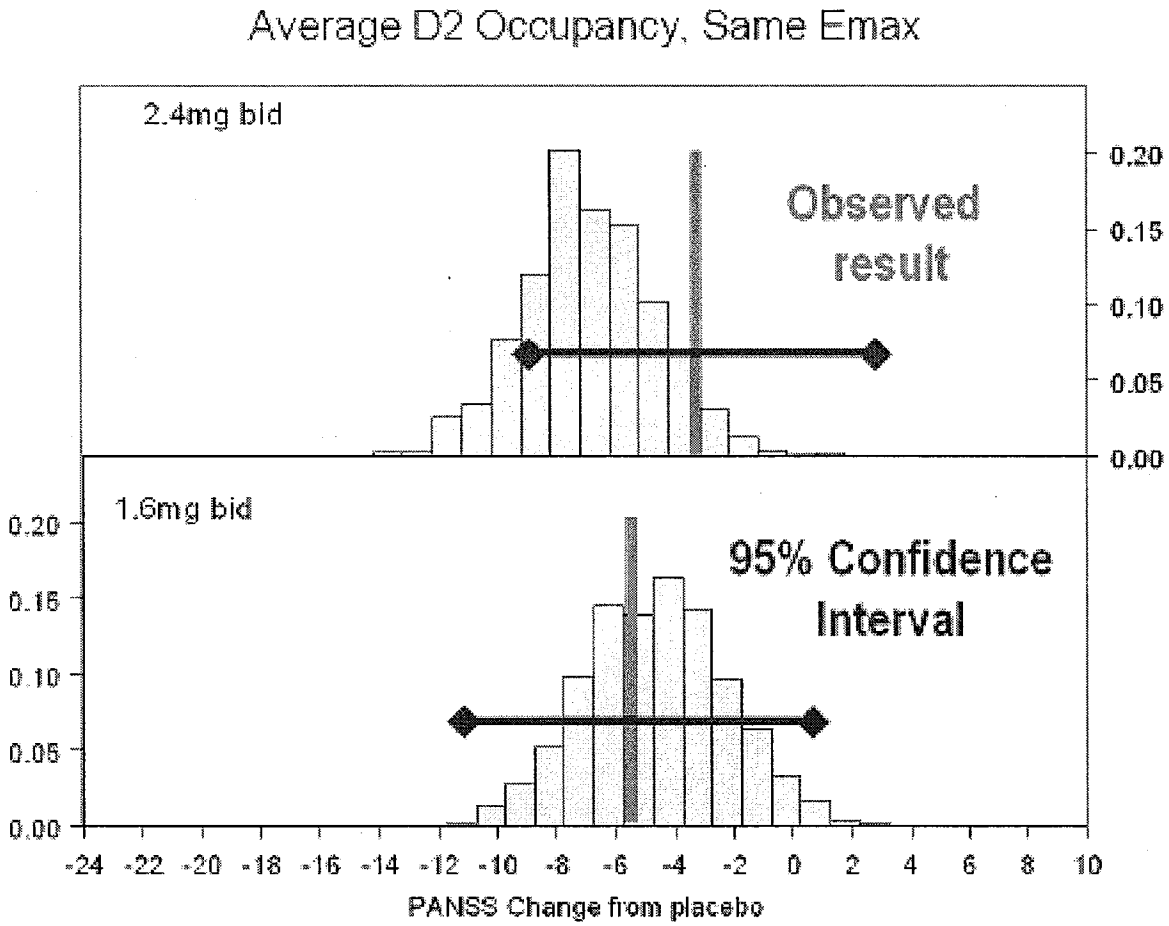
Table 165 Sponsor's Table 11. Predicted likelihood of showing a significant difference from placebo for each of the two doses in study 041-013, for the four different simulation scenarios.

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

5.6.1.2.7.2 Validation

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

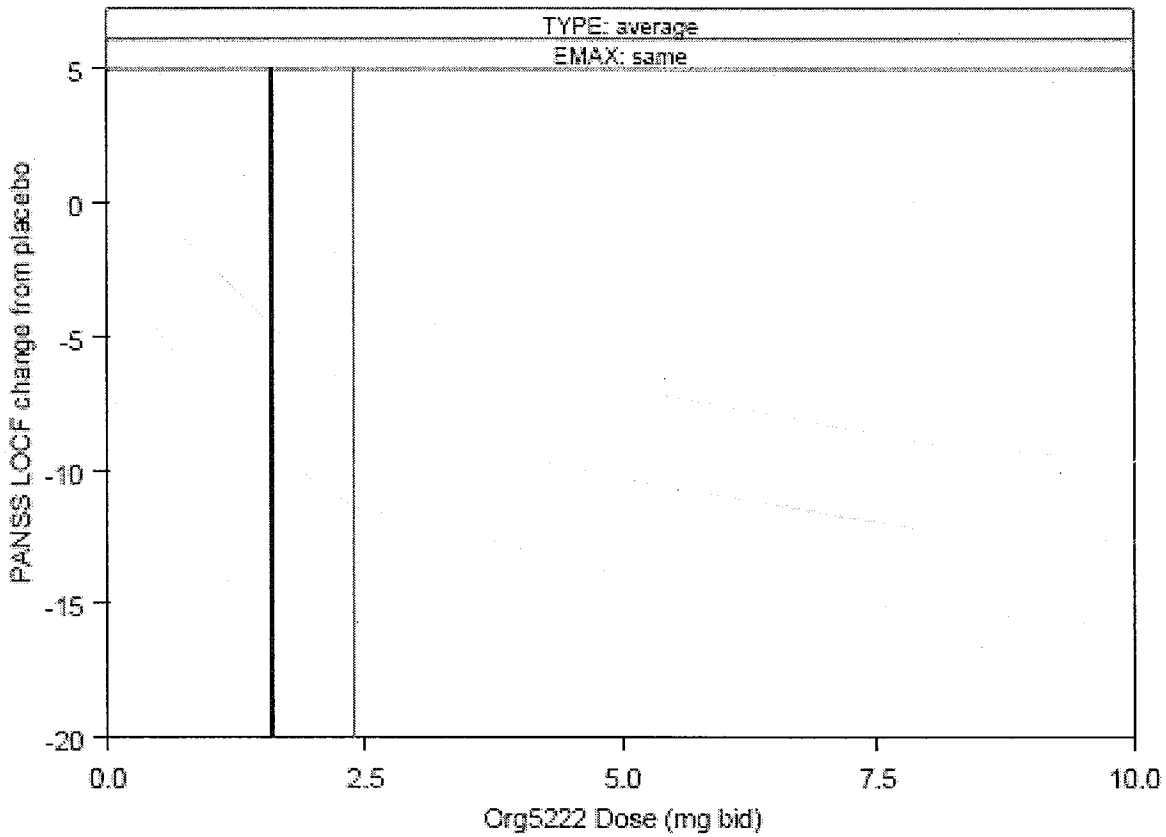
Figure 148 Sponsor's Figure 14 Actual results from study 041-013 shown with estimate and 95% CI, in comparison to distribution across 1000 simulated replicates showing predicted mean LOCF PANSS change from placebo.



5.6.1.2.7.3 Dose Prediction

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

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

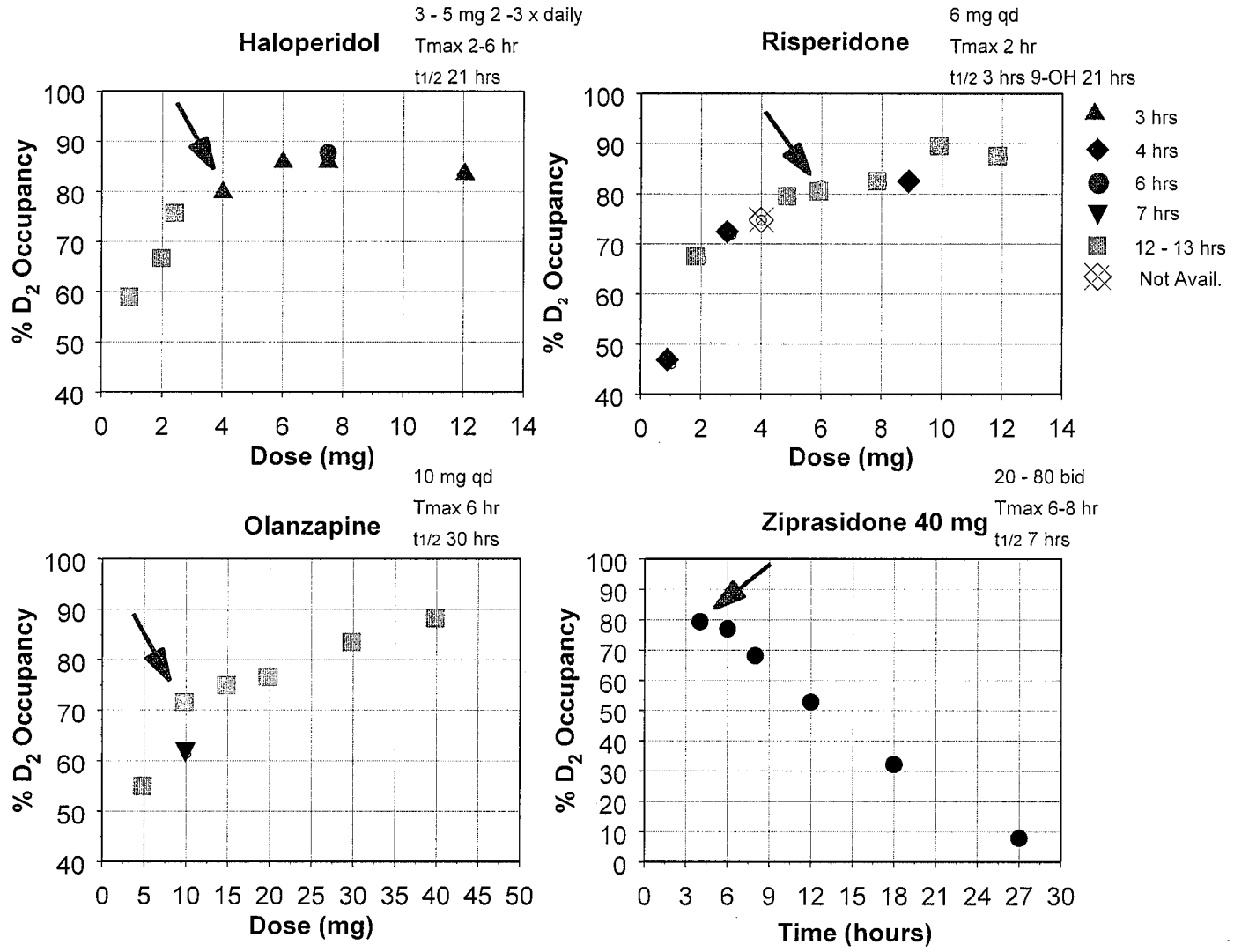


5.6.1.2.8 Reviewer's Dose Estimates Based on Analysis of PET Studies

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

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

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



5.6.1.2.8.1 Conclusions

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

Source: Clinical Summary

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

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

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

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

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

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

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

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

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

3.2 PRECLINICAL INFORMATION

Source: nonclinical summary

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

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

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

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

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

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

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

5.6.1.3 *Effect on QTc*

Asenapine prolonged QTc.

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

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

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

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

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

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

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

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

Table 167 Treatment Groups and Dosing in TQTc - Study A7501001

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

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

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

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

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

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

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

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

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

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

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

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

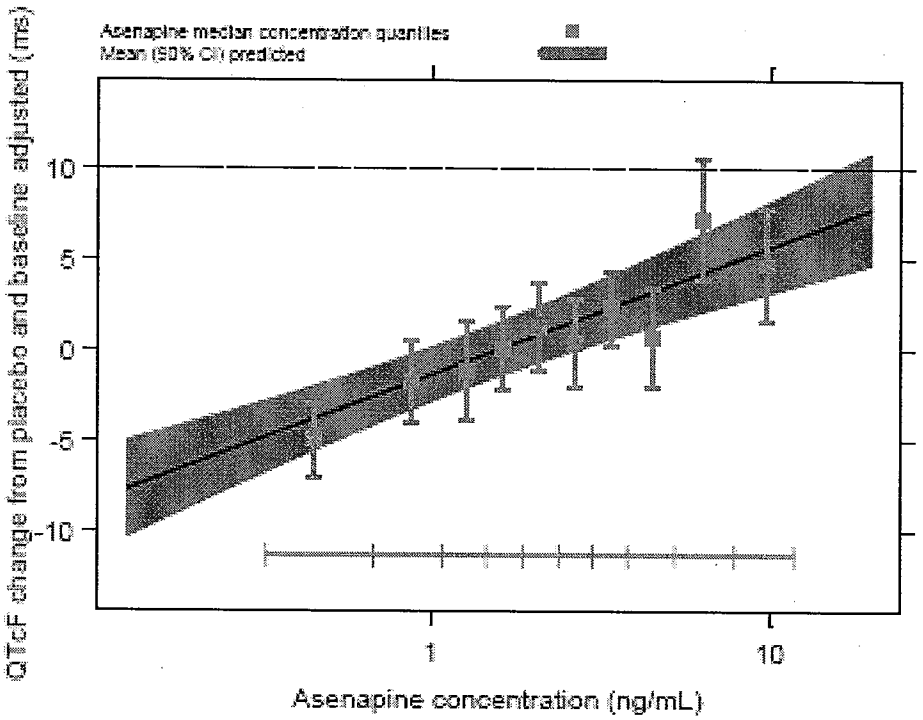


Figure 153 Linear Model of ΔΔQTcF vs. Quetiapine Concentration Overlaid with Mean QT Prolongation with 90% CIs at the Median-of the 10% Quantiles for Quetiapine Concentration.

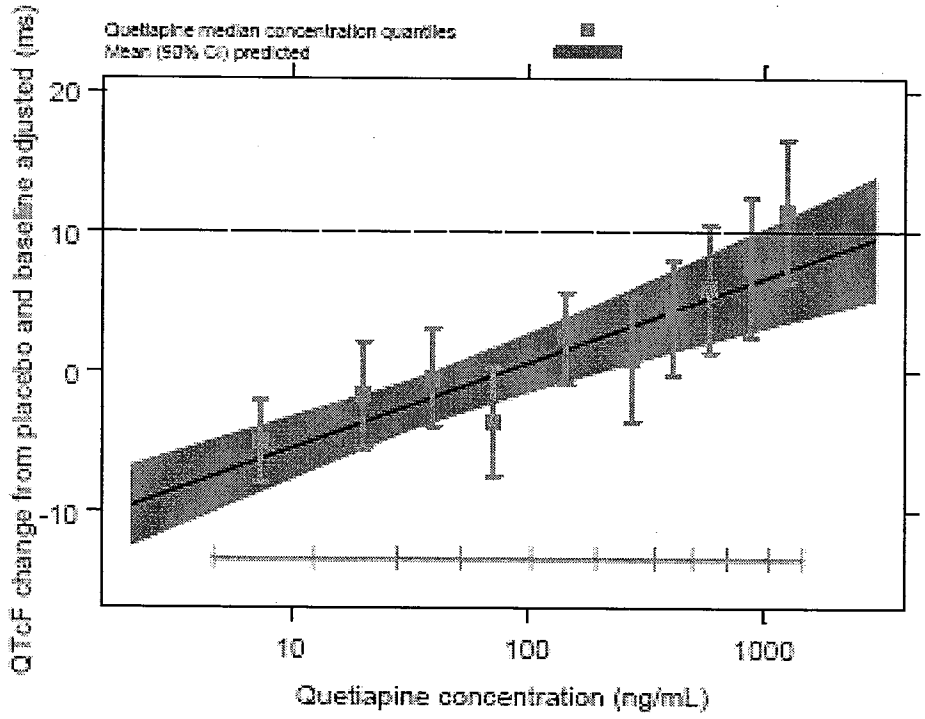


Figure 154 Steady State Asenapine Concentrations with Overlaid Mean Concentration vs. Time Profile Prediction with 90% CIs for Asenapine 20 mg SL BID. Data from Thorough QT study – A7501001

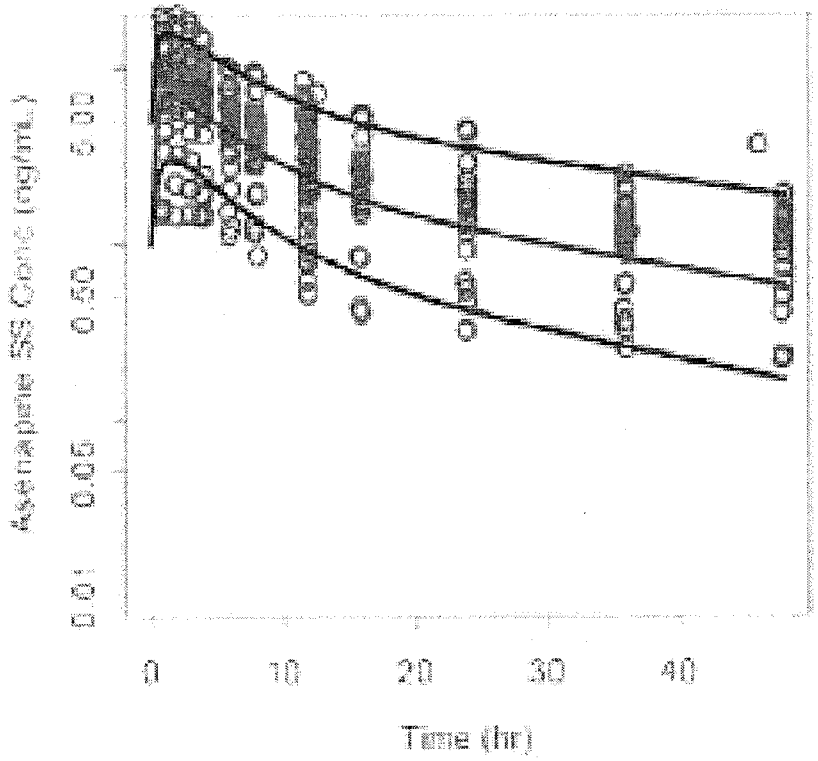
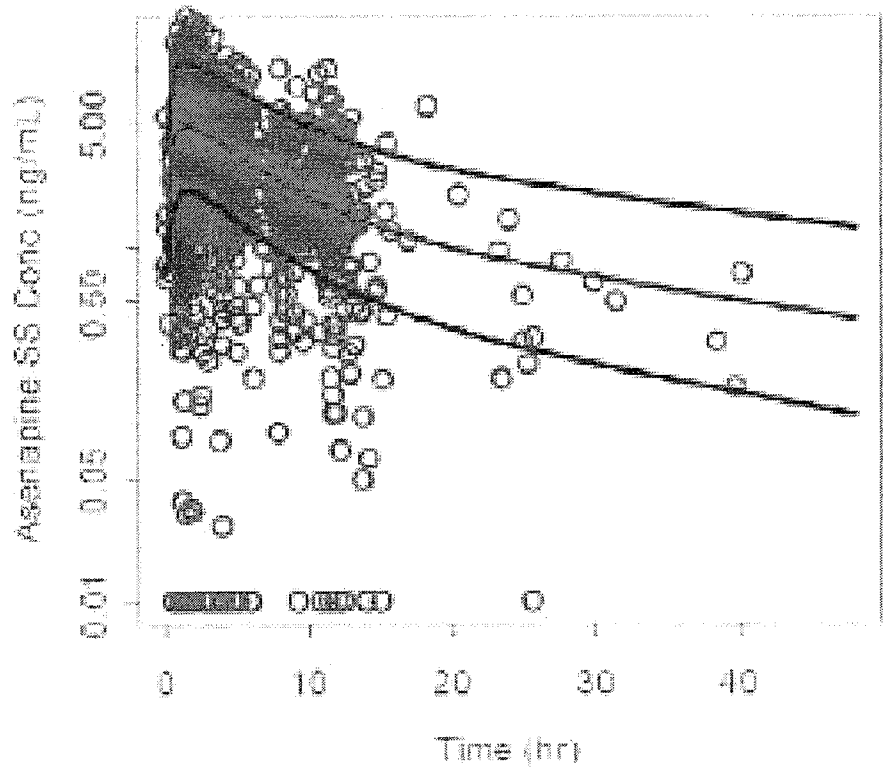


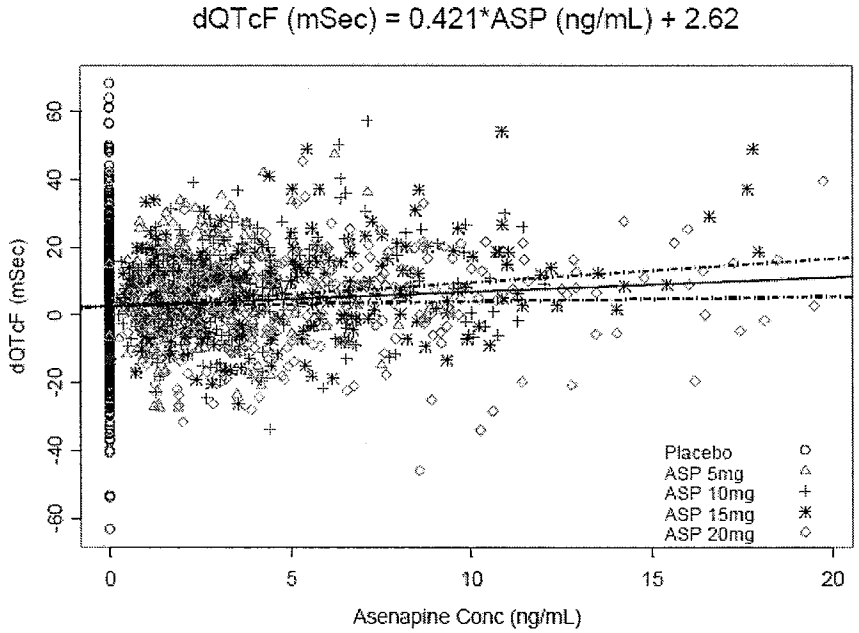
Figure 155 Steady State Asenapine Concentrations with Overlaid Mean Concentration vs. Time Profile Prediction with 90% CIs for Asenapine 10 mg SL BID. Data from TQT and phase IIb/III Studies



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

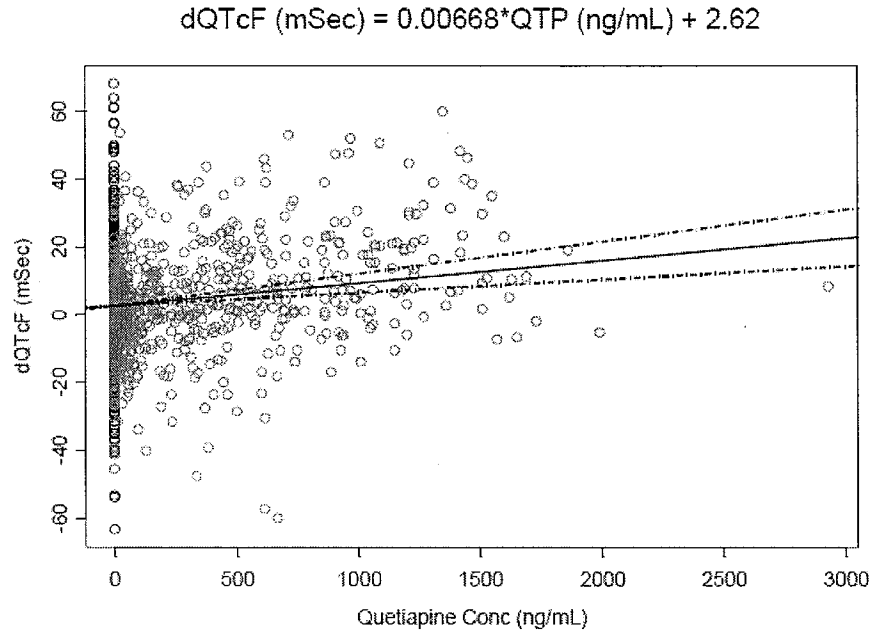
Figure 156 and Figure 158 shows the sponsor's linear models of ΔΔQTcF vs. plasma asenapine and quetiapine concentrations. It's clear that asenapine concentrations do go up to 20 ng/ ml and that most concentrations between 10 and 20 ng/ml are achieved by a dose of 20 mg BID followed by a dose of 15 mg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

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



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

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



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

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

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

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

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

Source: 11.1.2.01.01.06
[a] Post dose

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

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

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

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

Source: 11.1.2.01.01.05
[a] Post dose

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

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

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

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

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

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

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

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

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

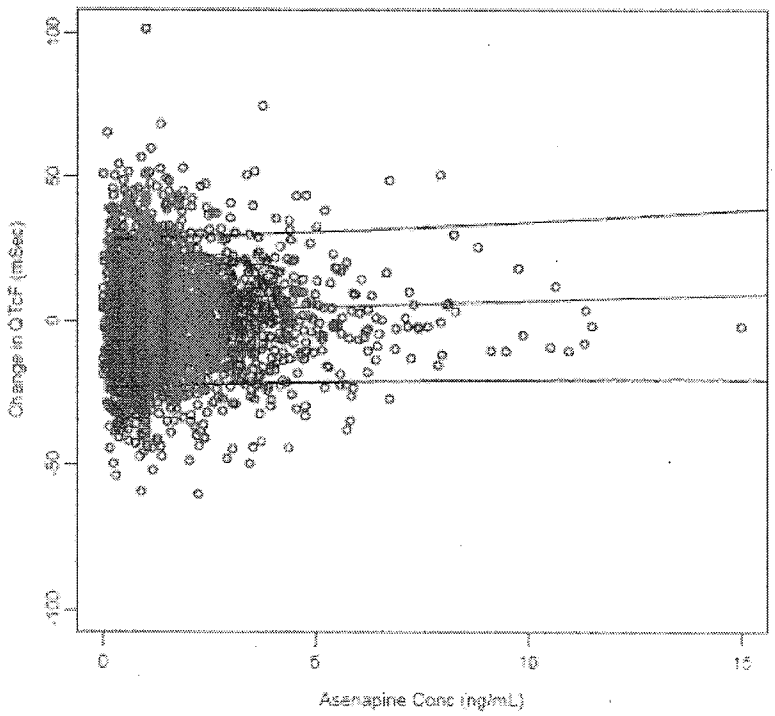
Figure 160 is claimed to be plot of observed ΔΔQTcF from the TQTc study vs. individual predicted concentrations based on a population pharmacokinetic model for a phase 3 schizophrenia trial of Asenapine 5 mg or 10 mg BID with sparse sampling.

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

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

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

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



Sponsor's Figure 4, page 20 from Study INT00036960

5.6.2 Exposure Response

5.6.2.1 Schizophrenia

5.6.2.1.1 Acute Treatment of Psychosis

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

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

- Of 4 studies only 2, the smaller initial phase IIb study 41004 and the last phase III study 41023, were positive. The other 2 phase III studies were negative.

- The active control risperidone failed to show efficacy in the positive phase IIb study 41004 in spite of adequate dosing and is therefore a 'failed' study.

- Only the lower dose of asenapine 5 mg BID and not the higher dose of 10 mg BID showed efficacy in the second positive study 41023.

- Although the most efficatious available antipsychotics were used at therapeutic doses, i.e. risperidone 3 mg BID, olanzapine 10 – 20 mg QD, and haloperidol 4 mg BID, the difference from placebo was minimal, i.e. ~5.6, -5.4 and -2.3, and -5.7 respectively. Whereas the difference from placebo expected with each of these compounds is on the order of at least -10 and closer to -15 units.

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

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

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

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

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

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

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

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

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

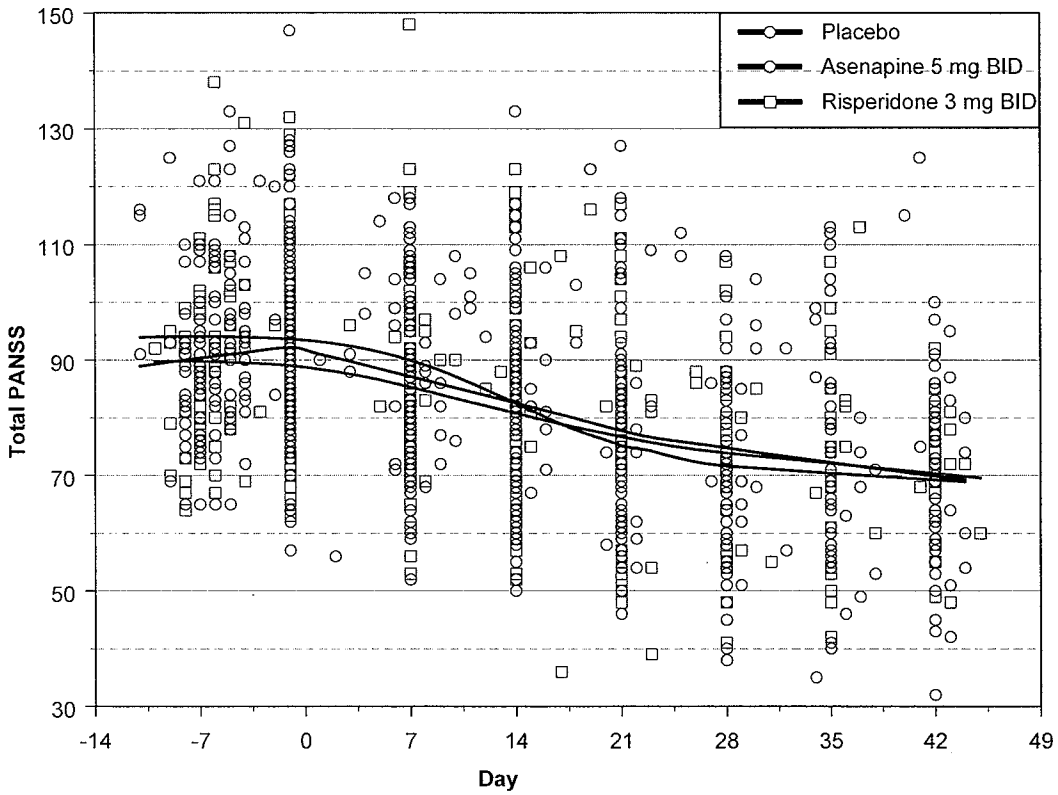
Source: Appendix A Table 41.1.S, Table 41.2.S, Table 41.3.S, and Table 41.4.S: referenced tables were (covariance structure = UN)
All values are mean (SE)
* indicates $p \leq 0.05$

5.6.2.1.1.1 Change in PANSS Score

5.6.2.1.1.1.1 Study 41004

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

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



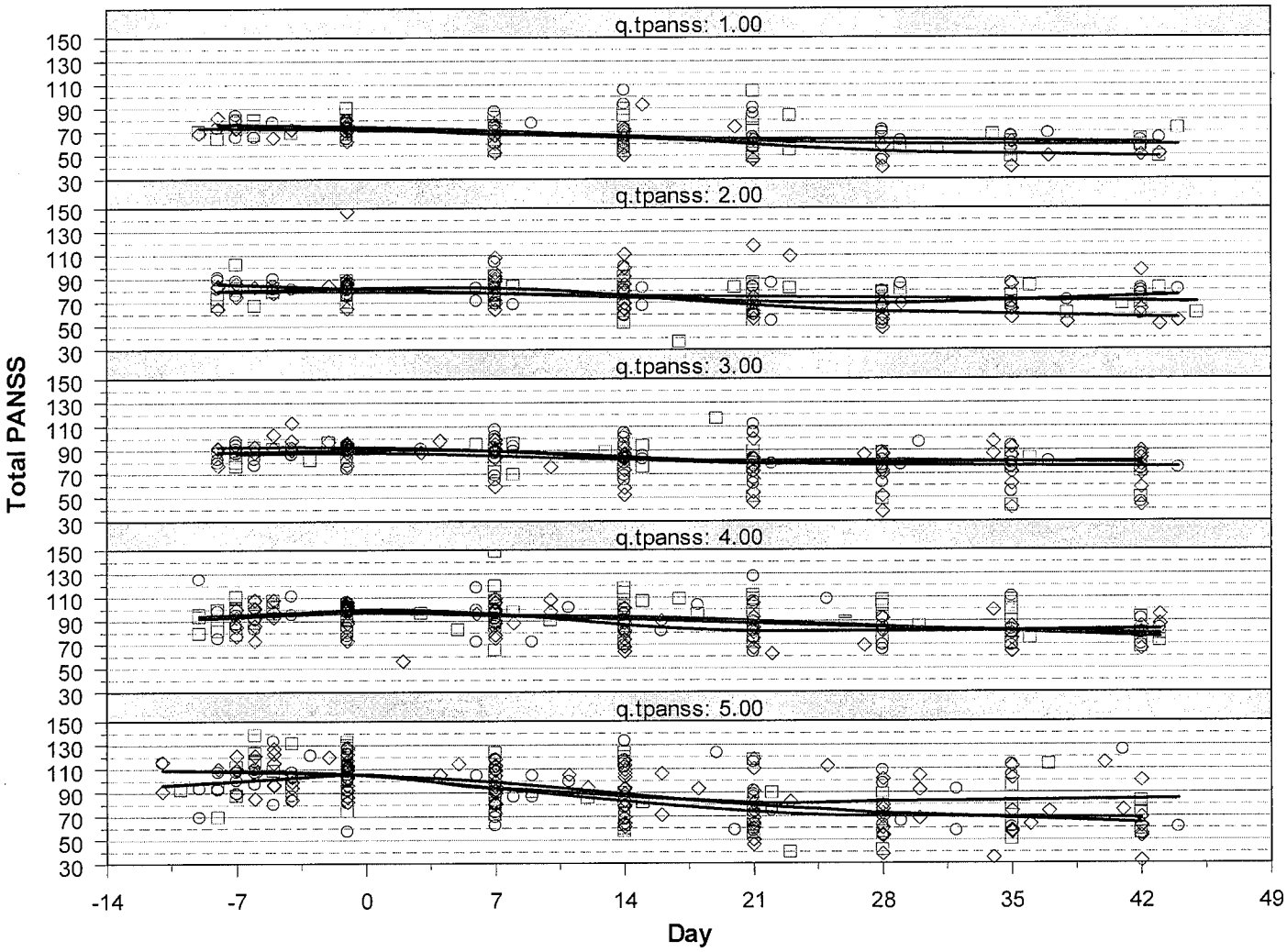
Next this reviewer examined the response while controlling for the initial severity of illness. To do this the highest PANSS score measured prior to treatment was determined for each subject. These scores were then divided into quintiles and the treatment responses for each quintile were compared. Table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

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

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

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

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



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

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

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

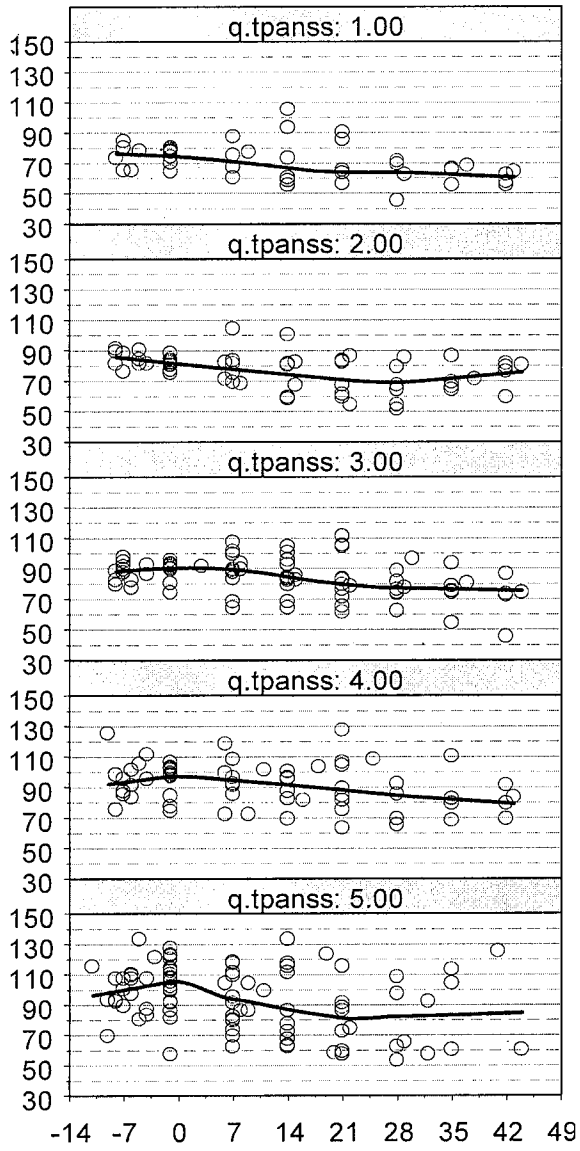


Figure 164 Total PANSS Score vs. Time (Days) for Asenapine 5 mg BID Treatment by Quintile of Severity - Study 41004

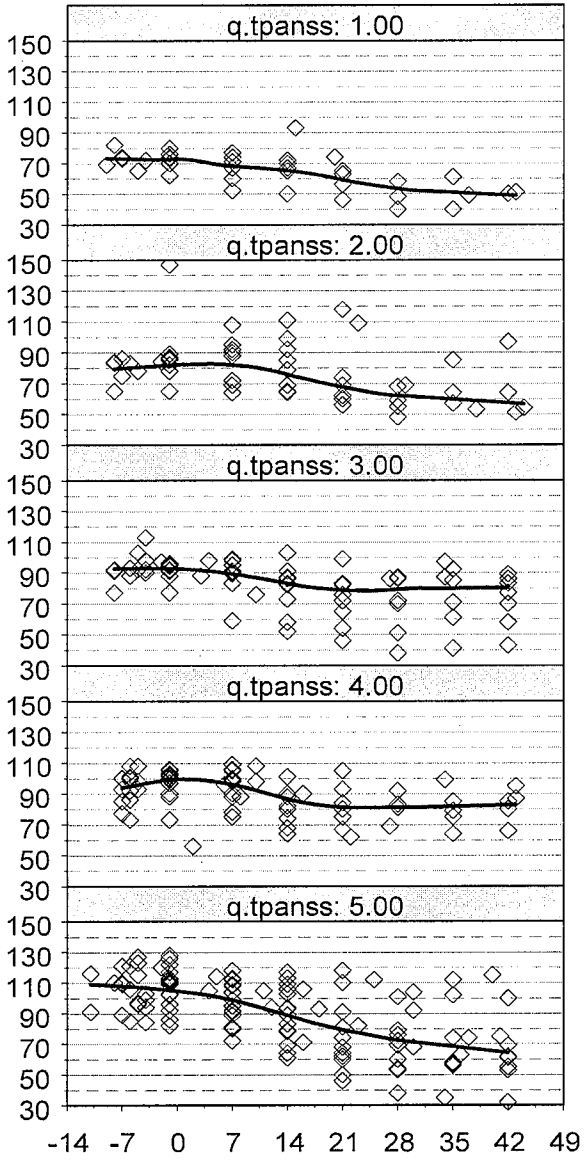
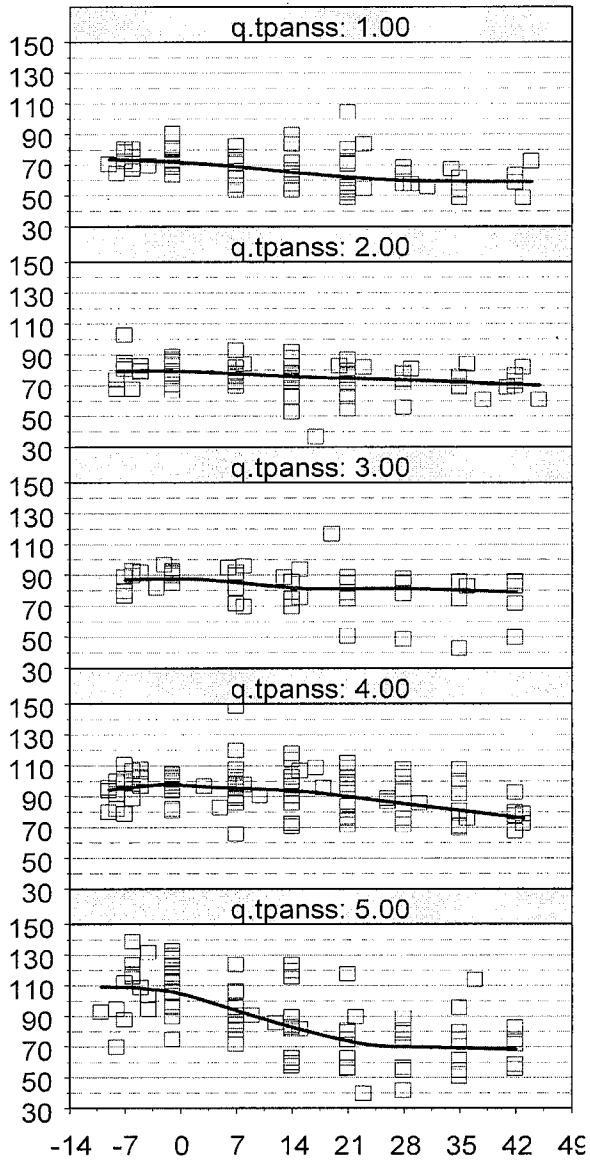


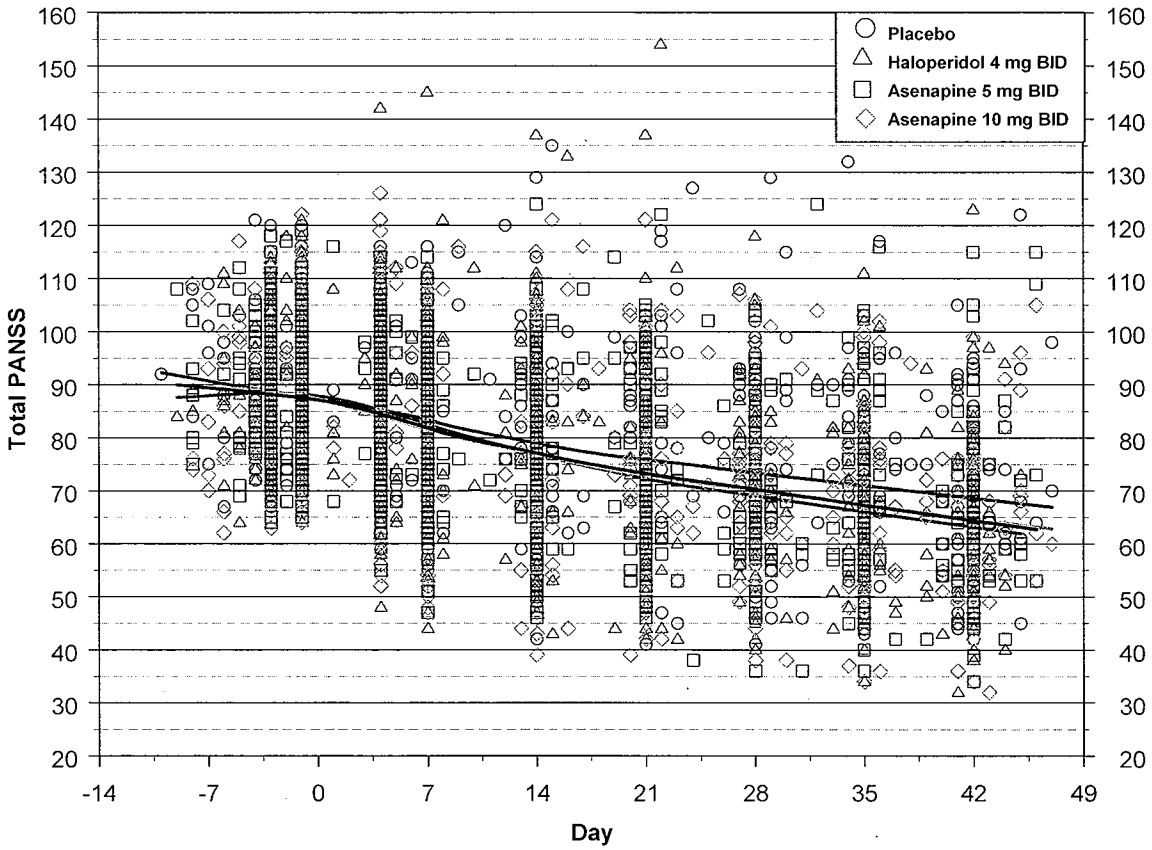
Figure 165 Total PANSS Score vs. Time (Days) for Risperidone 3 mg BID Treatment by Quintile of Severity - Study 41004



5.6.2.1.1.1.2 Study 41023

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

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



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

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

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

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

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

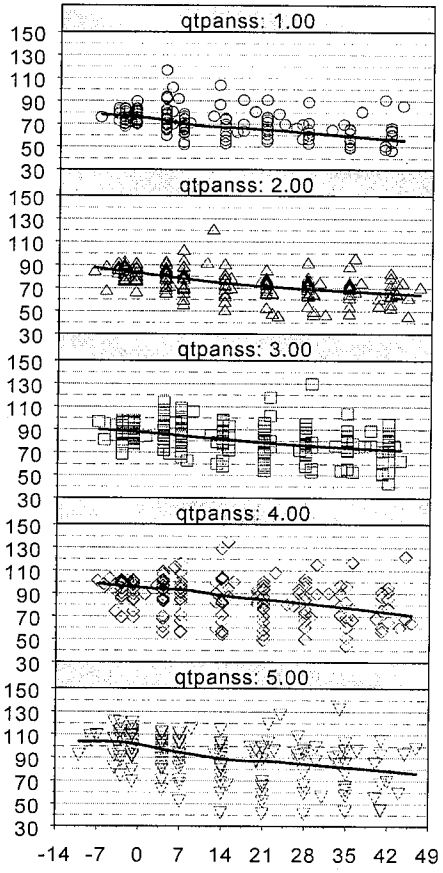


Figure 168 Total PANSS vs. Time by Quintile for Asenapine 5 mg BID – Study 41023

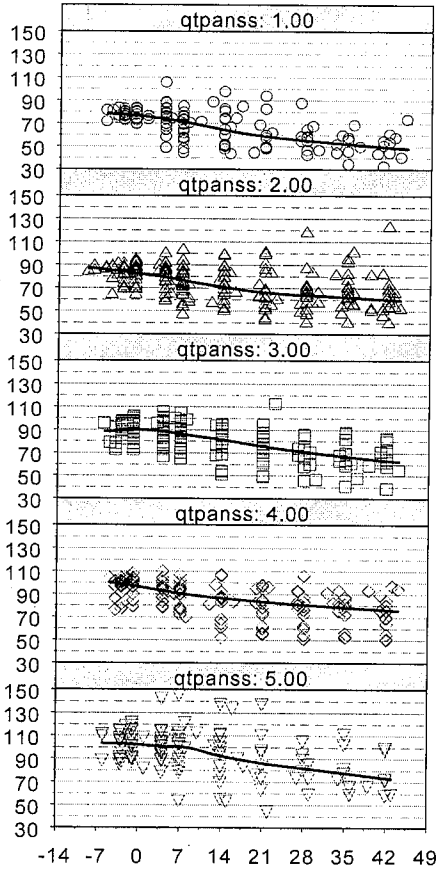


Figure 169 Total PANSS vs. Time by Quintile for Asenapine 10 mg BID – Study 41023

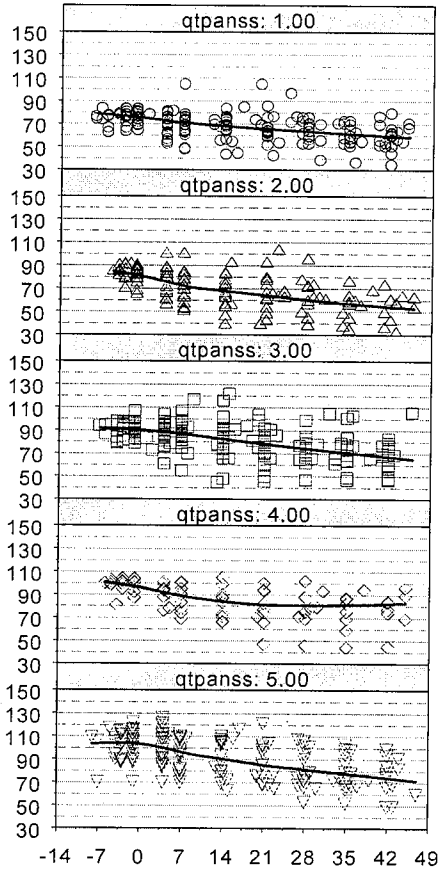


Figure 170 Total PANSS vs. Time by Quintile for Haloperidol 4 mg BID – Study 41023

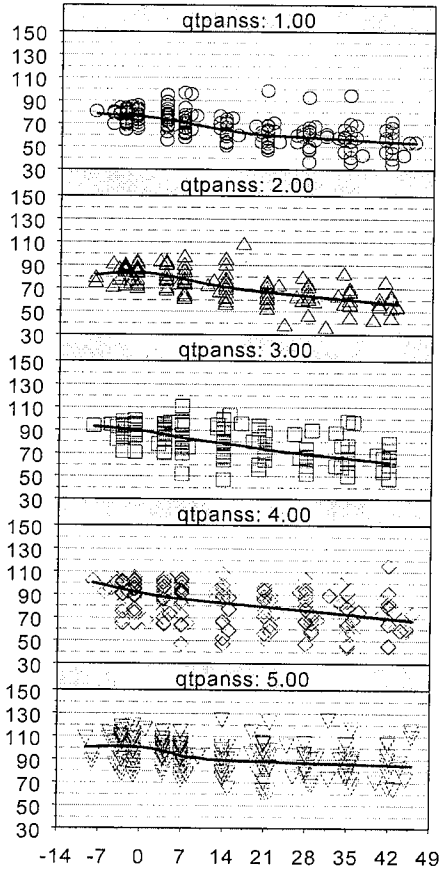


Figure 171 to Figure 174 shows similar plots but for positive PANSS score vs. Time by quintile for each treatment. Again there isn't any clear pattern for efficacy by severity of illness.

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

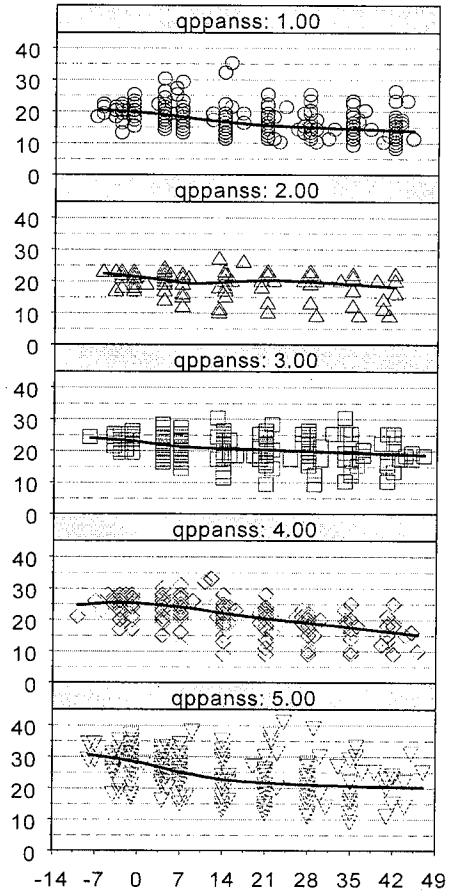


Figure 172 Positive PANSS vs. Time by Quintile for Asenapine 5 mg BID – Study 41023

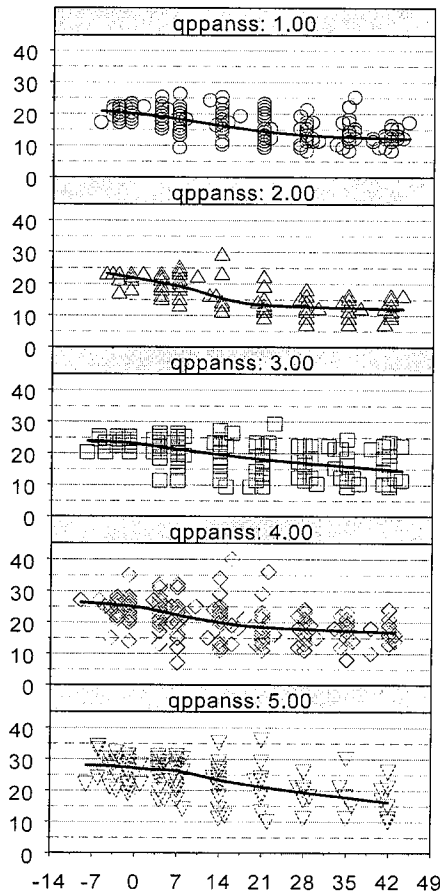


Figure 173 Positive PANSS vs. Time by Quintile for Asenapine 10 mg BID – Study 41023

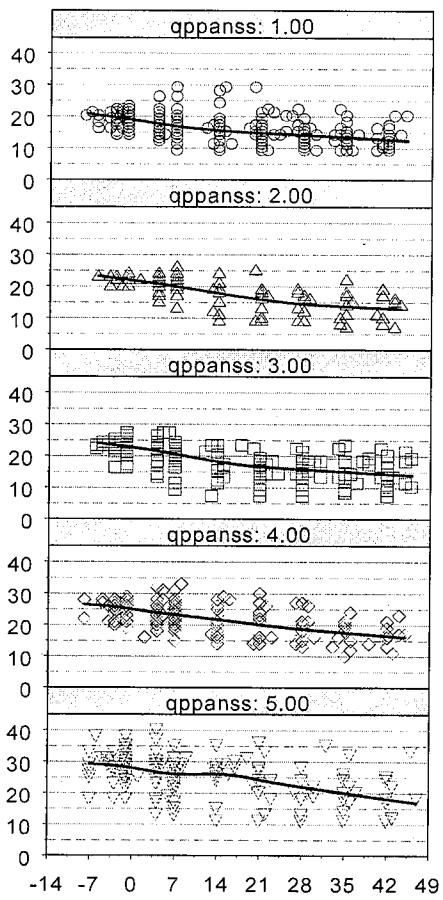
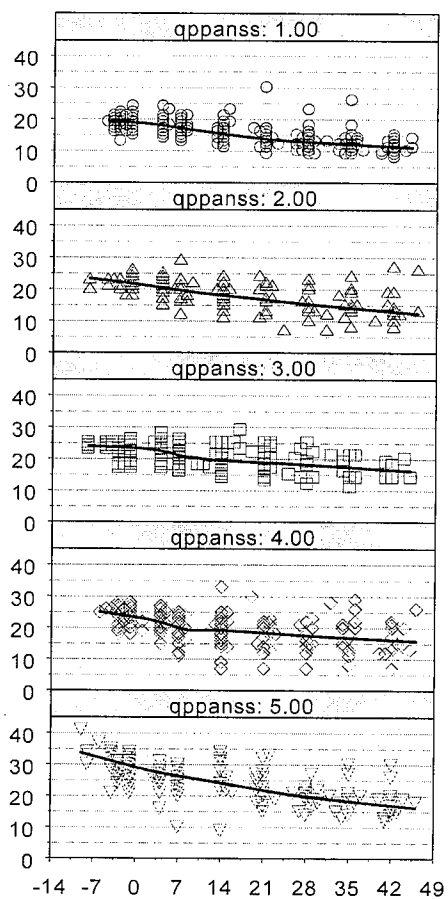


Figure 174 Positive PANSS vs. Time by Quintile for Haloperidone 4 mg BID – Study 41023



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

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

The specifice studies included in the ER analysis follow:

Phase IIb studies
- 41002
- 41013
- 41004

Phase III studies
- 41021
- 41022
- 41023

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

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

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

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

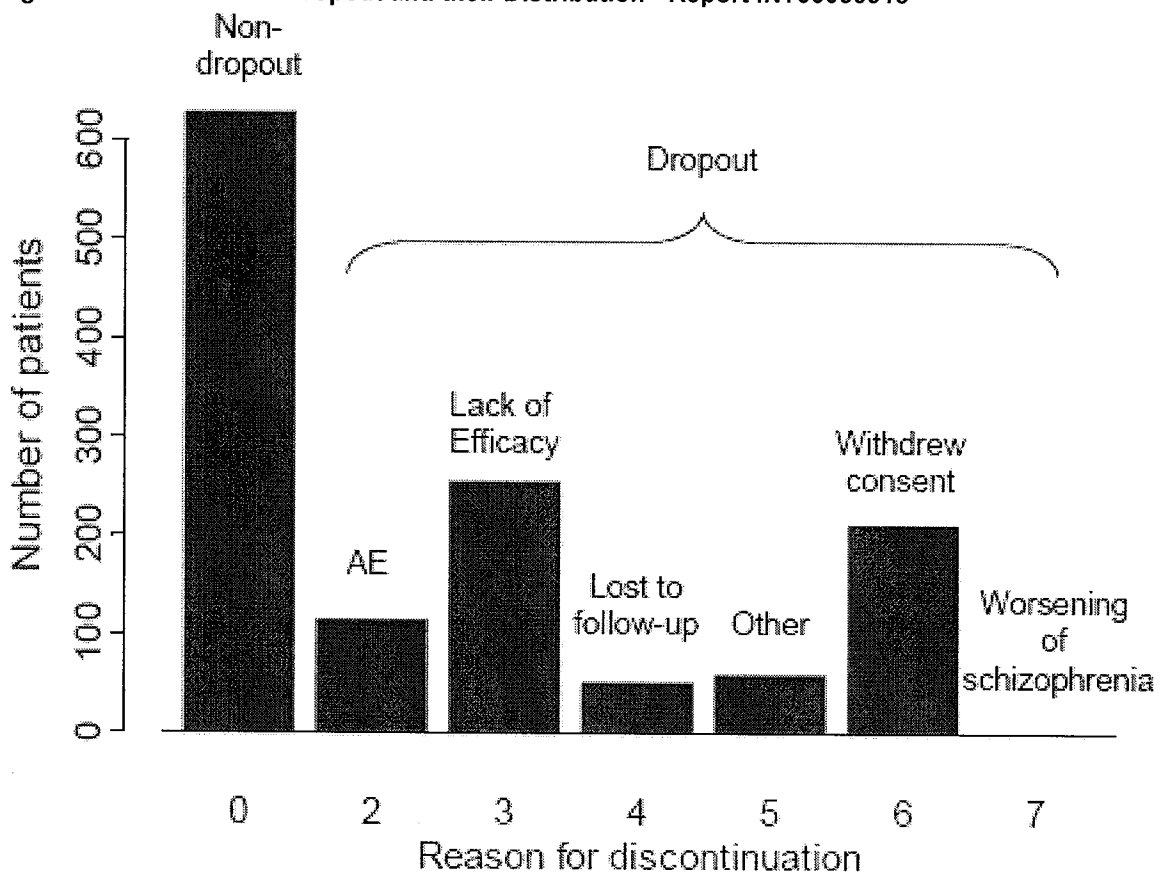
'A population pharmacokinetic-pharmacodynamic of Total PANSS time course was developed in NONMEM VI using AUC as a measure of asenapine exposure. In a first step a placebo model was

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

Drop Out Model

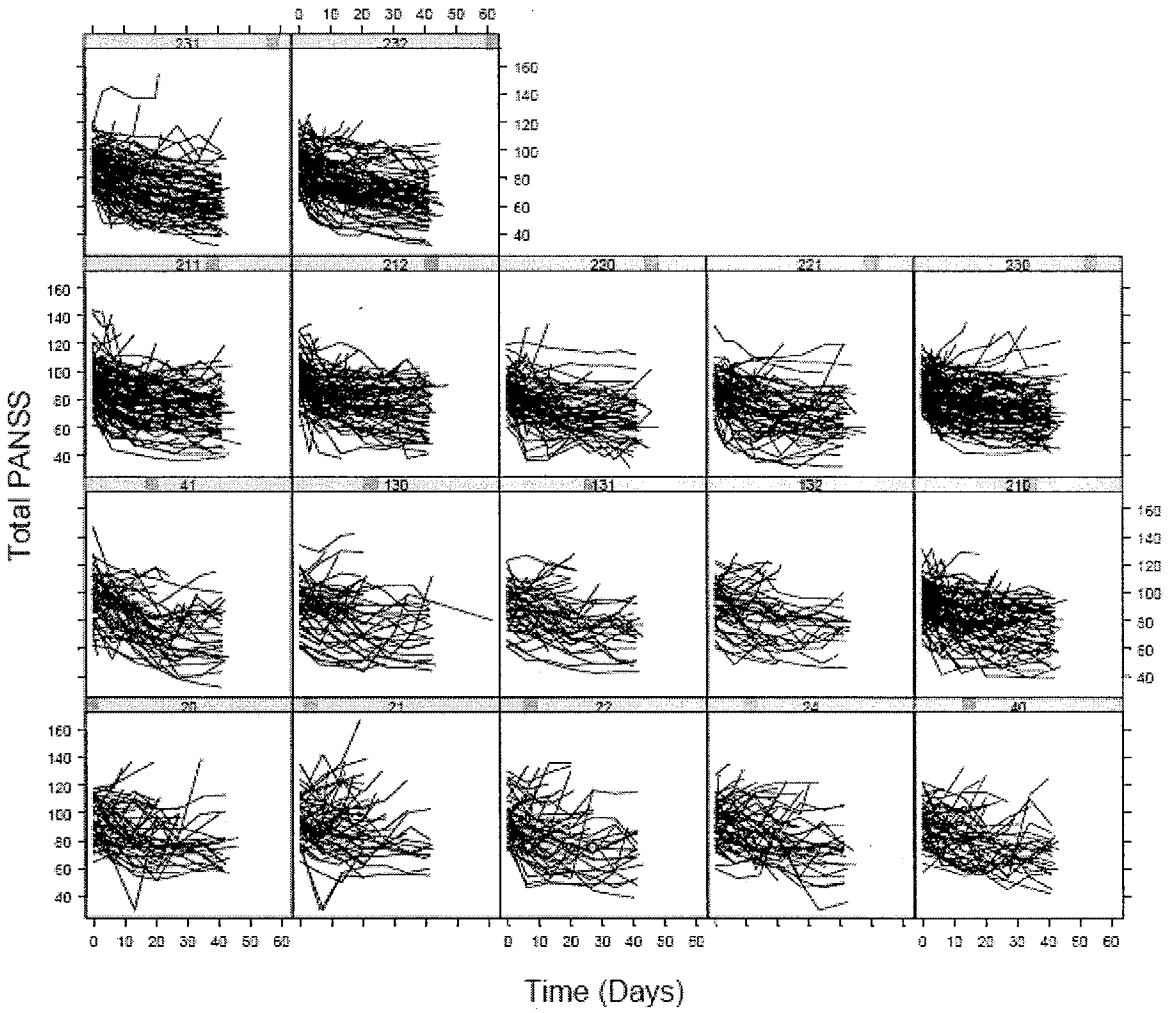
Figure 175 shows the categorization of reasons for drop-outs used by the sponsor. The large proportion of drop-outs categorized as lost to follow-up, other, and especially withdrew consent is troubling. In addition, that only one subject was assigned to worsening of schizophrenia is not believable as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

Figure 175 Reasons for Dropout and their Distribution - Report INT00039918



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

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



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

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

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

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

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

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

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

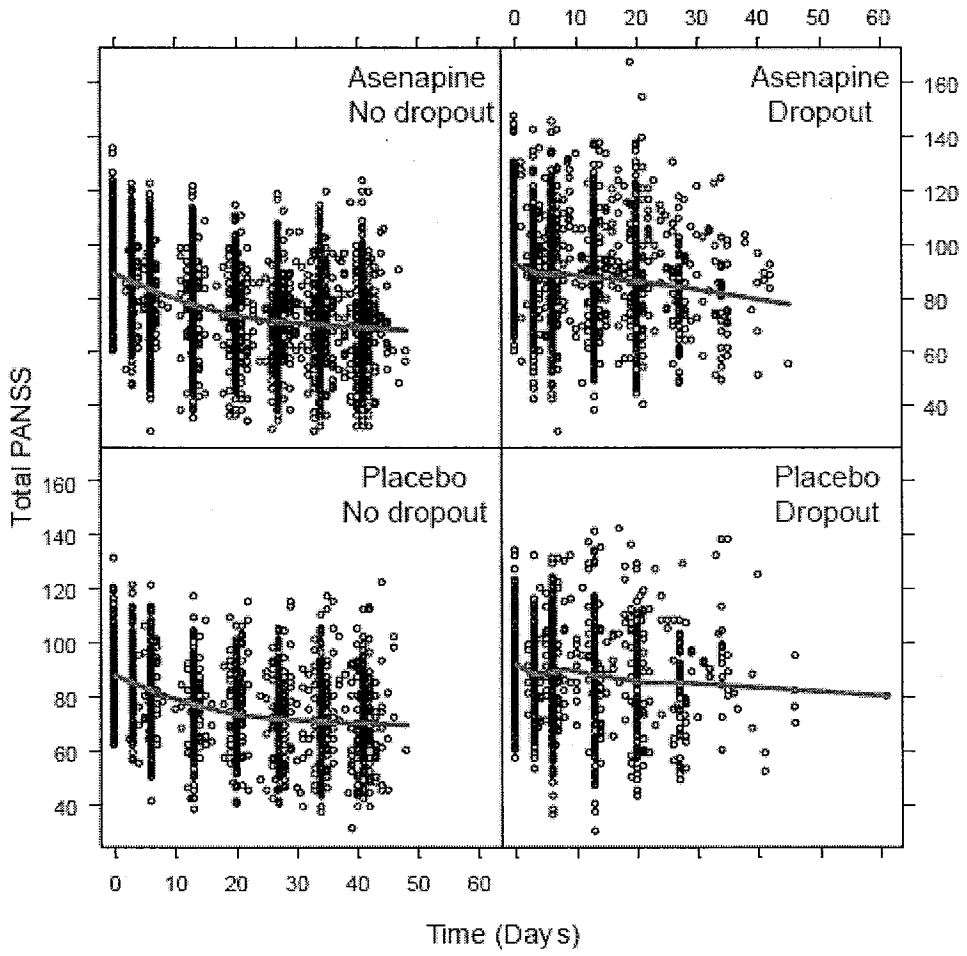
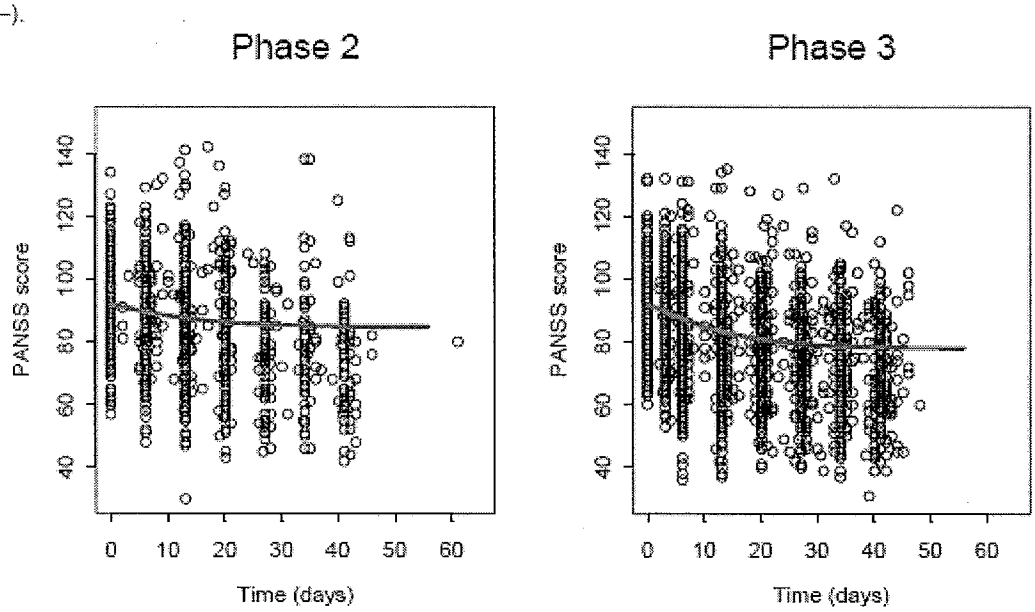


Figure 178 Typical PANSS Time Course as Predicted by the Final Placebo Model – Report INT00039918

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

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



Exposure Response Relationship for Asenapine

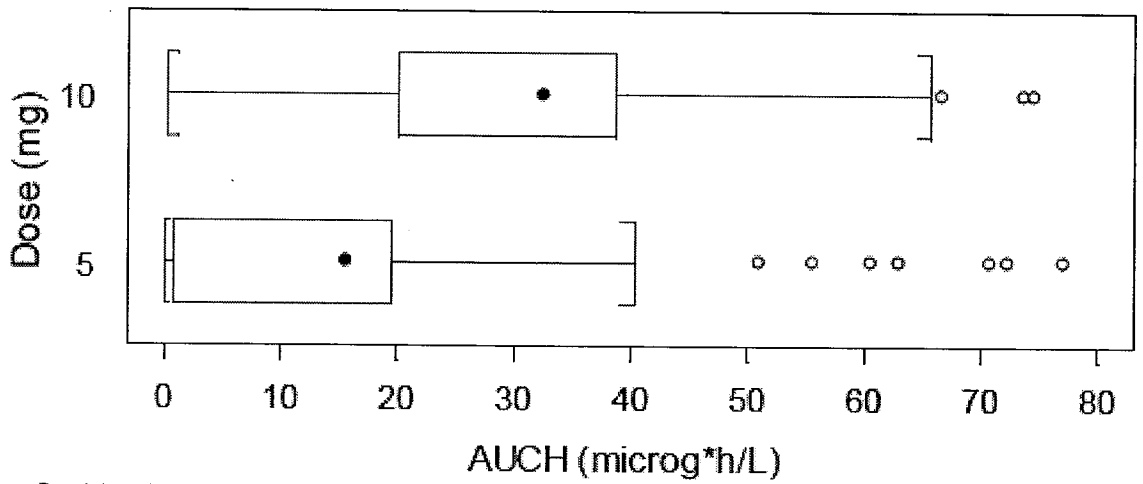
Exposure was assessed by AUCs assessed by sparse sampling and population pharmacokinetic modeling. The sponsor assessed various ways to model AUC, including the following:

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

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

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

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



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

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

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

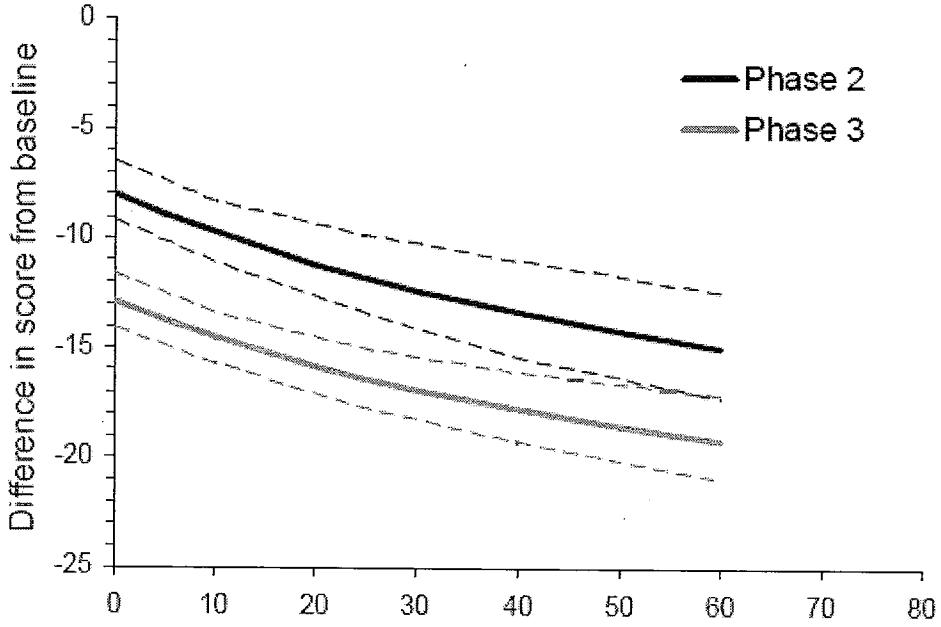
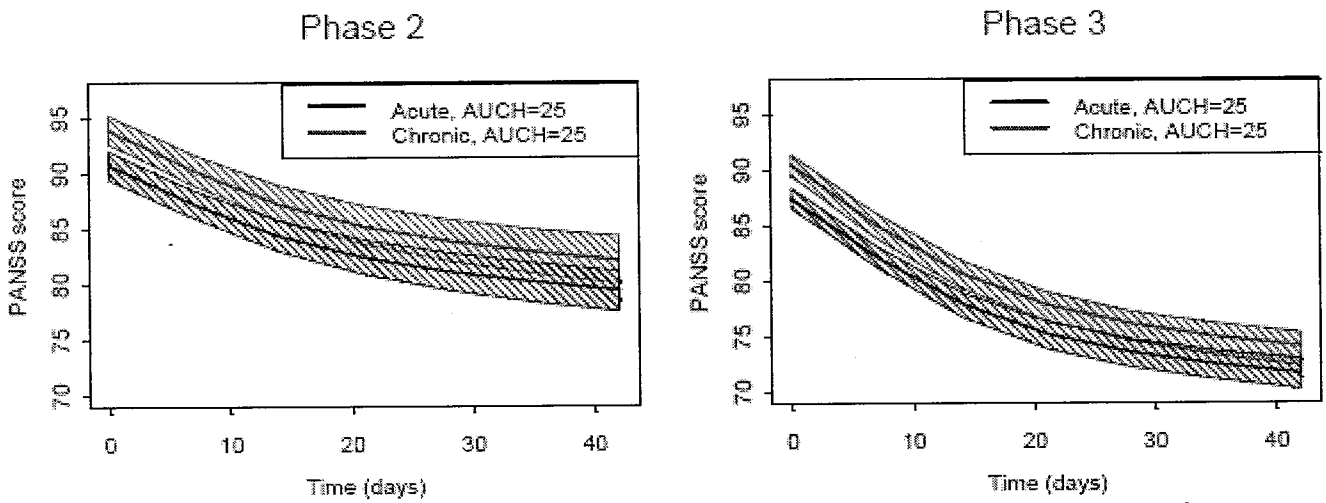


Figure 181 shows that when controlled for AUC this difference in response by study phase is partly due to the difference in baseline PANSS score as well as the duration of the current episode, however it's also clear that this cannot totally explain the difference as the 'chronic' subjects in the phase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

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



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

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

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

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

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

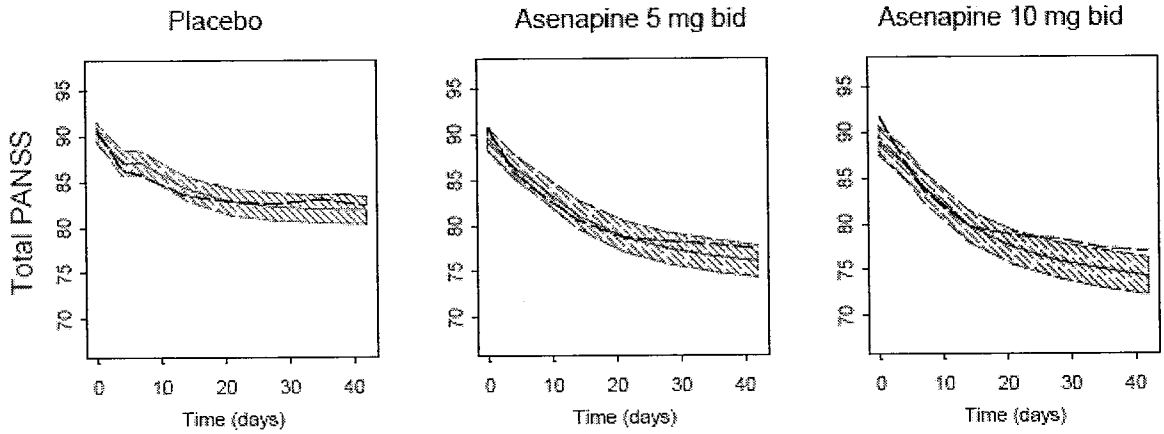
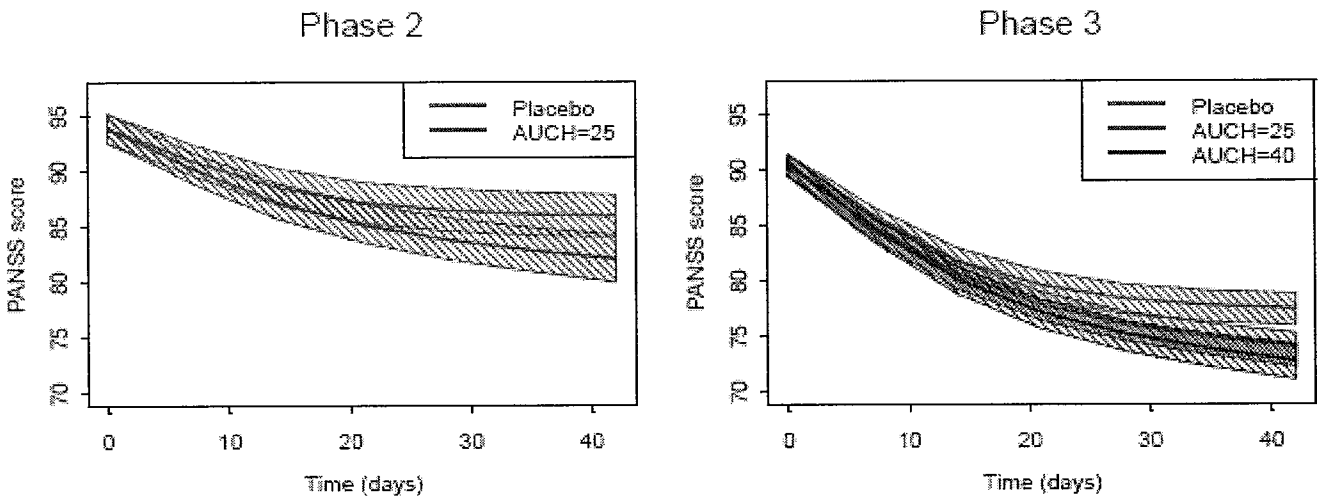


Figure 183 shows what the sponsor based this on. The sponsor assigned a typical AUC of 25 mcg/ml x hr^{-1} to a dose of 5 mg and 40 mcg/ml x hr^{-1} to a dose of 10 mg. Yet Figure 179 indicates that this is inappropriate as the true mean AUCs are respectively around 10 and 30 mcg/ml x hr^{-1}. This figure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

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



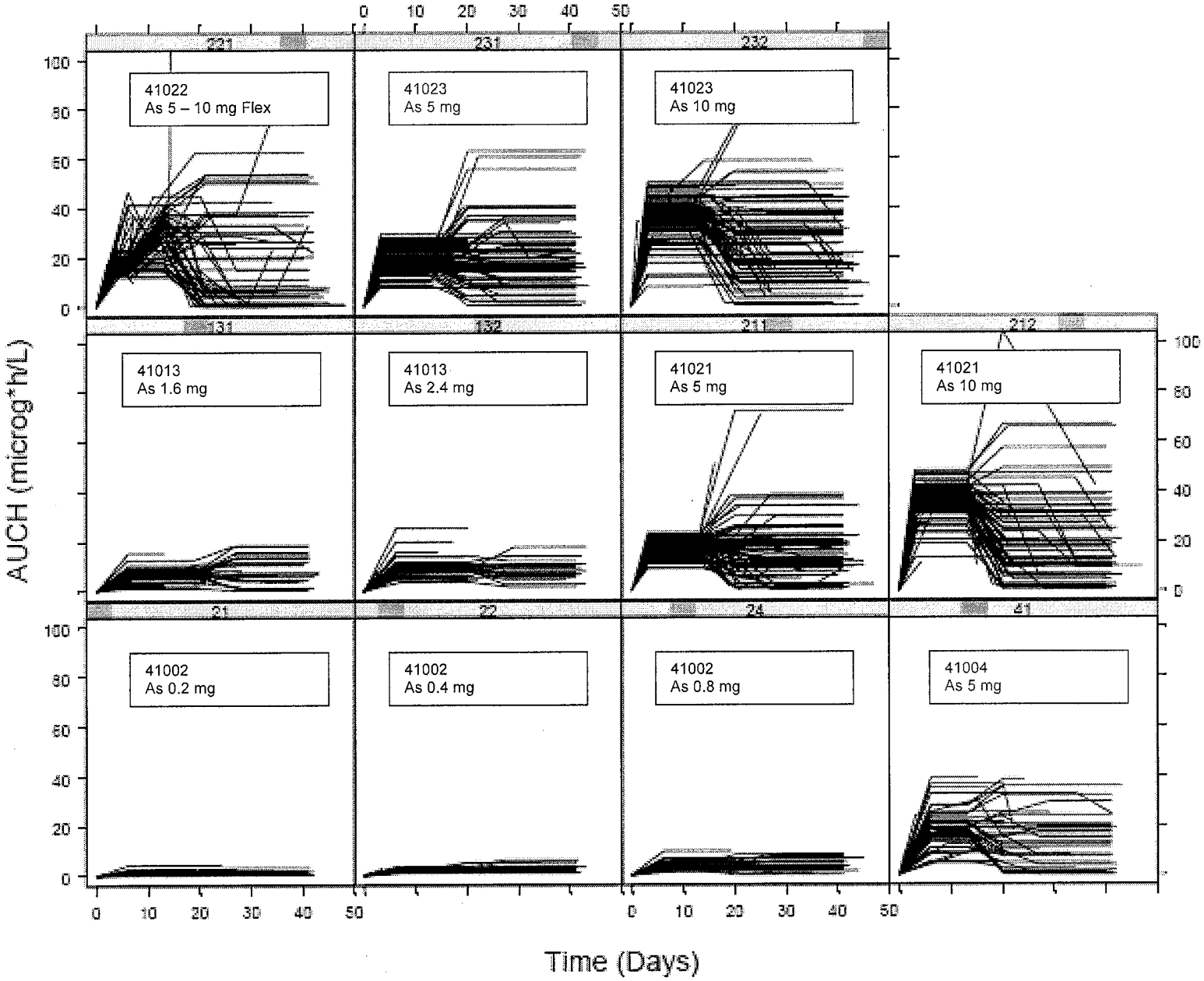
a Sponsor claims that graphs show the predicted mean and 90% CI for PANSS Score vs. time for placebo and for the typical individual AUC (AUCH) following 5 mg (AUCH=25 µg·h/L) and 10 mg (AUCH=40 µg·h/L).

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

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

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

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



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

5.6.2.1.1.2 Evaluation of Drop-Out Patterns

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

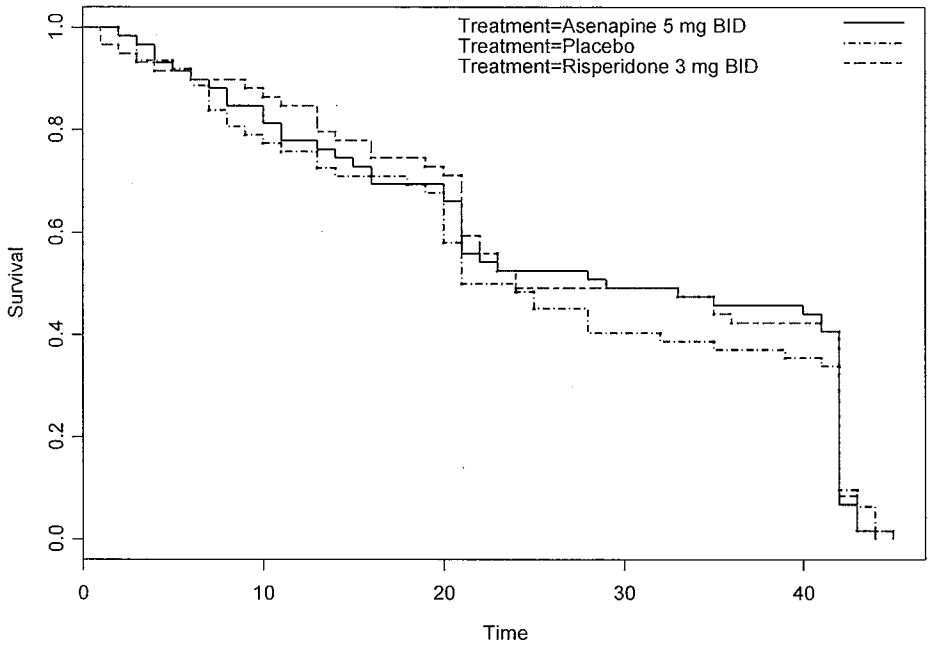


Figure 186 Kaplan-Meir Plot of Dropout Rate over Time by Treatment Group - Study 41023

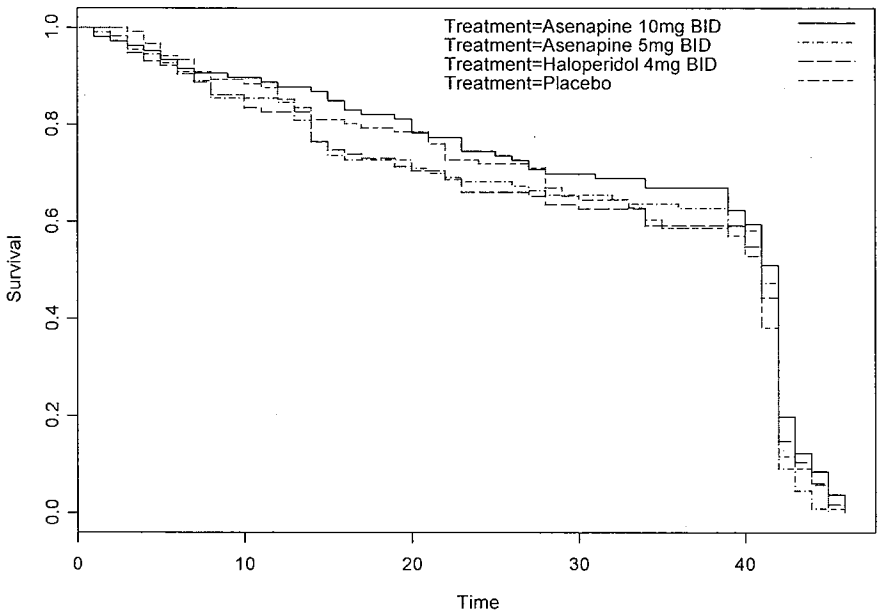


Figure 187 is an exploratory plot of dropout rates by intial disease severity in study 41004. It appears that for most subjects there is little difference in dropouts by treatment, whereas in the most severely ill patients after the first week of treatment drop outs increase for the placebo group and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

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

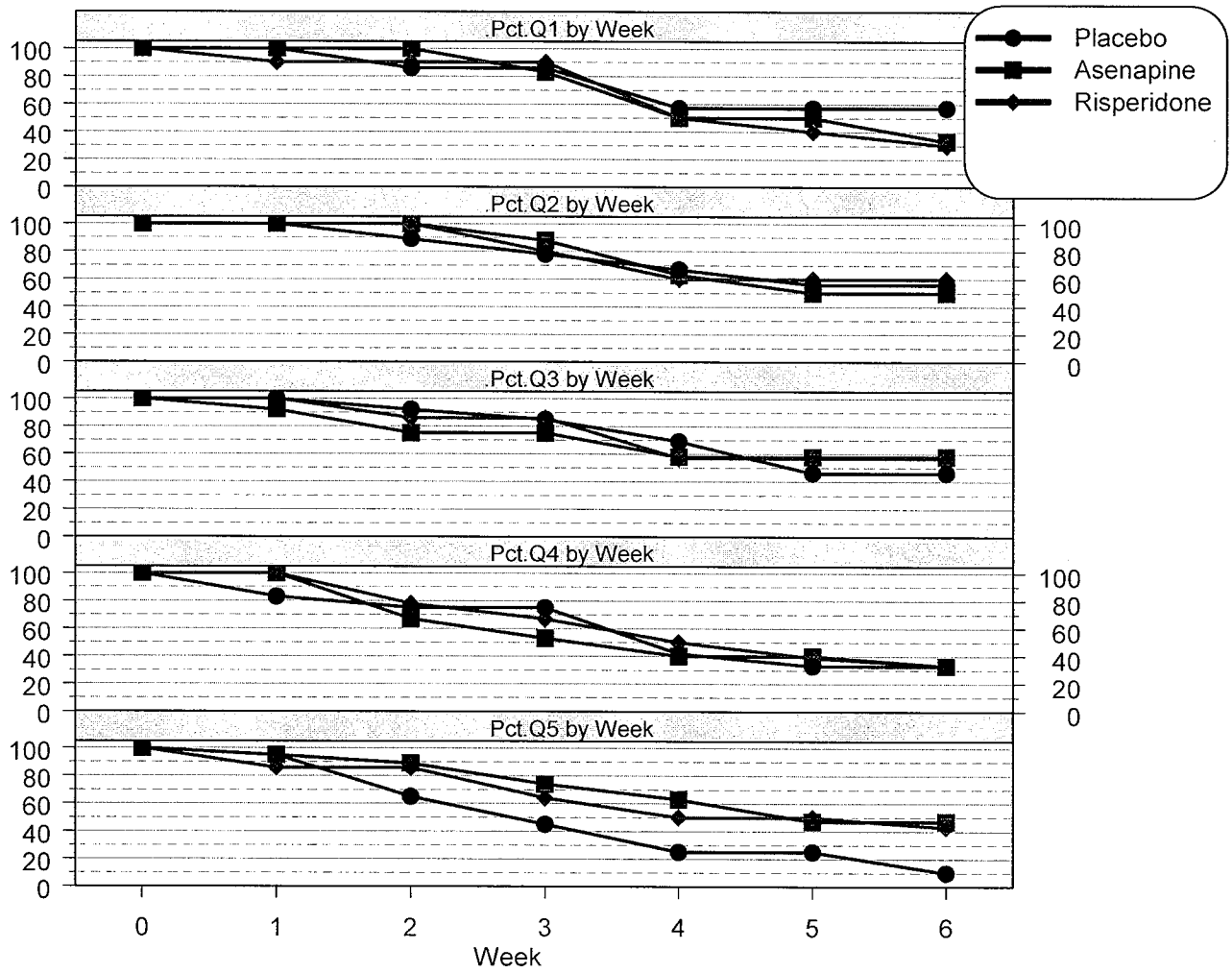


Table 177 and Table 178 show numerical calculations of drop out rates and odds ratios by treatment and initial disease severity for studies 41004 and 41023 respectively. Examination of Table 177 reveals an apparent pattern that in the phase II study 41004 with the more severely ill patients, the least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

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

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

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

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

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

5.6.2.2 *Bipolar Disorder*

5.6.2.2.1 Acute Efficacy

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

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

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

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

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

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

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

a excluding active control olanzapine

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

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

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

N = number
a1 missing value

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

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

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

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

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

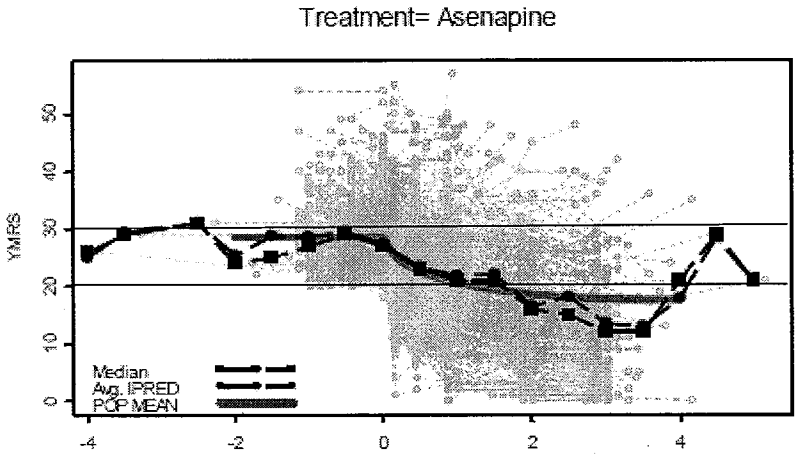


Figure 189 Observed YMRS Measurements and the Average IPRED and Population Mean Response for Placebo – Report INT00039919

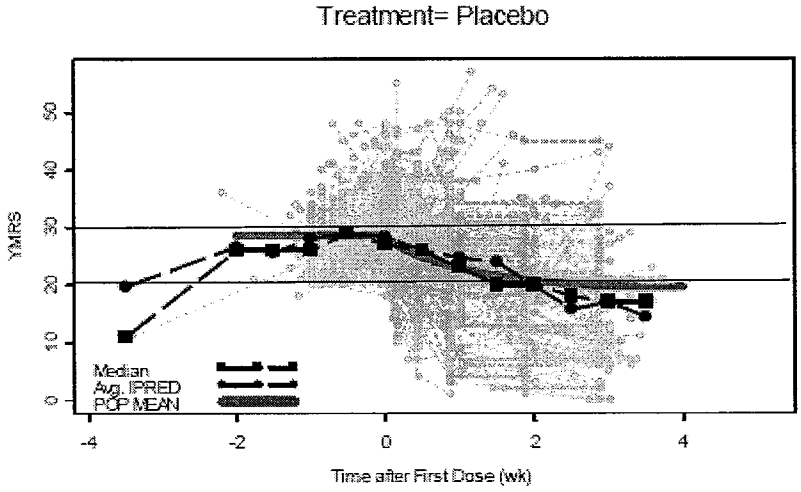


Table 181 of the Sponsor's analysis confirms that the differences although statistically significant may have minimal clinical significance.

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

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

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

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

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

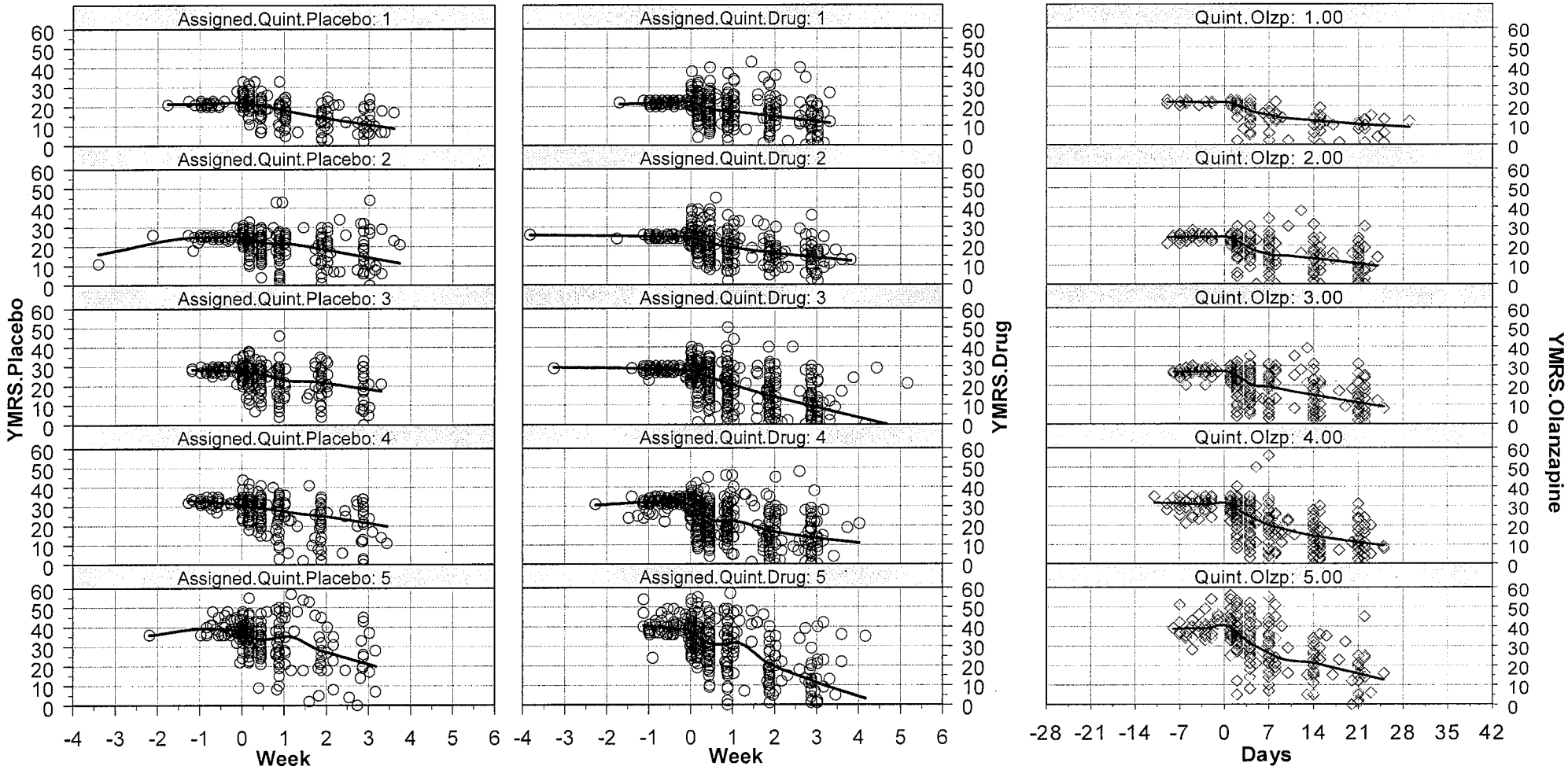
YMRS was then plotted over time using the actual day the evaluations were performed rather than the nominal day (visit) employed by the sponsor. It was noted that each of these steps resulting in the patterns becoming more readily visible, (data not shown), and emphasizes the importantance of using the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

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

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

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

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


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

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

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

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

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

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

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

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

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

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

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

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

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

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

5.6.2.2.1.3 Evaluation of Drop out Patterns

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

5.6.2.2.2 Maintenance Effect

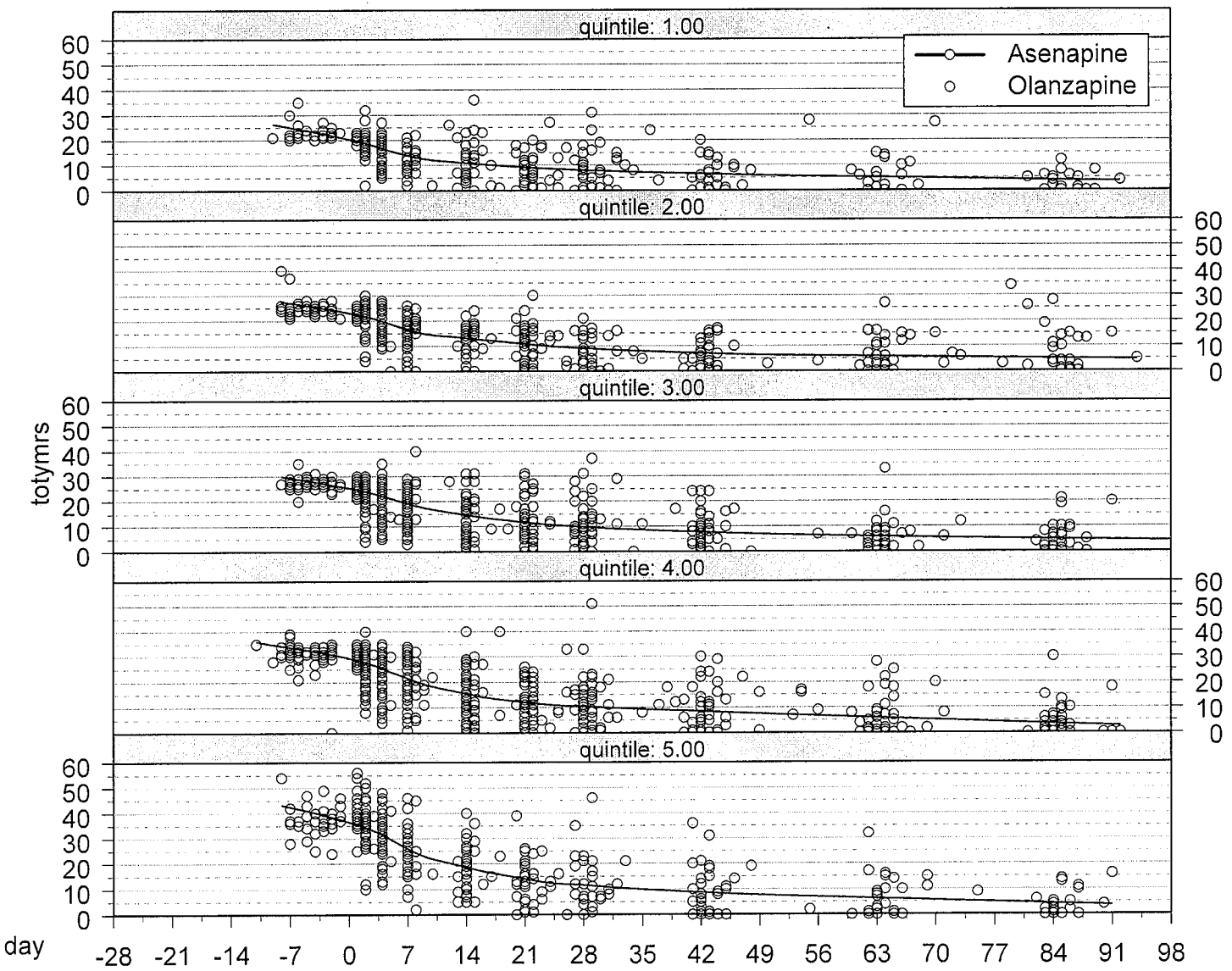
Study A7501007 was a double-blind, 40-week continuation study evaluating the safety of asenapine and olanzapine in the treatment of subjects with acute mania. The primary objective of this study is to characterize the longterm safety of asenapine and olanzapine in the treatment of acute mania in subjects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

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

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

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

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



5.6.2.3 *Extrapyramidal Symptoms*

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

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

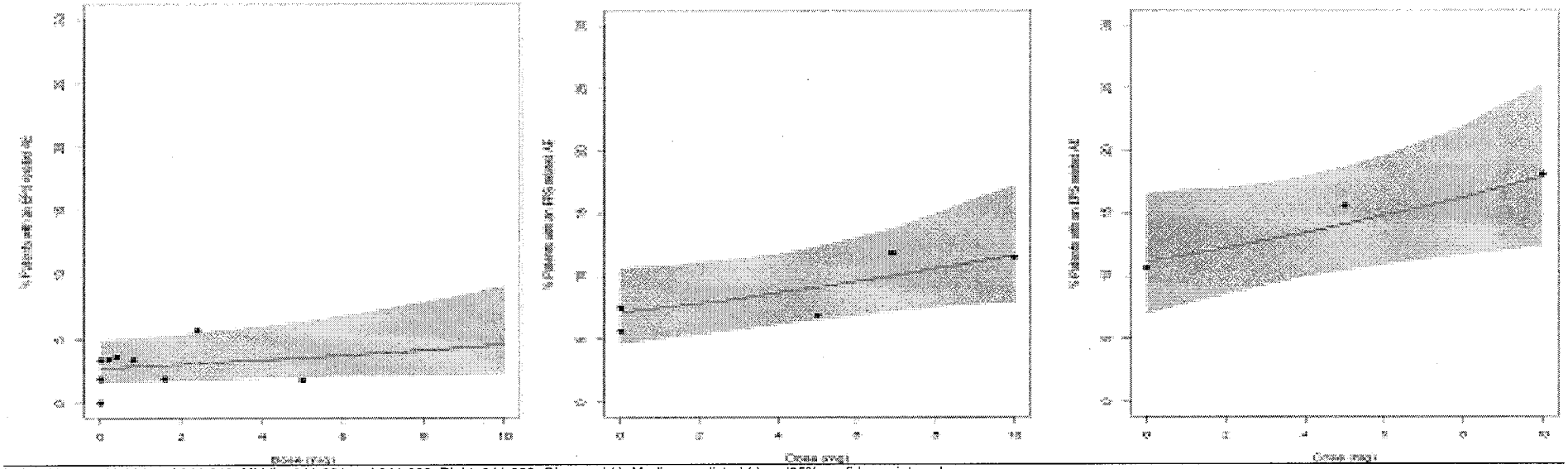
Possible dose- or exposure-response for asenapine using SARS scores and the incidence of EPS related adverse events were explored graphically. Model development was undertaken if a relationship was indicated. A time-to-event model was developed to describe the time to first EPS related AE. Bootstrapping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

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

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

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

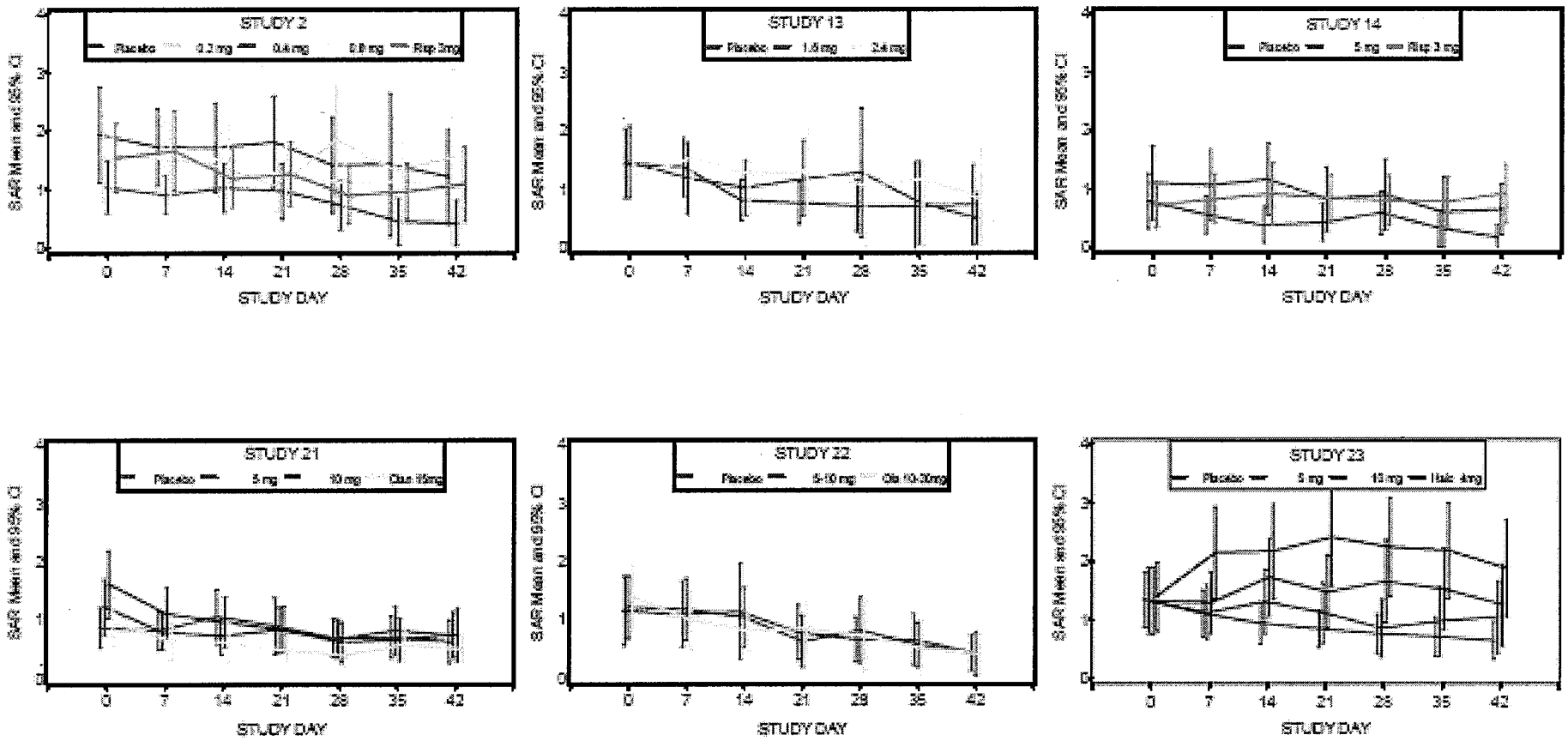
Figure 192 Proportion of Subjects with an EPS-Related Adverse Event in the Different Acute Schizophrenia Trials vs. Dose in Milligrams – Report INT00065682



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

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

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



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

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

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

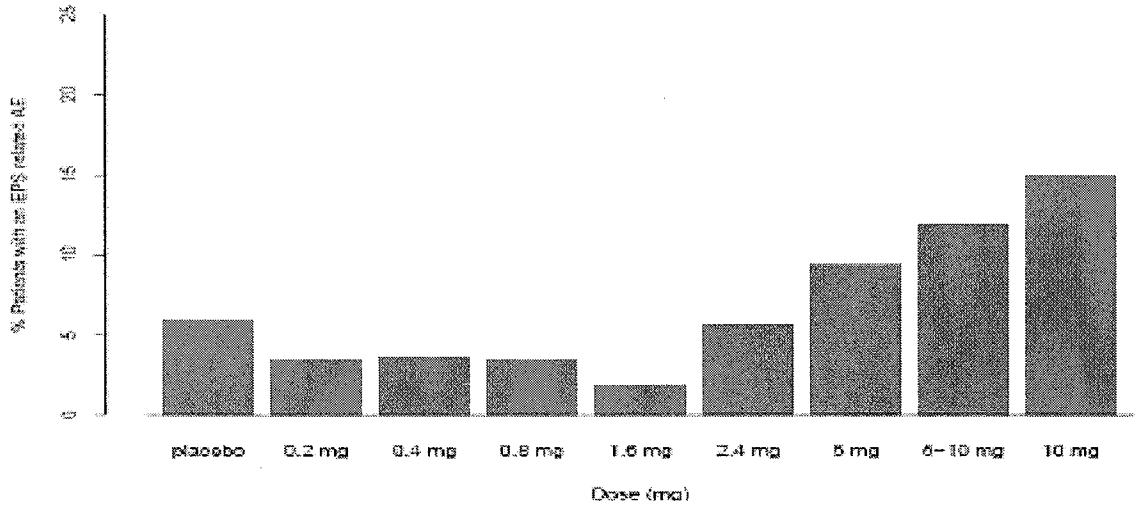


Figure 195 Histogram of EPS Rate vs. Asenapine AUC – Report INT00065682

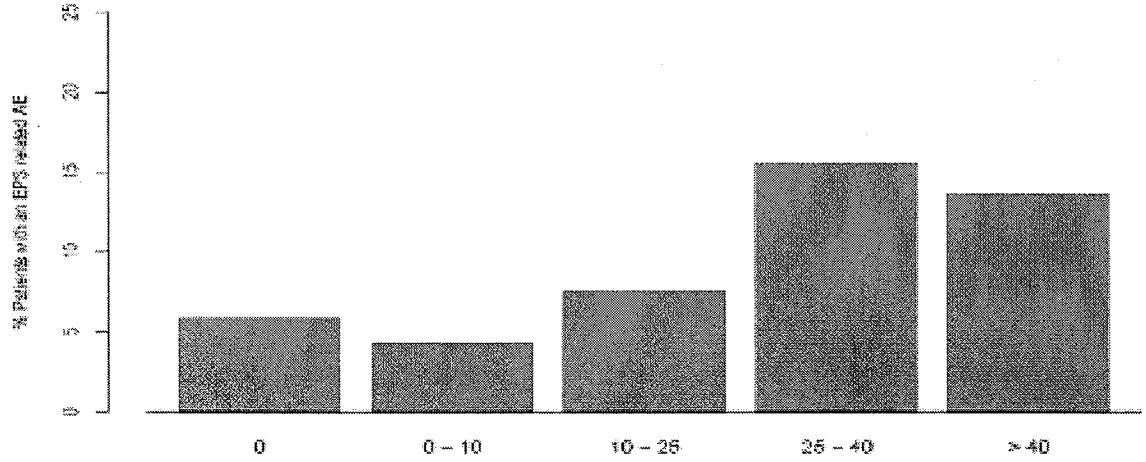
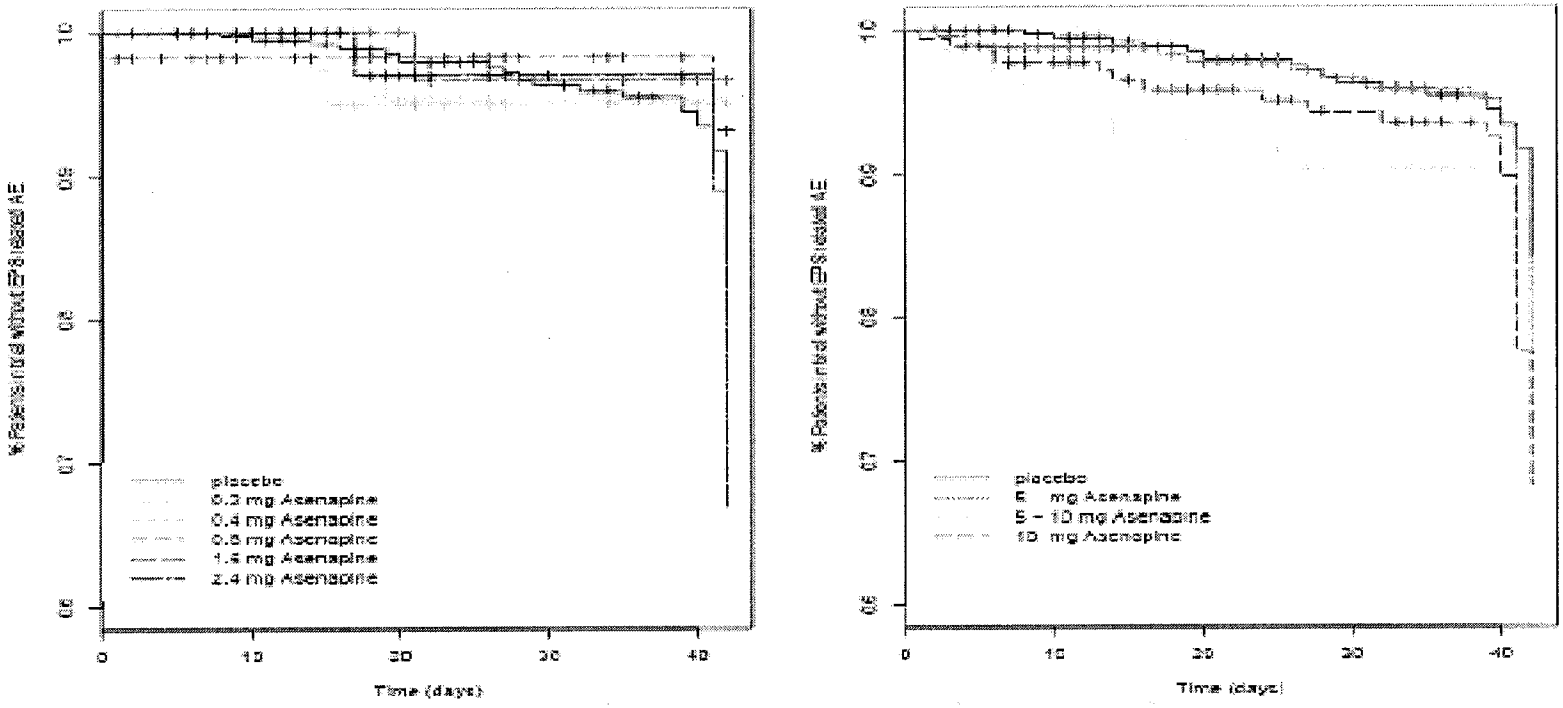


Figure 196 also indicates an increased incidence of EPS over time with asenapine doses of 5 - 10 mg as compared to placebo.

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



Source: Appendix A Figure 2-3.

5.6.2.4 Suicidality

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

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

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

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

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

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

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

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

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

Table 187 to Table 190 shows the information on suicidality.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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