5.6.3 Other Safety Issues

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

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

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

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

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

Abbreviated information on these serious AEs follow:

5.6.3.1 Hepatotoxicity

5.6.3.1.1 Single Rising Dose Oral Study 85029

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

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

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

No significant adverse events were reported for this trial.

5.6.3.1.2 PO MRD PK S/T Study 85136

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

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

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

V. Conclusion

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

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

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

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

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

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

Group No.	Subject No & Initials	Dose	Abnormal Tests	Day of Onset of rise	Time of Peak of rise	Day of 1st subsequent normal value	Severity
II	14.	3 mg bd	ALT	10	10	14	++
III	18.	10 mg bd	ALT	10	11	21	++
			AST	10	11	13	+
IIIA	101	20 mg bd	T.bili	2 & 10	2 & 10	5 & 14	+ & +
	102	Placebo	Alk Phos	Raised at screening and throughout			+
			ALT	14	14	21	+
	104	20 mg bd	ALT	10	15	-	++
			AST	0	2 & 14	5 & 21	+
IV	28.	30 mg bd	ALT	9	9	-	+++
			AST	9	9	-	+++
	29.	30 mg bd	ALT	0	12	15	+++
			AST	10	12	14	+
			GGT	0	6	15	+
	30.	30 mg bd	ALT	6	11	-	+++
			AST	6	9	37	+++

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

b(6)

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

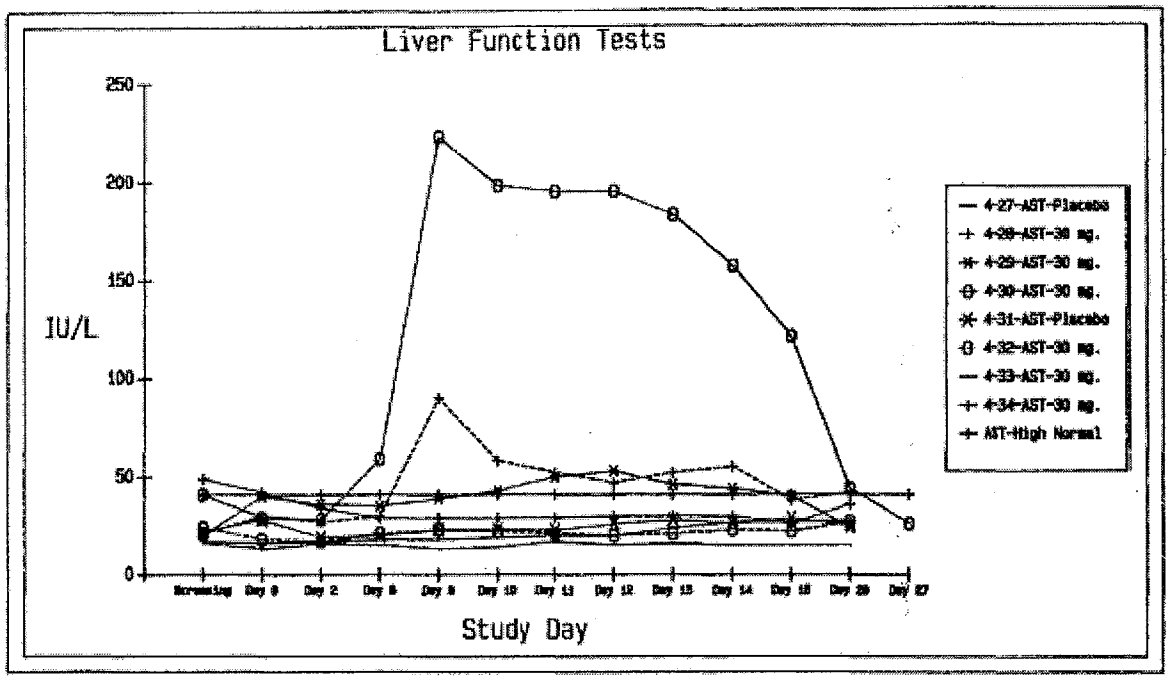
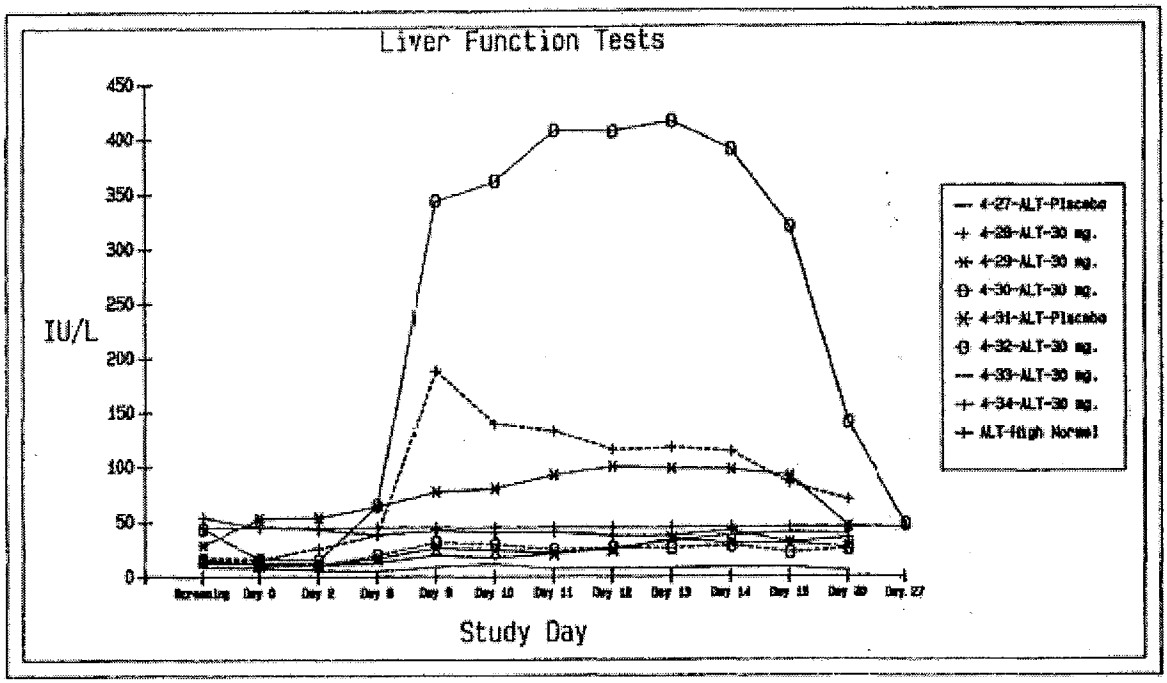


Figure 203 Plot of Significantly Elevated Liver Function Tests (> 3X ULN) vs. Time - Case 2 – Study 85136



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

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

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

5.6.3.1.4 Paroxetine Drug Interaction Study - Study 25525

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

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

Figure 204 Text from Paroxetine DDI Study 25525

Seven clinically relevant abnormalities were observed in Sequence A.

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

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

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

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

Figure 205 Text from Paroxetine DDI Study 25525 (continued)

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

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

No clinically relevant abnormalities were observed in Sequence B.

5.6.3.1.5 Thorough QT Study - Study A7501001

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

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

5.6.3.1.6 Relative BE Study New Formulation - Study 41009

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

5.6.3.2 *Cardiotoxicity*

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

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

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

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

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

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

Additional information on events indicative of cardiotoxicity follow:

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

5.6.3.2.1 IV Study - Study 25506 - Nov 1992

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

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

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

Figure 206 Text from IV Study 25506

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

Figure 207 Text from IV Study 25506 (Continued)

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

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

Figure 208 Text from IV Study 25506 (Continued)

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

Figure 209 Text from IV Study 25506 (Continued)

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

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

Figure 210 Cardiologist's Report from IV Study 25506

b(4)

Re: (b)(4) 001 026 5222 I.V. STUDY

Thank you for asking me to assess this 27 year old chap who had an unfortunate event as a result of participating in a normal volunteer study. I've looked at the sequence of ECGs and there's no doubt that he became asystolic and as you pointed out you had to perform cardiac massage to sustain an output. It is interesting looking at the sequence of events because in the first instance there's obviously sinus arrest but then as he recovers there's evidence of AV conduction abnormalities also with a gradual return back to normal sinus rhythm.

With regard to him, he's always been fit, well and very active and though he currently works as a casino manager, in the past he's had a healthy lifestyle being an ex-marathon runner and still keeping reasonably fit. He's single, a non smoker, only drinks alcohol at the weekends. He's never been ill apart from a road traffic accident five years ago when he had some cervical spine damage.

EXAMINATION

He looks fit and well. JVP not raised, sinus rhythm, blood pressure 110/80. There were no murmurs, there were two heart sounds, there was no suggestion of heart failure and the lungs were normal and clear.

INVESTIGATIONS

24 Hour Tape Recorded ECG: Normal sinus rhythm with respiratory variation.

2D Echocardiogram: Normal.

Treadmill Exercise ECG: He managed an above average 15 minutes going to his maximal heart rate of 194 beats per minute. There were no arrhythmias and no ischaemic changes.

Carotid Sinus Massage: Massage of both the right and left carotids did not induce any significant bradycardia.

OPINION

First of all I cannot identify any cardiac problem in (b)(4) and I've reassured him that there's no evidence of any cardiovascular disease.

Figure 211 Cardiologist's Report from IV Study 25506 (Continued)

Secondly, this almost certainly has to be classed as a drug induced effect with a serious adverse effect on the conducting system of the heart.

If you require any further report or details from me please let me know.

Kind regards,

Yours sincerely,

b(4)

CONSULTANT CARDIOLOGIST

5.6.3.2.2 Multiple Rising Oral Dose Study - Study 25501 – June 1993

Study 25501 was a multiple rising dose study to examine the pharmacokinetics in 12 young, healthy, male volunteers using Org 5222 both after a single oral dose (30 mg) and at steady state (5 days, 15 mg twice daily orally).

One subject had asystole for 8.7 seconds with a junctional escape rhythm. Even though this was a single oral dose of 30 mg and the asenapine exposures was low compared to what is typically seen with sublingual dosing, the N-desmethylasenapine exposures were similar to those seen in multiple dose studies with sublingual dosing, (see Table 191). It's noteworthy that the sponsor did not include the data range for the most important study in any of the summary tables for the pharmacokinetics. In addition, the study durations were short, (5 and 6 days), and with a half-life in some cases of a couple of days and likely time dependent kinetics for desmethyl-asenapine the true exposures at steady-state are likely underestimated.

Figure 212 Text from PO MRD Study 25501

A previous study showed that multiple dosing with Org 5222 15mg twice daily for six or more days increased serum alanine aminotransferase and aspartate aminotransferase in three out of six healthy, male subjects.

Figure 213 Text from PO MRD Study 25501 (Continued)

In a previous study at GDRU, intravenous Org 5222 was associated with a cardiac arrest. After oral administration the bioavailability of Org 5222 is minimal in most subjects.

Figure 214 Conclusions from PO MRD Study 25501

SUMMARY - CONCLUSIONS

After the single, oral dose of Org 5222 to the six subjects of the first group, the study was terminated due to a serious adverse event in one subject.

Two hours, 25 minutes post dosing the subject suffered an 8.7 second asystolic episode followed by junctional escape rhythm until sinus rhythm was restored. A subsequent 24-hour ECG was normal and no abnormalities were detected on echo cardiography. There were no other serious events. In general, subject's supine blood pressure and pulse rate showed only the random fluctuations expected. Apart from the subject who suffered the asystolic episode, there were no clinically significant changes in the 12-lead-ECG recordings following Org 5222 in the 5 other subjects. There were no clinically significant abnormalities on either physical examination, Multistix® urinalysis, clinical chemistry or haematology.

Figure 215 PK from PO MRD Study 25501

Pharmacokinetics

Blood samples were taken at pre-dose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 24, 36 and 48 hours after drug administration. Mean values (n=6) for the pharmacokinetic parameters are summarized in the table below.

Summary of the pharmacokinetic data

Parameter	Org 5222				Org 30526			
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.
C_{max} (pg.ml^{-1})	390	166	144	682	3813	617	3330	4930
t_{max} (h)	1.50	0.89	0.50	3.00	2.88	1.13	1.50	4.00
$AUC_{0-\infty}$ (pg.ml^{-1}.h)	3701	1146	1937	4988	44119	10804	29624	58452
$t_{1/2}$ (h)	7.87	1.96	6.27	11.13	10.54	1.50	8.54	12.11

SD = Standard Deviation; Min. = Minimal value; Max. = Maximal value

Conclusions

The Org 30526 plasma levels were considerably higher than those of Org 5222. The elimination half-life of Org 30526 was slightly, but significantly longer than the half-life of Org 5222. A single oral dose of 30 mg Org 5222 in healthy male subjects was not well tolerated as it produced a serious adverse event in one of the six subjects treated.

Table 191 Comparison of Selected Pharmacokinetic Metrics for Study 22501 and Multiple Dose PK Studies.

Metric	Cmax (ng/mL)			AUCτ[b] (ng/ml x hr^{-1})		
Study	Study 22501	25542	41012	Study 22501	25542	41012
Dosage Regimen	30 mg PO x 1	10 mg SL BID x 6 days	10 mg SL BID x 5 days	30 mg PO x 1	10 mg SL BID x 6 days	10 mg SL BID x 5 days
Asenapine	0.39 ± 0.18 0.14 – 0.68	5.57±2.36 0.94 – 8.81	8.84 2.17 - 15.5	3.7±1.2 1.9 - 5.0	28.2±16.0 6.0 – 53.5	37.3 16.5 - 58.1
Desmethyl-Asenapine	3.8 ± 0.62 3.33 - 4.93	3.14±1.2 0.48 – **5.16**	1.33 1.23 - 1.42	44.1±10.8 29.8 – 58.4	31.8±14.3 4.7 – **53.8**	12.7 11.0 - 14.4

a Text in red was not reported in clinical study report or in any summary tables, had to be extracted from raw data
b For single dose study AUC = AUCinf

5.6.3.2.3 Initial SL Single Rising Dose Study - Study 25509

The following is the background safety information from the initial sublingual dose study with a dose range of 10 - 100 mcg, (see Figure 216 and Figure 217).

What noteworthy about this summary is that it is precludes chronic oral dosing of greater than 4 mg / day due to safety reasons, which is equivalent to 8 – 12 mg /day administered sublingually. In addition it indicates that subjects with high Cmax's have serious AEs, and that interindividual variability results in greater risk in some individuals. Although it's reported that high Cmax's are potentially related to serious AEs individual Cmax's from these studies are not reported and it's unclear if this is related to asenapine or desmethyl-asenapine concentrations.

This was another study that this reviewer was told not to review as it did not include the proposed clinical dose range.

Figure 216 Text from SL SRD Study 25509

1.2 Summary of relevant safety data

Org SL94 appears to be safe in endocrinological, biochemical and haematological terms, however single high doses of Org SL94 may induce cardiovascular adverse experiences in animals and humans.

Single dose i.v. administration of Org SL94 to rats at dose levels up to 21 mg/kg caused no mortalities but was associated with neurological symptoms. The i.v. toxicity studies in rats and dogs with daily administration for 2 weeks at dose levels up to 3 mg/kg caused no overt signs of toxicity. Results from cardiotoxicity studies suggested that Org SL94 may cause postural hypotension at high doses.

In the initial Phase I studies in healthy male volunteers, single oral doses up to 30 mg Org SL94 did not cause any safety problems. In a two week multiple dose study oral doses up to 15 mg twice daily were administered. Time and dose dependent increases in ALT and AST serum levels were observed.

In two subsequent studies with healthy male volunteers, two serious adverse experiences (SAEs) were observed. The first SAE (cardiac arrhythmia - asystole) occurred 15 min after the i.v. infusion of 0.7 mg Org SL94 (given over 30 min), when the subject was asked to sit up. He required brief external cardiac massage and atropine and made a full

Figure 217 Text from SL SRD Study 25509 (Continued)

recovery. He was never unconscious for more than 30 seconds. The second SAE occurred 2 h 35 min after a single oral dose of 30 mg Org SL94 without an obvious precipitating factor. This subject collapsed whilst already sitting and recovered spontaneously. His ECG at the time of the collapse showed a prolonged sinus pause. The pharmacokinetic results revealed large inter-individual variation in oral Org SL94 plasma levels and relatively high C_{max} values were observed in the individuals exhibiting serious adverse events. However, in view of the limited data it is not possible to draw definite conclusions as to the quantitative relationship between C_{max} and the SAE. The oral bioavailability of Org SL94 was calculated to be approximately 1%.

Three Phase II studies have been conducted with orally administered Org SL94 in the treatment of schizophrenic patients. The results indicate that the highest dose applied (4 mg/day) may be considered the minimal effective dose. No safety problems were encountered.

From a safety point of view, chronic administration of doses higher than 4 mg/day is precluded for two reasons: 1) the risk of hepatotoxicity 2) due to the fact that low oral bioavailability predisposes to highly variable plasma levels, patients may be put at increased risk for cardiovascular adverse experiences.

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

The sponsor states that there were 12 serious AEs however other than indicating the number of AEs they are not identified in any way. In addition two subjects withdrew due to "hypotension" 2 withdrew consent and 2 for other reasons however they were not identified so even the hypotension cannot be verified.

In the background information the co-sponsor (Pfizer) identified the above cardiac arrhythmias as Neurally Mediated Reflex Bradycardia, (see Figure 218). It is inconceivable to this reviewer how the sponsor can make this statement.

Figure 218 Pfizer's Discussion of Previously Observed Cardiotoxicity – Study A7501015

In early trials, a total of 4 young healthy male volunteers experienced an untoward adverse experience identified as Neurally Mediated Reflex Bradycardia (NMRB) with sinuspause; ie, 1 subject after receiving 0.15 mg asenapine by the sublingual route, 1 after receiving placebo via the sublingual route, 1 after receiving 30 mg via the oral route, and one 45 minutes after receiving 0.7 mg/30 min asenapine intravenous. All occurred after the first dose and after postural challenge. This reflex is seen in 5%-10% of the general population and is benign and self-limiting. It occurs typically secondary to postural changes, younger age, and high vagal tone (low resting heart rate).

5.6.3.2.5 Pivotal BE Study (TBM vs. CTF) - Study A7501016

Study A7501016 was a pivotal bioequivalence study of a To-Be-Marketed formulation using (b) (4) asenapine to the Clinical-Trial-Formulation that used (b) (4) asenapine. The D95 for the (b) (4) (b)

The following is from the clinical study report:

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

This was a single dose study with a 5 mg dose that included both healthy men and women. Due to the lack of time further evaluation was not feasible but needs to be done, including evaluation of exposure response.

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

For study 41026 with single 5 mg doses and low bioavailability in young healthy volunteers the sponsor reported a variety of AEs that may be indicative of cardiotoxicity. The sponsor's descriptions follow: It's unclear if these are the same or different subjects and if they refer to the same AEs or not. A minimum of 4 subjects were effected, 3 with the formulation with the lower bioavailability. Additional review would be needed to clarify this.

'Vital signs: several adverse events regarding vital signs were reported. Three subjects had a vasovagal reflex after treatment with the (b) (4) tablet and one subject after treatment with the (b) (4) (b) (4) tablet.

One subject showed hypotension after treatment with the (b) (4) tablet. Two subjects showed orthostatic hypotension after treatment with the (b) (4) tablet.

One subject (Subject 20) had a neurally mediated reflex bradycardia (without loss of consciousness) in supine position after treatment with the (b) (4) tablet.

Another subject (Subject 23) had a neurally mediated reflex bradycardia (without loss of consciousness) after standing up after treatment with the (b) (4) tablet.'

However, the description of subject 20 is not consistent with othrostatic hypotension.

5.6.3.2.7 Paroxetine Interaction Study - Study 25525

Study 25525 was a multiple dose interaction study of asenapine 5 mg SL BID with paroxetine 20 mg x and dextromethorphan 30 mg. See section 5.5.7.5.2 CYP2D6 Interactions - Study 25525 for a description of the study design.

The following AEs were described:

Besides Afib requiring cardioversion, a myocardial infarction (possibly two), and hepatotoxicity were the most serious AEs observed.

8.7.1.3 Discontinuation Due to Adverse Events

Eight subjects discontinued the trial. Six subjects discontinued due to adverse events.

Sequence B

The main observation is the drop out of subject 29 (101029) a black male due to an SAE (atrial fibrillation), which was considered related to the treatment with asenapine in combination with (steady state concentrations of) paroxetine at Day 13.

Subject 29. At Day 13 (07 November 2005) during Sequence A (Day 8 asenapine day after DM) atrial fibrillation was reported. The subject was dosed at 08:38 hr with 20 mg paroxetine and at 09:08 hr with 5 mg asenapine. Atrial fibrillation started 1 hr and 22 minutes after administration of 5 mg asenapine and was ended after chemical cardioversion with sotalol at 09:27 the next day. The investigator judged the SAE of mild intensity and probable related to either asenapine or paroxetine or the combination of both trial medications. After the trial, the subject visited the cardiologist of the CWZ for several assessments.

The cardiologist concluded that the subject had no structural heart disease (see for more details Appendix A, narratives). In this period (lasting until March 2006) the subject was diagnosed with presumably diabetic ketoacidosis due to new-onset of diabetes mellitus at 02 March 2006. The outcome of the SAE was recovered with sequelae (diabetes). The investigator judged this SAE of severe intensity and unlikely related to asenapine, unlikely related to paroxetine and not related to dextromethorphan administered at Day 11.

*Subject 37 (treatment **sequence B**) showed a vasovagal syncope when he went to the toilet a few minutes prior to placebo dosing. The investigator judged the subject not eligible for participation without knowing he had been given placebo. Therefore, this subject was actually discontinued due to a pre-dose adverse event.* (reviewer's note – this subject had received paroxetine for 1 week and this was two days after dextromethorphan so it was only pre-dose with respect to asenapine).

Sequence A

During **Sequence A**, 4 subjects discontinued the trial due to the occurrence of AEs.

Subject 09 dropped out due to ECG changes (negative T in II, III and AVF, main reason), non-cardiac chest pain, pain between scapulae and shortness of breath at Day 7. (Day 2 of asenapine)

Subject 14 dropped out due to hypertension (154/88 mmHg with a PR of 93 bpm, main reason), mental restlessness, insomnia, intermittent night sweating, emotional lability, fatigue, nightmares, myalgia shoulders and neck and headache at Day 9. (Day 4 of Asenapine)

Subject 08 dropped out at Day 15 due to persistent moderate headache (main reason), drowsiness and intermittent nightmares. (Day 10 of asenapine 1 day after paroxetine day 4 after DM)

Subject 15 dropped out due to elevated ALAT (main reason) and elevated ASAT at Day 15. The ALAT concentration increased to a maximal value of 474 U/L at Day 16 (Upper Normal Limit (ULN): 50 U/L) (day after paroxe Day 4 DM)

Subjects 08 and 15 discontinued dosing with asenapine but completed all other assessments and were not replaced.

Although samples were taken for genotyping, genotyping was not performed.

In addition to these AEs other AEs seen included restless legs syndrome in 54% in the paroxetine arm and in the asenapine Arm diarrhea 71% and agitation 18%

For paroxetine the labeling lists the following AEs (tremor 8%) 2% bradycardia QT prolongation (warning labeling suggests it's due to a DDI with thioridazine. AEs states no clinically significant ECG changes seen but listing of individual AEs by body system lists as rare).

High pre-dose asenapine concentrations are explained as due to carryover due to dextromethorphan but review indicates it may be due to suicide inhibition due to asenapine 2 weeks earlier.

5.6.3.2.8 Imipramine DDI Study - 25526

No serious AEs were listed, however there several cases of prolonged QT as well as elevated triglycerides similar to what was seen in other studies.

In this subject there was a subject who was found unconscious 1.3 days after dosing with imipramine 75 and 10 days after dosing with asenapine. Although it was not ascribed to asenapine the timing is similar to that seen in subject 37 in study 25525 and a drug interaction with one or more other drugs a week or two after a single dose of asenapine cannot be ruled out.

Structurally similar drugs manufactured by the sponsor that cause significant sedation like asenapine are specifically labeled to avoid alcohol and benzodiazepines due to excessive sedation. The manner of the labeling suggests that this was more than class effect labeling.

Figure 219 Text from Imipramine DDI Study 25526

Reason for subject narrative:
Adverse event (syncope e.c.i.).

Demographic data:
Healthy, non-smoking subject

Date of birth	: [redacted]	b(6)
Race	: Caucasian	
Sex	: Male	
Height	: 186 cm	
Weight	: 75,6 kg	

Exposure to trial medication:

Drug name and regimen	: Period 1 (Treatment C): A single sublingual dose of placebo asenapine (Org 5222) on 03-OCT-2005. A single sublingual dose of 5 mg asenapine and a single oral dose of 75 mg of imipramine on 04-OCT-2005. Period 2 (Treatment B): A single oral dose of 75 mg imipramine on 11-OCT-2005.
Treatment start	: 03-OCT-2005
Treatment stop	: 11-OCT-2005

Description event:
On Wednesday 12-OCT-2005 (day 2 of the second dosing period, treatment schedule: C, B, A), the subject discontinued the trial due to smoking. Smoking was prohibited during the trial. At screening, he had given incorrect information about his smoking habits.
Before discharge on Day 2, 12-OCT-2005 at 17:00 h, i.e.32.5 hours after dosing of imipramine only, vital signs were normal, and there were no adverse events. The trial CPRM agreed to discharge him on the afternoon of Day 2.

On 14-OCT-2005 investigator was notified that the subject was found unconscious at the Nijmegen train station at about 09:00 h on 13-OCT-2005. Another subject from this same trial reported that subject 08 regained consciousness spontaneously, the exact time is unknown, but within 5 minutes after falling. The subject was transported by ambulance to the Hospital in Nijmegen. Policemen were involved due to aggressive behaviour of the subject. The ambulance arrived at the emergency department at 09:50 h, the subject was conscious at that time. There is no information available about his state of consciousness during the ambulance ride. The start time of the syncope is 09:00 h, exact stop time unknown. On arrival at the hospital it was documented that the subject was conscious. Therefore, that time was chosen as the stop time of the event syncope. The subject was examined by a physician and released at 12:10 h with the diagnosis: collapse of unknown origin. ECG was normal, and comparable to the ones made at our site. The hospital physician stated that the subject smelled quite a bit, it is not specified which smell it was. As subject had been drinking, it was most probably the smell of alcohol. (On 14-OCT-2005, consent was given to retrieve this information.)

According to subjects' wife, he had called her at around 12:15 h on 13-OCT-2005 to inform her he was coming home. He told her that he had fainted that same morning due to the medication. Since then she had not heard from him and his whereabouts were unknown.

Before noon, on 14-OCT-2005, investigator was informed that subject 08 was again at the Nijmegen train station. He agreed to come to the trial site for medical examination.

Figure 220 Text from Imipramine DDI Study 25526 (Continued)

Subject said he drank a "few" beers, but denied drug abuse. However, we received reliable information that he did indeed use cannabis after discharge.
Subject 08 remembered passing out at the train station on 13-OCT-2005, and waking up in the hospital. He could not recall how and when he left neither the hospital, nor a conversation with the physician about a diagnosis. He recalled walking around town in Nijmegen all day long, feeling "out off the world". He apparently spent the night in a nearby hotel.
He did not go home (as he had promised his wife) because: "He knew he was heading for trouble" because he had to inform her that he was dismissed for non-compliance.

Physical examination was performed; an agitated, drunk man with a few cuts and bruises. He smoked constantly; there were no signs of psychosis or neurologic abnormalities. ECG, standing and supine vital signs were normal, heart rate elevated (98 bpm).
Laboratory results were not clinically relevant abnormal, except for an alcohol promillage of 2.2.
Due to agitation, a urine drug screen was not performed.

In consultation with our independent medical consultant, it was decided that it was not necessary to have this subject evaluated by a psychiatrist.

Conclusion:

- Syncope e.c.i., but most probably due to alcohol intoxication, possibly facilitated by cannabis abuse and imipramine dosing (on 11-OCT-2005 at 08:35)
- In agreement with the trials' CPRM, it was not filed as an SAE as it was not potentially life threatening, nor a prolonged hospitalization
- No reason for suspicion of cardiac of neurologic origin of the syncope
- Relation to the study medication imipramine: doubtful, asenapine: none

5.6.3.2.9 Other Studies

An additional factor that's worrisome is that a number of subjects are listed in these single dose studies of 5 mg SL tablets as dropouts from the studies due to noncompliance, and in some cases it's clear that these are the subjects with the highest exposures. It's hard to understand how compliance would be an issue with a single dose, and without additional information including inspection of the raw case report forms these subjects should be considered as possibly experiencing serious AEs.

Although the QT Team acknowledged a number of AEs and worrisome indicators in their review including effects on calcium channels which are expected to result in conduction defects, these were not highlighted.

On April 14, 2008 at 3 PM this reviewer spoke with Suchitra Balakrishnan the medical officer on the QT review. She told me she was new and had taken over the QT review from another medical officer Dr. Grant. She had spoken to Dr. Norm Stockbridge and he had told her to only look at the QT review, the Integrated Summary of Clinical Safety and Investigator's Brochure. When I pointed out the serious nature and consequences in the elderly population she stated that she also had concerns. Consequently, I suggested that in the future she might wish to highlight any concerns for us that might need further review as medical officers typically don't review the phase I studies for safety.

She offered to do another review for other than QT effects, however I indicated that this would not be necessary presently but the medical division may decide to request a consult if another review cycle is needed.

Table 192 Summary of Selected Cardiac AEs

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

5.6.3.3 *Agranulocytosis and Pancytopenia*

After finding serious AEs due to drug-drug interactions in clinical pharmacology studies this reviewer checked the deaths (and was going to check the serious AEs) in the overview of clinical safety. In the 'ongoing studies' this reviewer found two deaths with no cause listed and suspicious laboratory values. Figure 221 and Figure 222 show plots of the hematology lab values over time. Based upon visual inspection of the lab sheets it was initially thought that these were potential cases of aplastic anemia, upon plotting the data this needs to be revised to neutropenia with a developing pancytopenia with death likely due to agranulocytosis.

When the number of subjects who have been on drug for 52 weeks or longer are considered, the rough incidence of death due to agranulocytosis is 2 / 626 (or 1 in 313). There are also several other deaths attributed to respiratory arrest and pneumonia that need to be investigated. If these other suspicious deaths are considered it's even higher (~ 1 in 150).

Figure 221 Hematology Values Prior to Death for Subject 132017 -Study P25520

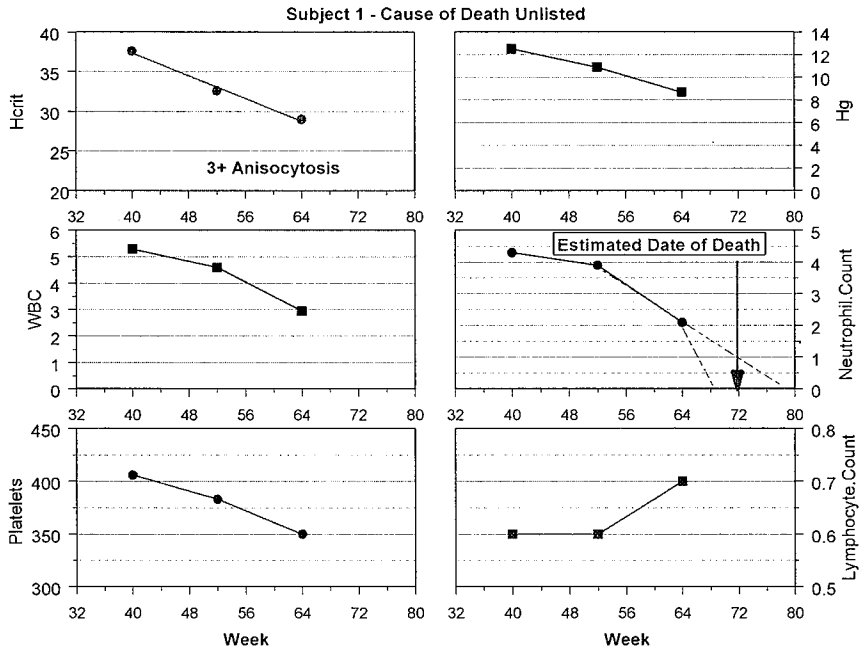
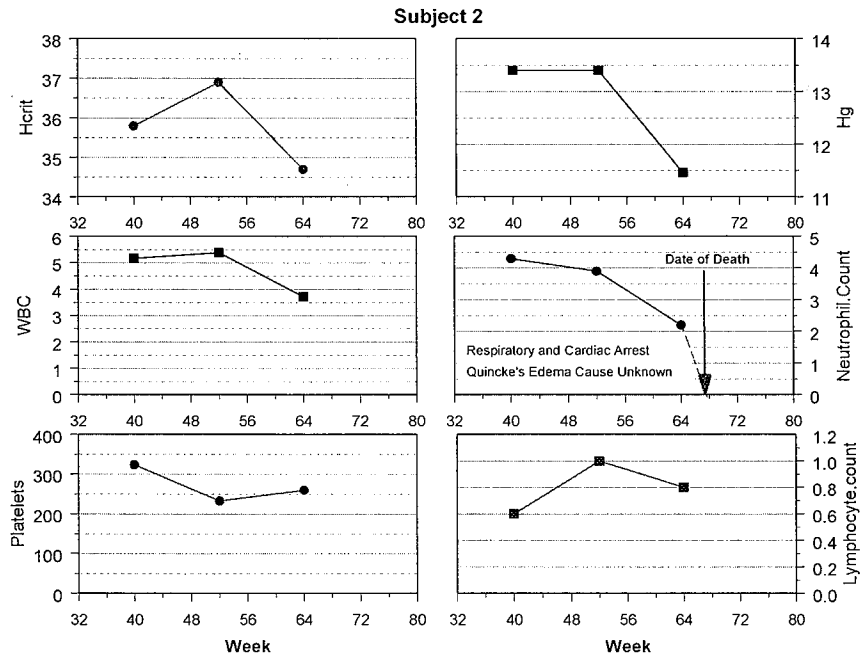


Figure 222 Hematology Values Prior to Death for Subject 241041 -Study P25520



5.6.3.4 Drug-Drug Interactions

Although not addressed in this review it was repeatedly observed that triglyderides were elevated with asenapine. In addition since asenapine has an N-oxide metabolite blood dyscrasias are a possibility. Both of these issues need to be addressed in future review cycles. For blood dyscrasias trends for trends for decreases in hematologic parameters may suggest the possibility and should be looked at.

In study 41009 one subject had an exascerbation of psychosis that may be due to an interaction between asenapine and over-the-counter allergy medications, specifically dextromethorphan and possibly pseudoephedrine. Other possibilities include an exascerbation of psychosis, also possibly due to these OTC drugs beginning prior to the treatment with the investigational agent, combined with use of a subtherapeutic dose or an experimental agent that would be ineffective for this patient.

STUDY AND TREATMENT DATA

Protocol number: 041009
Site Number: 01
Treatment: Org 5222, 10 mg
Test product: Org 5222, 5 mg

Subject number: 0012
Subject initials: —

b(6)

REASON FOR SUBJECT NARRATIVE SUMMARY

Serious Adverse Event: SAE# 0218-01D **Schizophrenic Reaction** *(Bipolar Schizoaffective Disorder)*

BASELINE DEMOGRAPHIC DATA

Date of birth: — b(6) (Age: 32 yrs)
Gender: Male
Height: 183 cm
Weight: 87.3 kg

EXPOSURE TO STUDY MEDICATION

Drug name	Total daily dose	Unit	Route	Day start	Day stop	Days on drug
Org 5222	10	mg	SL	24-Jun-01	02-Jul-01	9

DESCRIPTION OF EVENT

This 32-year-old Caucasian male took the study drug from 24-Jun-01 through 02-Jul-01. Current antipsychotic therapy was Geodon™. Prior to enrolment in the study, the subject presented with insomnia and increased anxiety. The symptoms were treated with Ambien® and Ativan®, respectively. Both symptoms continued until the follow-up period. The subject complained of having "racing thoughts" on 29-Jun-01, and on 30-Jun-01 was noted to be hyperverbal. On 01-Jul-01, the subject was reported to be intrusive and unable to maintain personal affairs outside a structured environment. The subject was admitted to the hospital with a diagnosis of bipolar schizoaffective disorder. The following day, the subject completed participation in the trial of Org 5222 and was restarted on Geodon™ at 40 mg BID. Moderate to severe increase in agitation and psychosis were noted in the follow-up period. In addition to Geodon™, treatment included Haldol®, Cogentin® and Depakote®. The event reportedly resolved on July 19, 2001.

ADDITIONAL RELEVANT INFORMATION

None

RELEVANT MEDICAL HISTORY

None

RELEVANT CONCOMITANT MEDICATION

Drug Name	Total Daily dose	Unit	Route	Start Date	Stop Date	Indication
Cardizem® CD	300	mg	PO	??-May-01	Cont	High Blood Pressure
acetylsalicylic acid	2	tab	PO	??-Jun-01	Cont	General body discomfort
ibuprofen	2	tab	PO	??-Apr-01	Cont	General body discomfort
Robitussin®	2	tsp	PO	??-??-1975	Unknown	Seasonal Allergies
Sudafed®	2	tab	PO	??-??-1975	20-Jun-01	Seasonal Allergies

Ativan®	2	mg	PO	23-Jun-01	Cont	Anxiety/Agitation
Ambien®	10	mg	PO	22-Jun-01	Cont	Insomnia
ziprasidone	80	mg	PO	??-Sep-99	21-Jun-01	Schizoaffective Symptoms

OTHER RELEVANT ADVERSE EXPERIENCES

Adverse experience	Day start	Day stop	Intensity	Action	Outcome	Causality
Insomnia	22-Jun-01	17-Jul-01	Moderate	None	Recovered	Unlikely
Increased anxiety	23-Jun-01	19-Jul-01	Moderate	None	Recovered	Unlikely
Racing thoughts	29-Jun-01	17-Jul-01	Moderate	None	Recovered	Unlikely
Hyperverbal	30-Jun-01	17-Jul-01	Moderate	None	Recovered	Unlikely
Increased agitation	14-Jul-01	14-Jul-01	Severe	None	Recovered	Unlikely
Increased psychosis	14-Jul-01	14-Jul-01	Severe	None	Recovered	Unlikely

RELATION TO STUDY DRUG
According to the investigator the event was **unlikely related** to trial medication.

Ziprasidone half-life 9 - 10 hr

There was also a neonatal death and a death due to complications 2 months status post of a hernia repair. No detailed information was submitted and needs to be requested however the possibility of interactions with narcotic analgesics and anesthetic agents needs to be kept in mind and evaluated.

6 Appendices

6.1 Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-177	**Brand Name**	Sycrest®
OCPB Division (I, II, III, IV, V)	I	**Generic Name**	Asenapine Maleate
Medical Division	Psychiatry	**Drug Class**	Antipsychotic
OCPB Reviewer	Ron Kavanagh	**Indication(s)**	Schizophrenia Acute Bipolar I
OCP Team Leader	Ray Baweja	**Dosage Form**	SL Tablet
INDs	51,641	**Dosing Regimen**	BID
Date of Submission	August 31, 2007	**Route of Administration**	Sublingual
Estimated Due Date of OCP Review	March 4, 2008	**Sponsor**	Organon
PDUFA Due Date	June 30, 2004	**Sponsor's Agent**	N/A
Division Due Date		**Priority Classification**	S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			**Also QBR**
Labeling	X			**Structured Product Labeling**
Reference Bioanalytical and Analytical Methods	X	16		**10 full 6 partial methods**
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	13		
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	3		
Cell Transport:	[redacted]	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	[redacted]	[redacted]		
multiple dose:	X	4		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	7		
In-vivo effects of primary drug:	X	2		
In-vitro:				
Subpopulation studies -				
ethnicity:	X	1		
gender:				
pediatrics:	X	1		
geriatrics:	X			
renal impairment:	X	2		
hepatic impairment:	X	2		
PD:				
Phase 2:	X	3		
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:	X	7		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	2		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	3		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]		
Genotype/phenotype studies:	X	1		
Chronopharmacokinetics				
Enantiomeric Interconversion	X	1		
Pediatric development plan	X	1		
Literature References	X	30		
Total Number of Studies		>90		

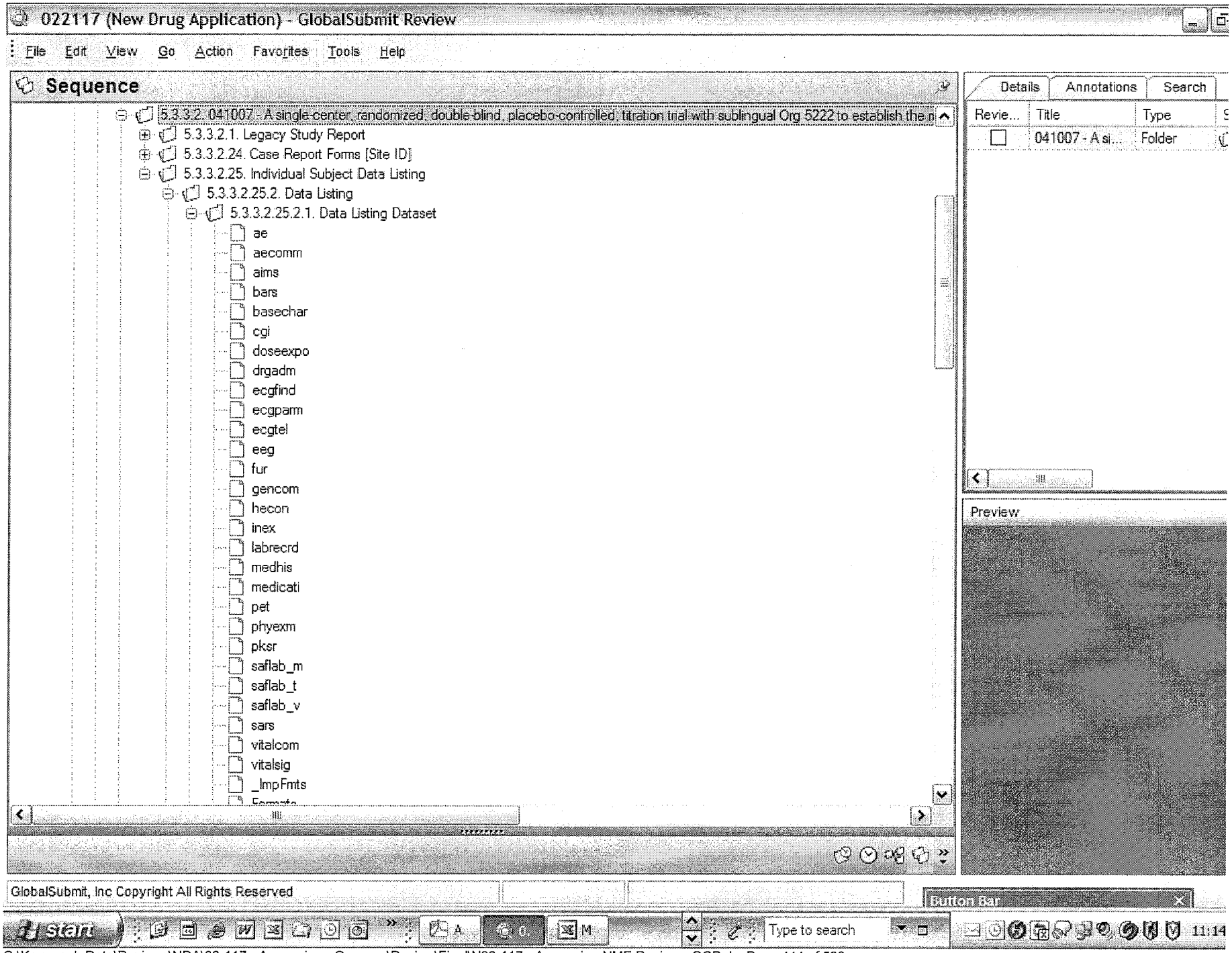
Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Gender Effect** **Age Effect** **Effect of Hepatic Impairment.** **Suicidality especially with dose and with maintenance therapy.** **Effect of Smoking. Especially in Bipolar Disorder.** **Minimum Effective Dose especially in bipolar disorder.**	
Other comments or information not included above	Pilot GRMP NDA See Attached Appendices for Comments and Additional Information.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

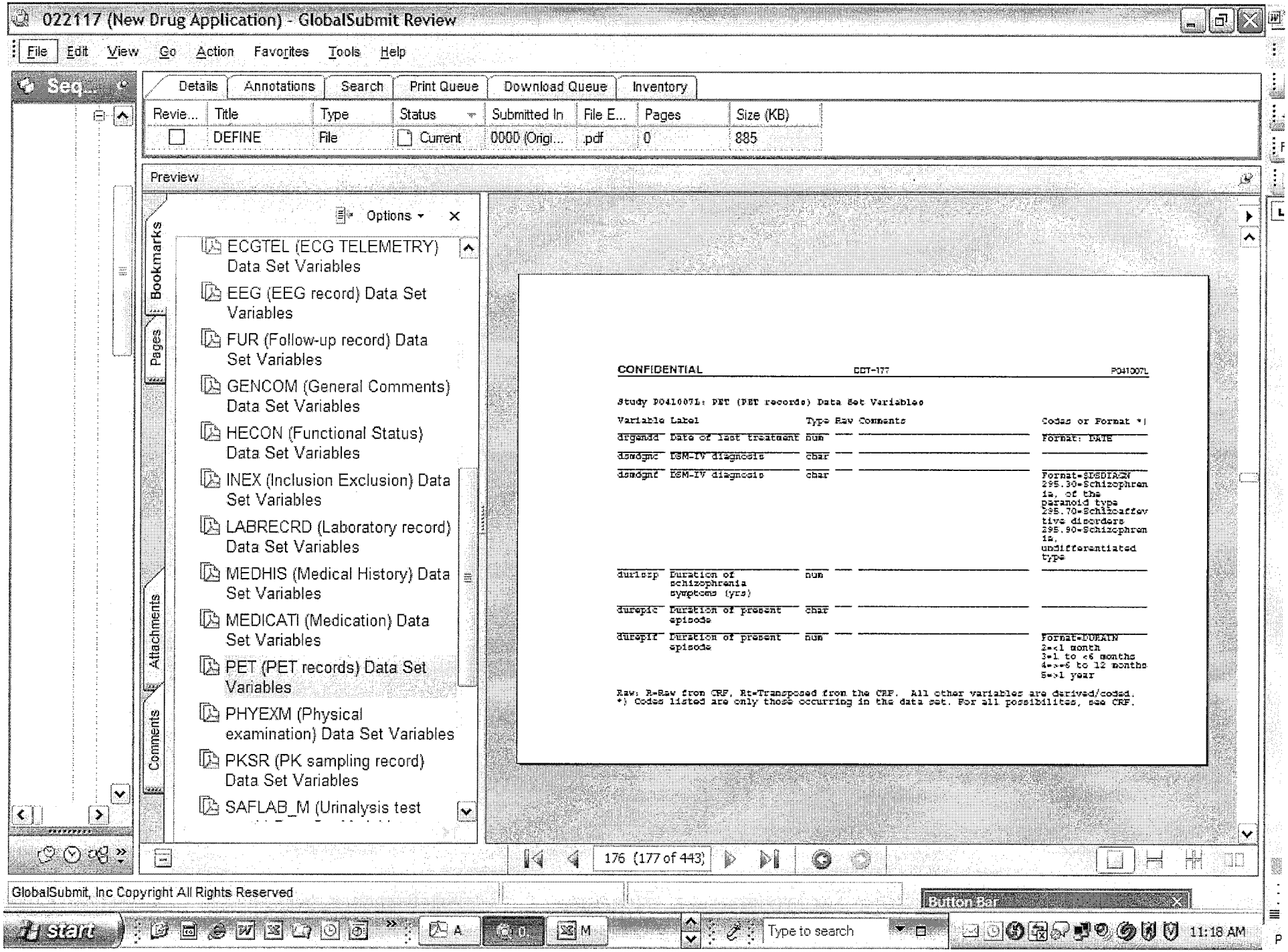
CC: NDA 22-077, HFD-850 (P. Lee, GobburuJ)
HFD-860 (KavanaghR, UppoorR, BawejaR, M. Mehta)
Psychiatry (KeidrowK, Updegraff), CDR

APPENDIX 1

Table 193

eCTD/GSReview Format	Number of Studies	Comments
Biopharmaceutic		
BA	6	
BE	6	
Bioanalytic	14	
Biomaterials		
Protein Binding	4	
Metabolism	14	
Cell Transport	1	
Pharmacokinetics		
Healthy Subjects	7	
Patients	3	
Intrinsic Factors	6	
Extrinsic Factors	6	
Pop PK	2	
PD & PK/PD	5	
Subtotal	***74***	54,976 Pages
Efficacy and Safety		
Schizophrenia		
Placebo	9	
Active Control no PBO	1	
Uncontrolled	1	
Integrated Study Reports		
ER	1	
ISE	1	
ISS	1	
Other Studies	25	Includes ER and PK Studies
Bipolar		
Placebo	2	
Active Control no PBO	1	
Uncontrolled	0	
Integrated Study Reports		
ER	2	
ISE	1	
ISS	0	
Other	3	
Subtotal	***48***	
Total Number of Studies to Check	**122**	


022117 (New Drug Application) - GlobalSubmit Review
File Edit View Go Action Favorites Tools Help
Sequence
5.3.3.2. 041007 - A single-center, randomized, double-blind, placebo-controlled, titration trial with sublingual Org 5222 to establish the n
5.3.3.2.1. Legacy Study Report
5.3.3.2.24. Case Report Forms [Site ID]
5.3.3.2.25. Individual Subject Data Listing
5.3.3.2.25.2. Data Listing
5.3.3.2.25.2.1. Data Listing Dataset
ae
aecomm
aims
bars
basechar
cgi
doseexpo
drgadm
ecgfind
ecgparm
ecgtel
eeg
fur
gencom
hecon
inex
labrecrd
medhis
medicati
pet
phyexm
pksr
saflab_m
saflab_t
saflab_v
sars
vitalcom
vitalsig
_ImpFmts
Details
Annotations
Search
Revie...
Title
Type
041007 - A si...
Folder
Preview
GlobalSubmit, Inc Copyright All Rights Reserved
Button Bar
Start
Type to search
11:14


022117 (New Drug Application) - GlobalSubmit Review
File Edit View Go Action Favorites Tools Help
Details Annotations Search Print Queue Download Queue Inventory
Revie... Title Type Status Submitted In File E... Pages Size (KB)
DEFINE File Current 0000 (Origi... .pdf 0 885
Preview
Options
Bookmarks
Pages
Attachments
Comments
ECGTEL (ECG TELEMETRY) Data Set Variables
EEG (EEG record) Data Set Variables
FUR (Follow-up record) Data Set Variables
GENCOM (General Comments) Data Set Variables
HECON (Functional Status) Data Set Variables
INEX (Inclusion Exclusion) Data Set Variables
LABRECRD (Laboratory record) Data Set Variables
MEDHIS (Medical History) Data Set Variables
MEDICATI (Medication) Data Set Variables
PET (PET records) Data Set Variables
PHYEXM (Physical examination) Data Set Variables
PKSR (PK sampling record) Data Set Variables
SAFLAB_M (Urinalysis test
CONFIDENTIAL
DDT-177
P041007L
Study P041007L: PET (PET records) Data Set Variables
Variable Label Type Raw Comments Codes or Format *)
drgenid Date of last treatment num Format: DATE
dsmdgnc DSM-IV diagnosis char
dsmdgnf DSM-IV diagnosis char Format=$DSDIAGN 295.30=Schizophrenia, of the paranoid type 295.70=Schizoaffective disorders 295.90=Schizophrenia, undifferentiated type
duriszp Duration of schizophrenia symptoms (yrs) num
durepic Duration of present episode char
durepif Duration of present episode num Format=DURAIN 2=<1 month 3=1 to <6 months 4=>=6 to 12 months 5=>1 year
Raw: R=Raw from CRF, Rt=Transposed from the CRF. All other variables are derived/coded.
*) Codes listed are only those occurring in the data set. For all possibilities, see CRF.
176 (177 of 443)
GlobalSubmit, Inc Copyright All Rights Reserved
Button Bar
start
Type to search
11:18 AM

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: **Applicant:** **Stamp Date:**

Drug Name: **NDA Type:**

APPENDIX 2

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the sponsor submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			
2	Has the sponsor provided metabolism and drug-drug interaction information?			
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested at the earlier meeting (e.g.: Pre-NDA meeting), submitted in the appropriate format (e.g. CDISC)?			
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			
	Studies and Analyses			
5	Has the Sponsor made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			
6	Did the sponsor follow the scientific advice provided regarding matters related to dose selection?			
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			
8	Is there an adequate attempt by the sponsor to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			
10	Did the sponsor submit all the pediatric exclusivity data, as described in the WR?			
11	Is the appropriate pharmacokinetic information submitted?			

12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			
17	Was the translation from another language important or needed for publication?			

Any Additional Comments:

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

APPENDIX 3

Light Yellow not to be reviewed per OCP Management Instructions and Agreed to at November 9, 2007 Planning Meeting.

Light Green – May not need to be reviewed. However this needs to be confirmed.
Tan – Likely will only need superficial review.
Light Blue – Contains significant exposure response data

		N	Cohort						size	Datafiles							
										CDISC		Labeled	Location			Format	
										Any	PK			Raw Data	Comment	Metrics	Summary Stats
Bioanalytic		14															
Plasma & RBC binding		4															
In Vitro Metabolism		14															
Transport Study		1															
Studies With Sublingual Formulation																	
CP	Healthy Vol / Special Pop	29	F	29													
Biopharmaceutic	Particle Size				A7501016	Effect of Particle Size on BA of SL Tabs			922 106 75					T	Found via Hyperlink	T	T
	Organoleptic		(under other schizo ph III)		A7501024	Taste masking			565								
Bioavailability					25533	Absolute BA			375	Y	N	Y	App B	T		Text	T
					041026	Absolute BA											
					25506 (INT00035825)	Absolute BA (Combined 041036 & 25506		Not included in list of Safety Data Base in Summary Section	36 235 (5.3.5.4.1)	N		N	App A	T		Text	T
					041036	BE of Tablets vs. SL		Found in Table of all Clin Trials	555	N		No	App B	T		Text	T

					25537	Effect of Water on BA			2700	Y	N	N	App B	T	By individual	T	T
Bioequivalence					041009	2 way XO of 2 SL forms		Not included in list of Safety Data Base in Summary Section	1228 0113 0123 0083 0488				App B	T		T	T
					25512	3-Way XO sublingual, supralingual, buccal			1082 0133 0172	N	N	Part		Image		Image	Image
					041030	3-Way XO sublingual, supralingual, buccal			2099 0008 0135 0066	Y	N	No		T		T	T
					041014	1 x 15 mg vs. 3 x 5 mg	Not included in list of Safety Data Base in Summary Section		668 398 074	Y (30)				T	By Sequence	T	T
					A7501015	BE of 5 mg SL tabl Pivotal BE Study			1047 0076 0066 105 144			No	Found by hyperlink to BE metric summary table in CSR	T		T	T
SRD S/T					25509	SL 10 – 300 mcg			2474 0153 0124	Y	N			T	Tables and Figures not labeled	T	
MD S/T					25511	150 mcg SL BID			1671 0172 0321	Y	N			T		T	T
MD S/T					25514	200 mcg bid x 2 days then 300 mcg bid x 4.5 days			3193 0239 0218	Y	N			T		T	T
MD S/T					25542	Parallel 0.3 0.6 1 3 mg bid 0.3 1 3 5 mg bid 1 3 5 10 mg BID			1753 0168 0122 0112	Y	N			T		T	T

						1 3 5 10 15 mg bid 2 & 5 mg qd			0149 310							
					041028	SD Enantiomeric Interconversion			532 042 053	Y	N			T		T	T
					25532	MRD & 10 mg mass Bal			612 067 066 136 119	Y	N			T		T	T
Intrinsic Factors					25546	Japanese vs. Caucasian			4008 204 192 193 107 153 414	Y	N			T	Not laid out nice	T	T
					25522	Hepatic Impairment			875 82 66	Y	N			T		T	T
					A7501018	Hepatic Impairment			891 41 36 30 70 52	Y	N			T		T	T
					25521	Renal Impairment			766 82 58	Y	N			T		T	T
					A7501017	Renal Impairment			738 70 68								
Special Pops					A7501022	DB, Rand, Parallel Grp,PBO controlled MD S/T & PK study in Adolescents		1 – 10 mg bid	1131 70 73					No	Stamped Pfizer	NO	NO
Extrinsic Factors					041029	Effect of Food on BA			2141 0008 0134 0057	Y	N	Y	App B	T	T	T	
					25545	Effect of immediate			962	Y	N	N	App B	T	T	T	

						smoking by smokers on BA			0084 0107									
					25525	CYP2D6 DDI DM & Paroxetine			1965 66 69 86 86 76 139 206					T		T	T	
					25526	CYP2D6 DDI Imipramine			1746 41 70					T		T	T	
					25527	DDI Valproate			1468 59 43 59 31 96					T		T	T	
					25528	DDI Induction CBZ			1603 53 58					T		T	T	
					25529	DDI Cimetidine			1712 123 190					T		T	T	
					041033	DDI 1A2 Fluvox			1254 140 153 184					T		T	T	
					25540	Po vs. oral & charcoal			654 86 79 63 114					T		T	T	
QTc					A7501001	DB, Parallel QTc Study of Asenapine, Quetiapine, and PBO			4500									
					754-0046	Comparative ER on QTc			72									
					INT00065	ER on QTc												
PD					25510	PET Study			194									

									219 15								
					25516	PET Study			329 132 13								
					86033	PET Study			52 227								
					25503	PET Study			54								
					041023												
	Pxts	8		8	041001	DB, pbo-ctrl MD MTD titration S/T study in subjs with Schizo and Schizoaffective		0.2 – 0.8 mg BID									
					041007	DB, pbo-ctrl MD MTD titration, S/T study in subjs with Schizo and Schizoaffective and a PD-PET subj-study in healthy vols		0.5 – 4.8 mg bid									
					041009	2- way XO rel BA of diff form SL tabs		2.5 mg & 5 mg bid									
					041012	Rand DB PBO Ctrl S.T study		20 mg bid									
					041014	2-way XO rel Bio and Safety Study		3 x 5 mg vs. 1 x 15 mg									
PK/PD					INT 39258	Dose Finding – Dose Response			85								
Ph II/III	Safety / Eff	14	Ph II Schizo		041002	Dose Finding – Dose Response			9363	0.8 mg	Y						
					041004(ext 041502)	Efficacy vs. Risperidone	Pop PK		6190	5 mg bid	Y						
					41502	"			1632	"	N						
					041013	Dose Finding – Dose Response	Ph II PK/PD		5034	1.6 mg? 2.4 mg?	Y						
					INT 00032958	Dose Finding – Dose Response											
					041500			0.2 mg bid 0.4 mg bid	2229		Y	trough					

								0.8 mg bid									
					(ext 041002) 041590 (ext 041500) (ext 041013)												
					041505		PK/PD	1.6 mg 2.4 mg	1884		Y	trough					
			Ph III Schizo Short Term	3	041021		PK/PD	5 mg bid 10 mg bid	4785		Y						
					041022	Vs. Olanzapine	PK/PD	5 mg bid 10 mg bid	4146		Y						
					041023	Efficacy vs. Haldol short	PK/PD	5 mg bid 10 mg bid	5161		Y						
			Ph III Schizo Long Term		25517		PK/PD Pop PK	5 mg bid 10 mg bid Flex dose	4628 18806 23663								
			Bipolor Mania 3 weeks	1	A7501004				2238	Y	Y				Pop PK Intensive Sampling		
			Bipolor Mania 3 weeks	1	A7501005				2155	Y	Y				Pop PK Intensive Sampling		
			Bipolor Mania 9 weeks		A7501006 (extension to the 2 short term studies A7501004 & A7501005)				3143 1037		N						
Pop PK					INT 00036661	Pop PK			228 6								
Pop PK					INT 00063719	Pop PK			63 3								
					INT 00039913	ER Model			56								
					INT 00043090	LOCF vs. MMRM			12								
					INT00039918	M&S ER			98 3								
Ongoing																	
	Schizo	12			25520 (ext 25517)				12								

					25543 25544 (ext 25543); A7501013 A7501014 (ext A7501013) A7501012 A7501021				12 10 13 10 8 5								
					041512 (ext 041021/022)	Long term extension vs. Olanzapine			10								
					041513 (ext 041023)	Long term extension vs. Haldol			7								
	Bipolar				A7501007 (ext A7501006); A7501008 A7501009 (ext A7501008)				12 11 8								
					25501	SD MD Tablets	30 mg		282								
					25506	Absolute BA Tablets			235								
					25507	SD PK Tabs			179								
					85029	SRD S/T Tabs			172								
					85136	RD Study of Tablets			376								
					25504	Efficacy Study Tablets			2135								
					87039	Efficacy Study Tablets			430								
					25505	Efficacy Study Tablets			944								
					CNS-9041	MRD PK tablets in Japanese			90								
					CNS-9141	MRD PK tablets in Japanese			36								
					CNS-9241	MD Parallel pilot efficacy in Japanese Tablets			38								
					041026	Rel BA Tablet vs. SL			235								
Total		**63**															

54 50 other studies

10 6 partials

REPORTS OF BIOANALYTICAL AND ANALYTICAL METHODS FOR HUMAN STUDIES

Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Trial Status; Type of Report	
SDGRR 3569	Validation of the gas chromatographic mass spectrometric assay for the determination of Org 5222 in human plasma	Org 5222	Completed full	136
SDGRR 3570	Validation of the gas chromatographic assay for the determination of Org 30526 in human plasma	Org 30526	Completed full	69
R&DRR NL0012937	Method transfer validation of the GC-MS assay for the determination of Org 5222 in human plasma	Org 5222	Completed full	28
R&DRR NL0039449	Re-validation of the GC-MS assay for the determination of Org 5222 in human plasma	Org 5222	Completed full	21
R&DRR NL0054225	Validation of the LC-MS-MS assay for the determination of asenapine (Org 5222), Org 30526 and Org 31437 in human plasma	Org 5222 Org 30526 Org 31437	Completed full	67
R&DRR NL0061697	Amendment I to R&D RR NL0054255	Org 5222 Org 30526 Org 31437		14
R&DRR NL0058575	Re-validation of the LC-MS-MS assay for the determination of asenapine (Org 5222), Org 30526 and Org 31437 in human plasma	Org 5222 Org 30526 Org 31437		58
R&DRR NL0065058	Amendment I to R&DRR NL0058575	Org 5222 Org 30526 Org 31437		18
R&DRR INT00013367	Amendment II to R&DRR NL0058575	Org 5222 Org 30526 Org 31437		13
R&DRR NL0046846	Cross-validation of the LC-MS-MS assay for the determination of Org 5222 and Org 30526 in human plasma	Org 5222 Org 30526		80
R&DRR INT00003244	Validation of a method for the determination of asenapine-glucuronide (Org 216761-0) in human Li-heparin samples by LC-MS/MS	Org 216761-0		69
R&DRR INT00003248	Validation of a method for the determination of asenapine-glucuronide (Org 216761-0) in human urine samples by LC-MS/MS	Org 216761-0		103
R&DRR INT00006666	Validation of a Method for the Determination of Org 5222 and Org 30526 in Human Urine Samples by LC-MS/MS	Org 5222 Org 30526		131
R&DRR NL00005948	Validation of the LC-MS-MS assay for the determination of asenapine, Org 30526 and Org 214025 in human plasma	Org 5222 Org 30526 Org 214025		79
R&D RR INT00029604	Amendment 1 to NL00005948	Org 5222 Org 30526 Org 214025		

19 in vitro

REPORTS OF STUDIES PERTINENT TO PHARMACOKINETICS USING HUMAN BIOMATERIALS

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	
PLASMA PROTEIN BINDING STUDY REPORTS				
PK	SDG RR 2972	In vitro binding of [3H]-Org 5222 to male rat, dog and human plasma proteins and in vivo plasma protein binding after a single oral dose of [3H]-Org 5222 to male rats	Org 5222	15
PK	DM2005-005222-007	Plasma protein binding of asenapine (Org 5222) and N-desmethyl asenapine (Org 30526) in human, rat, dog, monkey, rabbit and mouse plasma, human alpha1-acid glycoprotein and human serum albumin	Org 5222 Org 30526	30
PK	DM2005-005222-015	Plasma protein binding of 11-hydroxyasenapinesul fate in human, rat and rabbit plasma	Org 214025 (asenapine 11-O-sulfate)	11
PK	R&DRR NL0029630	An in vitro binding study with Org 5222 by mouse, rat, rabbit, dog and human erythrocytes	Org 5222	23

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Trial Status; Type of Report	
REPORTS OF HEPATIC METABOLISM AND DRUG INTERACTIONS STUDIES					
PK	SDGRR 2874	In vitro metabolism of Org 5222 by rat, dog and human hepatic microsomes	Org 5222	Completed full	15
PK	SDGRR 5067	In vitro metabolism of Org 5222 by rat and human hepatocytes	Org 5222	Completed full	15
PK	R&DRR INT00003054	An in vitro metabolism study with Org 5222 by male mouse, rat, rabbit, dog and human liver microsomes	Org 5222	Completed full	33
PK	R&DRR NL0060905	An in vitro metabolism study with Org 5222 by male mouse, rat, dog and human and female rabbit hepatocytes	Org 5222	Completed full	36
PK	DM2006-005222-013	Determination of the Enzyme Kinetics and UGT Involved in the Metabolism of asenapine to the N-Glucuronide Conjugate of asenapine	Org 5222	Completed full	6
PK	R&DRR NL0010293	Characterization of human cytochrome P450 enzymes involved in the in vitro metabolism of Org 5222	substrate = asenapine inhibitor = fluvoxamine, ketoconazole	Completed full	28
PK	R&DRR NL0060848	A second characterization of the human cytochrome P450 enzymes CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4 involved in the in vitro metabolism of asenapine (Org 5222)	substrate = asenapine inhibitor = furafylline, orphenadrine, MPEP: 1-(1-methyl-1-phenylethyl)piperidi ne, tranylcypromine, benzylnirvanol, quinidine, ketoconazole	Completed full	37
PK	R&DRR NL0017588	The inhibition of the human cytochrome P450 enzymes CYP1A2 and CYP2D6 by Org 5222 (in vitro)	substrate = CEC: 7-ethoxy-3-cyanocoumarin, AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-	Completed full	29

			methoxy-4-methylcoumarin inhibitor = asenapine, furafylline		
	R&DRR NL0048836	The assessment of the human cytochrome P450 enzyme CYP2D6 with Org 5222 and its metabolites Org 30526 and Org 31438 in vitro"	substrate = AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin inhibitor = asenapine, N-desmethyl, N-oxide, quinidine coumarin, DBF: dibenzylfluorescein, MFC: 7-methoxy-4-trifluoromethylcoum arin, BzRes: benzyloxyresorufin, BQ: 7-benzyloxyquinoline		24
	R&DRR NL0050059	The assessment of inhibition of the human cytochrome p450 enzymes with asenapine (Org 5222) and its metabolites Org 30526 and Org 31437 in vitro	inhibitor = asenapine, N-desmethyl, N-oxide, furafylline, tranylcypromine, quercetin, sulfaphenazole, ketoconazole		50
PK	R&DRR NL0013163	The inhibition of the human cytochrome p450 enzymes CYP2C19 and CYP3A4 by Org 5222 (in vitro)	substrate -mephenytoin, testosterone inhibitor - asenapine, tranylcypromine, ketoconazole	Completed full	20
PK	R&DRR NL0050307	The assessment of inhibition of the human cytochrome P450 enzyme CYP2D6 with Org 10968 and Org 10969 (both enantiomers of asenapine (Org 5222)) in vitro	substrate - AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin inhibitor - (R,R)-asenapine, (S,S)-asenapine, quinidine	Completed full	21
PK	DM2005-00522-009	Inhibition of P450 enzymes	substrate -phenacetin, bupropion, amodiaquine, diclofenac, S-mephenytoin, dextromethorphan, felodipine, midazolam, testosterone inhibitor - asenapine	Completed full	15
PK	RR 764-04914	Induction potential of asenapine (Org 5222) on Cytochrome P450 enzymes 1A2 and 3A4 in human hepatocytes	substrate: O-deethylase, testosterone 6beta- hydroxylase inducer: asenapine	Completed full	25
REPORTS OF STUDIES USING OTHER HUMAN BIOMATERIALS					
PK	DM2005-005222-008	In Vitro Transport Study of asenapine (ORG-5222) and N- Desmethyl asenapine (ORG-30526) in MDCK and MDR1 Cells	Org 5222 Org 30526	Completed full	22

APPENDIX 4

Size	**# Pages**	
Only Phase I Clin Pharm Studies excluding Forrmulations not to be marketed.		74,976
Including ER Studies	~160,000	

21-999 Paliperidone OROS ~ 50,000

Familiar with
Minimal ER
Assistance

NDA	Drug	Start	TL	Duration
21-999	Paliperidone OROS	3.5 months		
		4 months	b(4)	

Paliperidone OROS

Familiar with
Assistance Both QT and PM
They started in Feb and earlier not completed until and 8/3

Minimal ER
No Distractions – e.g. holidays, other submissions meetings.

Other

Metabolism Extremely Convoluted
Numerous Distractions

Original verbal agreement with timelines I had stipulated that it assumed there would be no meetings or other distractions

Asenapine

Large
Time
Distractions?
New computer format
Extensive ER
Not famailiar with computer software CDISC with take extra time to interpret convert reformat by hand

We can ignore QT because IRT will perform

Good opportunity for:

Training
Drug Disease State Modeling
E

Supposed to decrease Stresss

Reasonable Accommodation

Manuals and Library
Assistance – ER and training
New TL – direct all requests for timelines and status to RB, and not unduly stress.

CDISC Training

If don't follow standards Ireview etc. will spit it out.
Pseudo-CDISC
STDM Speak
2 day class
Chuck Cooper from Biostats: I "need significant support" .

Need to include version no.

Shunting of other work Iloperidone & Asenapine who would take the work.

APPENDIX 5

ESTIMATION OF TIME REQUIRED

Comparative Size of NDA

NDA #	Drug	# Pages	Comments
21-999	Paliperidone OROS	~ 50,000	
22-117	Asenapine	74,976	Includes only Phase I Clin Pharm Studies and excludes forrmulations not to be marketed.
		~160,000	Including ER Studies

Prior Benchmarks

NDA	Drug	Duration	
21-999	Paliperidone OROS	3.5 months 4 months	b(4)

Comments

Paliperidone OROS

Familiar with
Assistance Both QT and PM
They started in Feb and earlier not completed until and 8/3
Familiar with

Minimal ER
Assistance

Minimal ER
No Distractions – e.g. holidays, other submissions meetings.

Other

b(4)

Metabolism Extremely Convoluted
Numerous Distractions

Original verbal agreement with timelines I had stipulated that it assumed there would be no meetings or other distractions

Asenapine

Large
Time
Distractions?
New computer format

Not famailiar with computer software CDISC with take extra time to interpret convert reformat by hand

Important and Key Features

We can ignore QT because IRT will perform

Extensive ER
Quasi-CDISC Format
Unfamiliar with CDISC format
Do not have any database programming skills needed to manipulate and extract datasets for analysis

Will Need Significant Training and Assistance

Miscoding of Data – e.g. SAEs

APPENDIX 6

Exposure Response Evaluations

EFFICACY

- Extent
- Time Course
- Disease Progression

Schizophrenia

- Short Term
- Long Term

PANSS
+
-

Other measures?

Bipolar

- Short Term
- Long Term

YMRS
Others?

SAFETY

Neuroendocrine
e.g Prolactin, ADH
QT
CV – e.g. orthostatic hypotension
HR

EPS
Tardive Dyskinesia
Akathesia
Pseudo parkinsonism
Acute Dystonia
All EPS

Agitation / Aggression / Suicidality / Self Injurious Behavior

EEG & Sleep Changes

Comments: vs. Active Control

APPENDIX 7 Scoping Meeting

Date: November 16, 2007
Time: 10:00 AM – 11:00 AM
Location: White Oak Rm 3560
Attendees: Ron Kavanagh
Ray Baweja
Ramana Uppoor
Joga Gobburu
Rob Levin
Gwen Zornberg
Mitch Mathis
Tom Laughren

The following issues were discussed:

- **Effect of Bioavailability on Efficacy**

Clinical Division: Concern over differences in bioavailability and efficacy with inadvertent oral (F ≈ 2%) and buccal as compared to sublingual administration (F ≈ 32%) and the effect on efficacy was raised.

OCP:

This reviewer indicated that if efficacy was seen in clinical trials then the effect of bioavailability on efficacy should not be an issue except in certain patients who are predisposed to swallow more drug.

Other issues noted by OCP included:

Smoking
Solubility
Bipolar
10 min wait

Post meeting note: Gender and Food Effect
And toxicity with swallowing

6.2 *Mid-cycle Review Meeting*

NDA Mid-Cycle Review - OCP Pre-Meeting

NDA:	22-117
Nonproprietary Name:	Asenapine SL Tablets
Submission Date:	August 30, 2007
PDUFA Due Date:	June 30, 2008
Indications:	Schizophrenia Acute manic or mixed episodes associated with bipolar I disorder
Mid-Cycle Review Meeting:	Friday, February 1, 2008
OCP Pre-meeting:	Friday, January 25, 2008
Attendees:	Dr. Ron Kavanagh - Reviewer Dr. Ray Baweja – TL Dr. Mehul Mehta - DD

Safety

Hepatotoxicity

Information from the pop PK analysis resulted in the identification of approximately ½ dz individuals with significantly elevated bilirubins (2 with bili's 2.5 ULN and 5 with bili's 10 x ULN). Most of these cases were associated with the TQT study where higher than anticipated clinical doses are used. Increases in transaminases were also reported in a large fraction of subjects in the early phase I studies with orally administered drug, at even low doses e.g. 1.5 mg. In addition, in the paroxetine DDI interaction study (asenapine 5 mg SL) there was a single individual with increases in transaminases 12x ULN that was followed by an increase in bili 1.7x ULN, i.e. a potential Hy's Law case indicating possible direct hepatotoxicity.

The medical reviewer has been informed of and directed toward all cases identified so far. Formation of an N-oxide metabolite may be the basis for many of these observations. All antipsychotics have a low incidence of cholestatic hepatic injury and the cases of elevated transaminases identified with asenapine so far may be associated with dose and route of administration (high doses result in swallowing of more drug) as well as other factors (e.g. body size, age, gender, and drug interactions). Further review and analysis is needed to determine how best to minimize risk as well as to make an informed risk:benefit analysis, and more information will likely need to be requested from the sponsor in the next few weeks. Thus it is premature to make any recommendations at this time.

Myocardial Infarction

A case of T-wave depression with chest pain temporally associated with asenapine's Tmax suggests the possibility of drug induced MI. (see latest labeling for clozapine).

QT Prolongation

Positive QT study. Maximum reported effect at 10 mg BID [ddQTcF 13.5 (3.9 – 17.1)] with an inverted U dose response. The dose response relationship is likely due to alteration in metabolic profile due to dose dependent first-pass effect.

Diabetes

Onset of diabetes mellitus presenting with ketoacidosis 3 – 4 months S/P asenapine. Although the timing would typically be thought of as arguing against it, delayed onset DM is known to occur, (e.g. pentamidine). However, no acute hypoglycemia was seen as is typically the case with pentamidine.

Suicidality

Preliminary ER analysis indicates that when time of exposure is placebo matched there is no clear difference in either direction from placebo.

Metabolism

Extremely high intrinsic clearance drug

4 Primary metabolic pathways
- N-desmethylation
- N-oxidation
- N-glucuronidation
- 11-oxidation (P450 vs. FMO)

CYP2D6 – Strong inhibitor
- Causes increased exposure to paroxetine (a potent CYP2D6 inhibitor in its own right).
- Average ~20 fold (up to ~45 fold) increase in dextromethorphan in urine (cough/cold products)
- CYP 2D6 PMs – maybe at increased toxicity and as there might be shunting to an N-oxide or other metabolites. Further analysis is needed to work out consequences.
- *In vitro* data indicates that it's a suicide substrate inhibitor, and may be dose and route dependent.

UGT1A4 – polymorphic
- Similar concerns as CYP2D6

CYP1A2
- N-oxidation – May be CYP1A2
- Smoking study done in smokers
- Typically exposures to 1A2 drugs higher in women and elderly, however no studies performed in these populations

Clarifying information on structures of metabolites recovered in mass balance study has been requested and needs to be examined when it is eventually submitted

Biopharmaceutics and Route of Administration

Higher Doses – More Swallowed
More first pass effect
Appears to be important for hepatotoxicity

Food effect

High fat meal even 4 hours post dosing results in drop in AUC

Exposure Response

Schizophrenia
- Review not begun
- Appears to be flat dose response; 5 mg BID may be sufficient

Bipolar
- ER analysis indicates efficacy related to disease severity (as expected)
- May need limitation of efficacy claim based on disease severity. (Cut off based on YMRS).
- This may also effect maintainence claim – e.g. limitation to a subpopulation

Studies performed with 10 mg BID. Since efficacy in psychosis maxed out at 5 mg BID and there's a dose related safety issue, therefore limiting the dose should be considered. This may require an additional efficacy study at 5 mg BID.

PET studies

Information suggests old data may have been misinterpreted and may be better biomarker than currently thought. Needs further analysis.

Pop PK

Preliminary review indicates that cofactors used in analysis may not have been obtained at the appropriate time. More detailed analysis still needs to be performed.

Special Populations

Hepatic Impairment

Several fold increased exposures to total drug.
Increases in free drug exposures even higher.

Female

Not examined.

Elderly

Not examined.

Pediatrics

Preliminary report of PK in adolescents submitted with NDA.

As a pediatric indication was not included as part of this submission only a superficial examination of the study was performed to determine if the population was appropriate in order to provide advice to the sponsor as warranted so as to avoid unnecessary delays in the pediatric development program.

Pediatric population studied found to be non-representative of expected population and results of pediatric PK study is biased toward administration of possibly excessive and toxic doses.

Keep away from children due to potential dose related toxicity, (mg/kg basis), until adequate pediatric PK and efficacy studies performed.

6.3 Bioanalytical Assay Method Validation

Table 194 Assay Validation – Asenapine - GC/MS – Assay Method 3569

Laboratory	Scientific Development Group Dept of Drug Metabolism and Kinetics Organon The Netherlands
Method Validation Report Title	Validation of the Gas Chromatographic Mass Spectrometric Assay for the Determination of Org 5222 in Human Plasma
Method Validation Report #	3569
Date	05 December 1994
Analyst(s)	Maastrigt
Method Description	n-hexane Liquid –Liquid extraction.
Method Number	Included. No reference given.
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222
Internal Standard	
Sample Extraction Volume	1 ml/
Injection Volume	
Sample Storage Method	- 20 °C
Structural Model	Linear Model
Error Model	1/ (conc^2)
Software	
Software Validation	
Range	0.02 - 2.0 ng/ml free base
LLOQ	0.02 ng/ml
Bias Overall	0.05 -7.84 0.4 -12.63 2 -4.42
Bias - Intra assay	0.05 -10.47 0.4 -9.1 2 -5.0
Bias - Inter assay	
Overall Precision	0.05 15.3 0.4 15.0 2 13.9
Intra assay Precision	0.05 17.2 0.4 4.5 2 4.0
Inter (Between) assay Precision	
Matrix Effects	*Not tested.*
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	 Claimed no interference in 6 samples. (Inadequate description.) No interference. No interference with N-oxide. Others not tested. Not Tested.
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	 Stable 2 weeks. Not Stable at 1 month. Contrary to Claims.
Stability - Extracted **RT** **Refrigerated** **On Machine**	

b(4)

Table 195 Assay Validation – Asenapine - GC/MS – Assay Method 3570 MN136

Laboratory	Scientific Development Group Dept of Drug Metabolism and Kinetics Organon The Netherlands
Method Validation Report Title	Validation of the Gas Chromatographic Assay for the Determination of Org 30526 in Human Plasma
Method Validation Report #	3570 MN136
Date	December 1994
Analyst(s)	M. Gross
Method Description	SPE
Method Number	
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 30526 (N-desmethyl)
Internal Standard	b(4)
Sample Extraction Volume	1 ml
Injection Volume	
Sample Storage Method	
Structural Model	Quadratic
Error Model	1/ (conc)^2
Software	
Software Validation	
Range	0.2 - 10.0 ng/ml free base
LLOQ	0.2 ng/ml 1.56% 5.9% CV
Bias Overall	0.75 -2.9 2.0 3.3 7.5 -2.4
Bias - Intra assay	0.75 0.4 2.0 4.2 7.5 0.75
Bias - Inter assay	
Overall Precision	0.75 6.3 2.0 6.3 7.5 9.8
Intra assay Precision	0.75 2.7 2.0 7.2 7.5 10.7
Inter (Between) assay Precision	
Matrix Effects	*Not tested.*
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	Pooled plasma from 6 sources.
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	2- 3 cycles
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Table 196 Assay Validation – Asenapine - GC/MS – Assay Method NL0039449 (NL0012937)

Laboratory	Not Mentioned.
Method Validation Report Title	A Revalidation of the GC-MS assay for the determination of Org 5222 in human plasma
Method Validation Report #	NL0039449
Date	June 2002
Analyst(s)	
Method Description	Increase in upper limit of assay range.
Method Number	See validation report NL0039449
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222
Internal Standard	b(4)
Sample Extraction Volume	
Injection Volume	
Sample Storage Method	
Structural Model	quadratic
Error Model	1/ (conc^2)
Software	
Software Validation	
Range	0.02 – 20.0
LLOQ	0.02 -0.9% CV 6.4%
Bias Overall	0.06 0.1% 0.8 -2.2% 1.6 -5.8% 16 0.5%
Bias - Intra assay	
Bias - Inter assay	
Overall Precision	0.06 13.7% 0.8 11.1% 1.6 7.3% 16 6.8%
Intra assay Precision	
Inter (Between) assay Precision	
Matrix Effects	
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Table 197 Assay Validation – Asenapine - GC/MS – Assay Method NL00542055

Laboratory	Organon Walthrop Germany
Method Validation Report Title	Validation of the LC-MS-MS assay for the determination of Asenapine (Org 5222), Org 30526 and Org 31437 in human plasma
Method Validation Report #	NL00542055
Date	May 2004
Analyst(s)	Dingler E
Method Description	
Method Number	See validation report NL0054255
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222 (Asenapine) Org 30526 (N-Desmethyl-asenapine) Org 31437 (Asenapine N-oxide)
Internal Standard	^{13}C-Org 5222 b(4)
Sample Extraction Volume	SPE
Injection Volume	
Sample Storage Method	
Structural Model	quadratic
Error Model	1/ (conc^2)
Software	
Software Validation	
Range	0.1 – 20.0
LLOQ	0.02 -0.9% CV 6.4%
Bias Overall	0.06 0.1% 0.8 -2.2% 1.6 -5.8% 16 0.5%
Bias - Intra assay	
Bias - Inter assay	
Overall Precision	0.06 13.7% 0.8 11.1% 1.6 7.3% 16 6.8%
Intra assay Precision	
Inter (Between) assay Precision	
Matrix Effects	*Ion suppression of greater t*
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Claims it's Validated but also states.

"The validation was performed in ten anaytical runs of which five were accepted.
Run 1 – 7 were used before the method was slightly adapted which is described in Amendment I (R&D RR no. NL0053679) to protocol R&D RR no. NL0051303. Run 11, 13, 15 and 16 did not meet the acceptance criteria which can be explained with crosstalk between the samples for run 15. In run 13 the technician spitted a sample over the others. Run 12 was used to determine the stability in processed samples.
All QC samples with a deviation >30% from the nominal value were omitted from statistics.
The results of the validation experiments are tabulated in Table 1 up to Table 10."

Need to come back to.

Table 198 Assay Validation – Asenapine - GC/MS – Assay Method NL0058575

Laboratory	Organon Walthrop Germany
Method Validation Report Title	Re-validation of the LC-MS-MS assay for the determination of Asenapine (Org 5222), Org 30526 and Org 31437 in human plasma – Amendment I
Method Validation Report #	NL0058575
Date	January 2005
Analyst(s)	Dingler E
Method Description	Lowering limit of detection.
Method Number	See validation report NL0054255
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222 (Asenapine) Org 30526 (N-Desmethyl-asenapine) Org 31437 (Asenapine N-oxide)
Internal Standard	^{13}C-Org 5222 b(4)
Sample Extraction Volume	SPE
Injection Volume	
Sample Storage Method	
Structural Model	
Error Model	
Software	
Software Validation	
Range	
LLOQ	
Bias Overall	
Bias - Intra assay	
Bias - Inter assay	
Overall Precision	
Intra assay Precision	
Inter (Between) assay Precision	
Matrix Effects	
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Problem 7 validation runs of which 5 were accepted.

Table 199 Assay Validation – Asenapine - GC/MS – Assay Method NL00542055 (NL0061697)

Laboratory	Organon Walthrop Germany
Method Validation Report Title	Validation of the LC-MS-MS assay for the determination of Asenapine (Org 5222), Org 30526 and Org 31437 in human plasma – Amendment I
Method Validation Report #	NL00542055
Date	April 2005
Analyst(s)	Dingler E
Method Description	Addition of Long term stability results Addition of stock solution stability.
Method Number	See validation report NL0054255
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222 (Asenapine) Org 30526 (N-Desmethyl-asenapine) Org 31437 (Asenapine N-oxide)
Internal Standard	^{13}C-Org 5222
Sample Extraction Volume	SPE b(4)
Injection Volume	
Sample Storage Method	
Structural Model	
Error Model	
Software	
Software Validation	
Range	
LLOQ	
Bias Overall	
Bias - Intra assay	
Bias - Inter assay	
Overall Precision	
Intra assay Precision	
Inter (Between) assay Precision	
Matrix Effects	
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Due to confusion regarding the sponsor's validation reports this reviewer stopped reviewing with # TM130 and due to time constraints was unable to finish review of the Assays Validations and the performance of the analytic methods used.

6.4 *Identification of Elevated Bilirubins and Medical Reviewer Notification*

6.4.1 E-mail Notification and Request to Obtain Lab Records from Sponsor

---

From: Kavanagh, Ronald E
Sent: Friday, November 30, 2007 1:27 PM
To: Levin, Robert
Cc: Zornberg, Gwen; Baweja, Raman K; Mathis, Mitchell
Subject: Asenapine - Potential Safety Signal

Bob,

Sorry to make more work for you but I was going through the PET studies yesterday and saw a mention of a dose response for increases in LFTs in their early phase I studies. Also I was looking at the POP PK today and saw the range on Bili's went up to 11 mg/dL. I did a check of the data and found 20 subjects in the studies in the pop PK analysis with Bili's > 1.4 and 6 subjects with bili's of ≥10. This is in the TQT study and they didn't submit any labs with the study report so I've asked Keith to get them for the TQT study. The doses of asenapine in this study was 15 - 20 mg bid but I don't know if these subjects were on asenapine or quetiapine or PBO yet.

There's also a subject with Afib and another with Vtach in that study, and there was a mention of Afib in a healthy vol in another study. (I need to verify which study).

Since the mention of a dose response with LFTs is with the early studies when they were still using oral tabs, swallowing the tabs might be more of a safety issue rather than an efficacy issue due to the high first pass effect.

I'm attaching the information of the subjects from the POPPK analysis.

Have fun.

Ron

<< File: Study ID in Pop PK Analysis.doc >>

<< File: Study ID in Pop PK Analysis.doc >>

Study ID in Pop PK Analysis	Study ID	Study Description	Dose	Subject	Bilirubin
42, 46	ORG25542 ORG25546	RMD MTD	3 – 15 mg BID	1	1.46
42, 46	ORG25542 ORG25546			1	2.28
46	ORG25546	Caucasians & Japanese	10 mg BID	3	1.52
46	ORG25546			10	1.75
46	ORG25546			14	1.7
46	ORG25546			19	2.34
46	ORG25546			25	1.52
46	ORG25546			26	1.64
42	ORG25546			28	1.7
46	ORG25546			31	1.52
42, 46	ORG25542 ORG25546			37	1.46
42,46	ORG25542 ORG25546			37	1.64
46	ORG25546			41	1.52
46	ORG25546			144	1.46
16	A751016	BA particle size	5 mg SL SD	10011009	1.6
15	A751015	BE SL	5 mg SL SD	10011022	1.7
16	A751016	BA particle size	5 mg SL SD	10011058	1.7
15	A751015	BE SL	5 mg SL SD	10011069	1.7
1	A751001	TQT Study	15 - 20 mg BID MD	10050003	10
1				10050006	10
1				10050007	10
1				10050009	11
1				10050010	10
1				10050013	10

TQT study subj with Afib and one with Vtach

Also another study with Afib 25520?

Figure 223 Sponsor's Report of Dose Related Hepatotoxicity in Study SDGRR 2086 (1987) noted in PET Study Report

SDGRR 2086 (1987)

In a multiple dose safety study in healthy male volunteers, four dose levels have been used: 1,5 mg b.i.d.; 5 mg b.i.d.; 10 mg b.i.d. and 15 mg b.i.d. The scheduled duration of each dosing was 14 days. Orally administered Org 5222 15 mg b.i.d. induced time dependent abnormalities in liver function tests, predominantly a rise in plasma ALAT and ASAT levels, in 3 out of 6 subjects starting after 6 days dosing. The abnormalities were reversible and declined, after treatment was stopped on day 8 or 9, to normal levels by day 20 to 27. There are signs of some liver function disturbance in the 10 mg b.i.d. treatment with one out of 6 subjects showing raised plasma ALAT and ASAT levels. One out of 4 subjects in the 5 mg b.i.d. group showed a small increase in the plasma ALAT level. No ALAT or ASAT level changes were observed in the 1,5 mg b.i.d. group. No other effects were found

6.5 Requests to Sponsor

A telephone conference was held with the sponsor on December 5, 2007, regarding clarification and timing of a request for datafiles. In addition the sponsor was requested to provide the chemical structures of all metabolites, along with any codes, (e.g. HPLC-2 U27, F18), their chemical names, and to include the percentage recoveries. The sponsor asked for the reason and this reviewer explained that it was simply to make certain that this reviewer had made assignments correctly and he could not be certain of their accuracy without confirmation. The sponsor agreed to this request, however in their response which was included in the cover letter for Amendement 011 BB submitted December 28, 2007, the sponsor was nonreponsive and simply referred to the reviewer to the same information already provided, (see Figure 224,).

Figure 224 Sponsor's Response to OCP Data Request from Cover Letter of Amendment 011 BB

Please provide chemical structures of metabolites from human in vivo studies including percent recoveries.
Reference is made to the metabolite profiling analysis of the human ADME trial (25532). This analysis is reported in Report INT00003211 titled *Profiling of a metabolism study with [^{14}C]-labelled asenapine in healthy volunteers*. The report was submitted in the NDA as part of Module 4, Section 4.2.2.5 and provides a complete overview of all isolated and identified metabolites of asenapine following sublingual administration, including chemical structures. Recoveries of metabolites were quantitatively assessed in urine and feces and are presented per individual in Table 9-6 and Table 9-7 of this report. A summary of the structures of the major metabolites and the proposed biotransformation scheme of asenapine can be found in Module 2.7.2, Figure 6.

6.6 April 11, 2008 Consult Request from Medical Team Leader

From: Zornberg, Gwen Sent: Fri 4/11/2008 11:03 AM
To: Kavanagh, Ronald E; Baweja, Raman K
Cc: Laughren, Thomas P; Mathis, Mitchell; Kiedrow, Keith; Zornberg, Gwen
Subject: NDA 22117 Asenapine Study A7501022

Dear Ron, Dear Ray,

I am certain that you are aware of this pediatric study for your NDA review, however, to be thorough though for your easy reference, I'm just following up from the wrap-up meeting to give you the study number of the blinded 3- week, pediatric (ages 12-17 years) tolerability, safety, PK study, which was reduced to 10 days after notification form Steve on 7 September 2005 that I had noted in our meeting for easy reference.

Thanks,

Gwen

6.7 Consults

6.7.1 Pharmacometrics Consult

In early November 2007 prior to the scoping meeting a pre-meeting was held with Drs. Kavanagh, Baweja, Uppoor, and Gobburu[14]. Dr. Kavanagh requested assistance from pharmacometrics due to the size and complexity of the NDA and in particular the extensive amount of pharmacometrics submitted including modeling and simulation for drug disease state modeling. Dr. Gobburu declined stating that pharmacometrics did not have the resources however Dr. Uppoor suggested to Dr. Gobburu that this could be revisited at a later date.

6.7.2 Pharmacogenomics Consult

Since none of the samples collected for pharmacogenetics were analyzed and no pharmacogenomic information was submitted a formal consult was not requested. This reviewer however did provide an overview of the possible pharmacogenetic issues to the pharmacogenomic reviewer early in the review cycle and recent publications regarding the pharmacogenomics of agranulocytosis and aplastic anemia in Ashkenazi Jews and Thai with clozapine were presented verbally during the briefing. In addition Dr. Urs Meyers graciously provided comments regarding the high incidendence of agranulocytosis with clozapine in Finland on May 12, 2008 after the OCP briefing.

6.7.3 Required Thorough QT Study Consult

The review of the thorough QT study that was performed by the Interdisciplinary QT team may be found in DFS folder N 022117 N000 30-Aug-2007 in file U:\PDF Reviews\QTIRT. NDA 22117(29Feb08).pdf

[14] Personal files with a formal justification for assistance are dated November 13, 2007 and were begun after the meeting.

6.8 OCP Briefing Slides

N.B. this version of slides contains corrections to slides 10, 13 and 62 requested by OCP management at the briefing. Otherwise slides are unchanged. These corrections include correction of labeling on effect on dextromethorphan and correction of dose correction in total radioactivity calculation (34.3 x from 33 x).

Slide 1

N22-117
Asenapine Sublingual Tablets

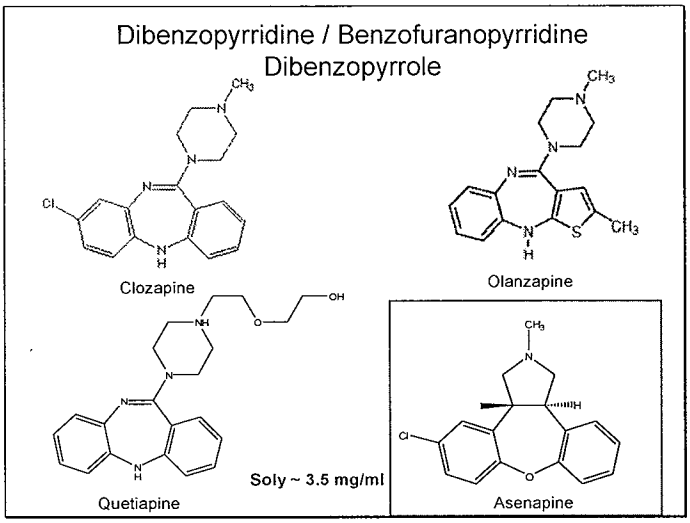
OCP Briefing
Ron Kavanagh, B.S.Pharm,. Pharm.D., Ph.D.
May 12, 2008

Slide 2

Background

- Antipsychotic
  - Very potent receptor antagonist
    - All Dopamine, Serotonin, α-Adrenergic, Histamine tested
- Proposed Indications
  - *"for the treatment of schizophrenia" (Acute 6 weeks)*
  - *For the treatment of acute manic or mixed episodes associated with Bipolar I disorder with or without psychotic features (acute 3 weeks)*
- Proposed Regimens
  - Schizophrenia: 5 mg – 10 mg BID SL
  - Bipolar I: 10 mg BID SL
    - No eating or drinking for 10 minutes after administration

Slide 3



Slide 4

	Olanzapine	Clozapine	Quetiapine
Elderly	BB	BB	BB
Suicidality			BB
Agranulocytosis / Neutropenia		BB	
Allergic rxn			
Cardiac and Circulatory Arrest		BB	
First Degree Heart Block			With OD
Tachycardia			
Heart Failure			
Myocarditis		BB	
Cardiac Arrest			
Extrasystoles			
Afib			
Brady			
CVA			
Liver Injury (LFTs)			
Jaundice			
Seizures		BB	
SJS			X
SIADH			
Wt Gain			
Diabetes			
Dyslipidemias			
Rhabdomyolysis			
Neuroleptic Malignant Syndrome			

BB = Black Box warning.

Except for SJS virtually all AEs are included in labeling for all 3 drugs.

Appears that these are class effects based on structure however they varying in frequency between drugs.

Slide 5

Receptor Class	Receptor Subtype IC50 for binding (nMol/L)							
Serotoninergic	5-HT1A	5-HT1B	5-HT2A	5-HT2B	5-HT2C	5-HT5A	5-HT6	5-HT7
IC50 nMol/L	2.5	4	0.1	0.2	0.03	1.4	0.3	0.1
Dopaminergic	D1	D2L	D2S	D3	D4	D4.7		
IC50 nMol/L	1.4	1.3	1.4	0.4	1.1			
Alpha Adrenergic	α1A	α2A	α2B	α2C				
IC50 nMol/L	1.2	1.1	0.3	1.2				
Muscarinic	M1	M2	M3	M4	M5			
IC50 nMol/L	8,128	31,623	21,380	9,120	2.5			
Histaminic	H1	H2						
IC50 nMol/L	1	6.17						
Reuptake Transporters	SERT	NET	DAT					
IC50 nMol/L	4	0.1	0.2					
Beta Adrenergic	?							
IC50 nMol/L								
Nicotinic	?							
IC50 nMol/L								

	Approx Conc / IC50
Red	≥10
Pink	1 to 10
Maroon	0.5 - 1

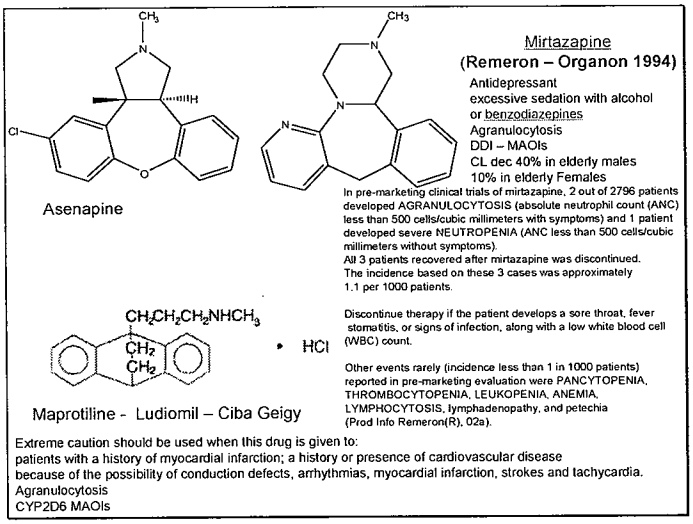
Only Binding
Virtually NO Information on agonism / antagonism

5HT2B – Agonists associated with Phen-fen cardiac valvulopathy

5HT2A and 5HT5A associate with appetitie

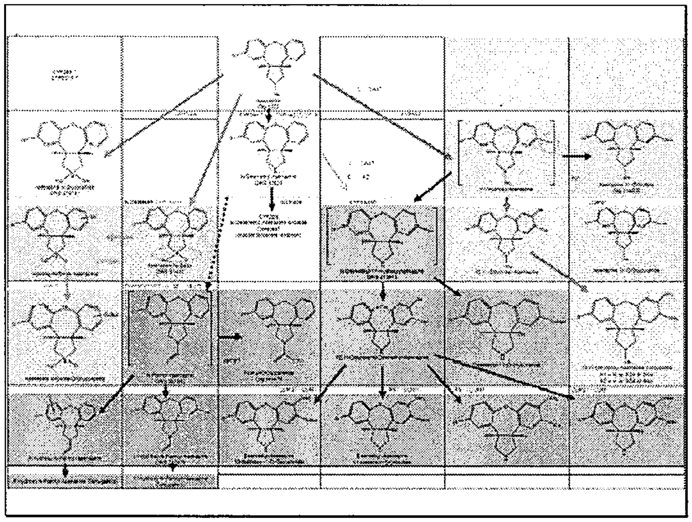
D4 associated with akathesia

Slide 6



Ludiomil because of case of possible DDI with CHF

Slide 7



Olanapine formyl metabolite via hydroxyl intermediate

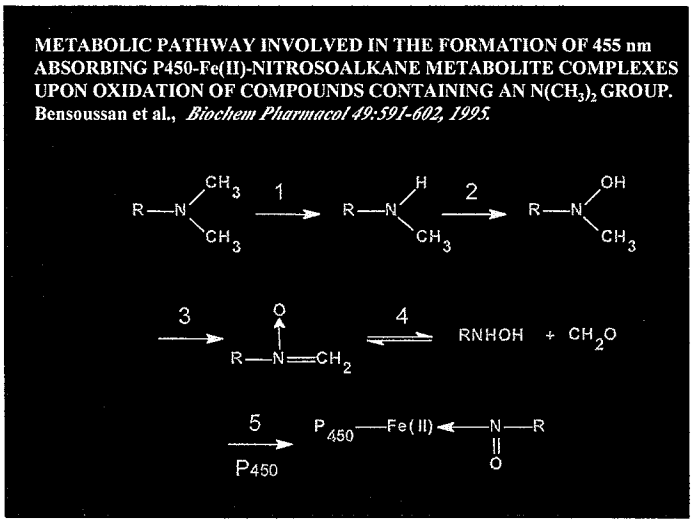
Slide 8

Table 1 Summary of Results of In Vitro Cytochrome P450 Inhibition Studies with Asenapine and Selected Metabolites

Study	Date	Test System	Enzyme	Inhibitor	Ki	Claimed Type of Inhibition
[illegible]	Dec [illegible]	Supersomes	1A2	Asenapine	[illegible] µMol	Competitive
			2D6		[illegible] µMol	Competitive
[illegible]	[illegible]	Supersomes	[illegible]	Asenapine	25.16	Uncompetitive
			3A4 (1) 3A4 (2)		[illegible]	Mixed-competitive ?
[illegible]	Aug [illegible]	Supersomes	2D6	Asenapine	[illegible] µMol	Competitive
				[illegible] N-Desmethyl	[illegible] µMol	Noncompetitive
				31437 N-Oxide	[illegible] µMol	Competitive
[illegible]	Oct [illegible]	Supersomes	1A2	Asenapine (N.B. CYP2D6 not studied)	[illegible] µMol	Competitive
			2A6		[illegible] µMol	Noncompetitive
			2C9		[illegible] µMol	Uncompetitive
			2C19		[illegible] µMol	Competitive
			3A4 (1)		[illegible] µMol	Noncompetitive
			1A2	[illegible] N-Desmethyl Asenapine (N.B. CYP2D6 not studied)	1.4 µMol	Noncompetitive
			2A6		[illegible] µMol	Competitive
			2C8		[illegible] µMol	Noncompetitive
			2C9		[illegible] µMol	Noncompetitive
			2C19		[illegible] µMol	Competitive
			3A4 (1)		[illegible] µMol	Competitive
			1A2	31437 N-oxide (N.B. CYP2D6 not studied)	No inhibition	
			2A6			
			2C8			
			2C9			
			2C19			
			3A4 (1)			
			3A4 (2)			
[illegible]	Oct [illegible]	Supersomes	2D6	[illegible] N-Oxide	[illegible] µMol	Competitive
			[illegible]	[illegible] N-Oxide	[illegible] µMol	Competitive
[illegible]	Dec [illegible]	Pooled Human Liver Microsomes (HLM)	CYP1A2	Asenapine	[illegible] µMol*	
			CYP2B6		> 30 µMol*	
			CYP2C8		> 30 µMol*	
			CYP2C9		> 30 µMol*	
			CYP2C19		> 30 µMol*	
			CYP2D6		[illegible] µMol*	
			CYP3A4		> 30 µMol*	
			[illegible]		> 30 µMol*	

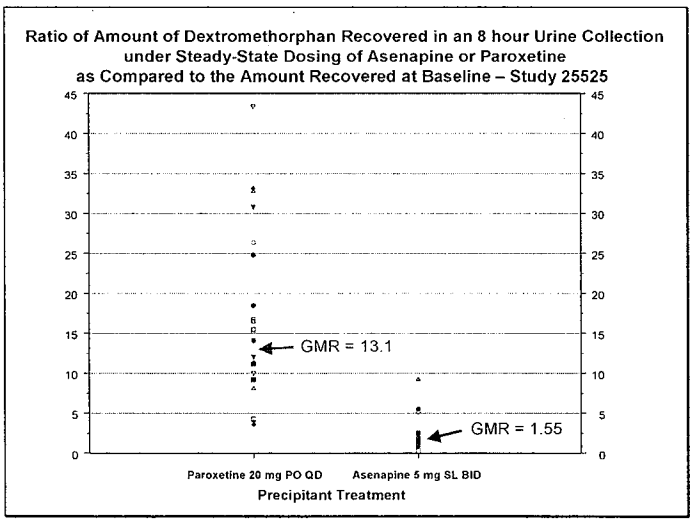
* [illegible]

Slide 9

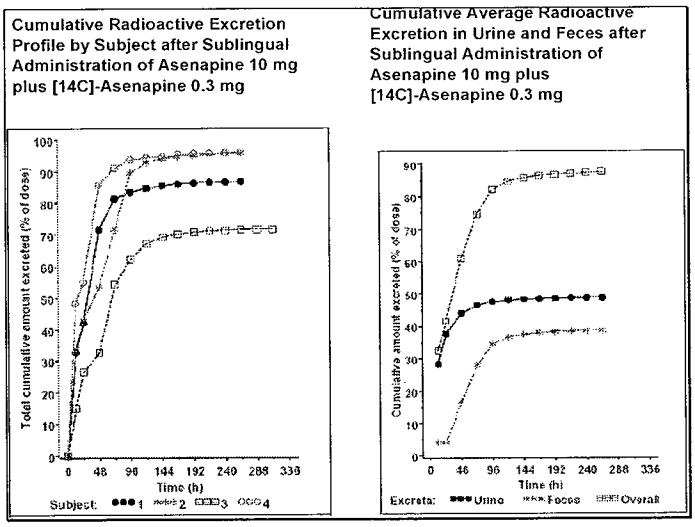


From FDA presentation 1999

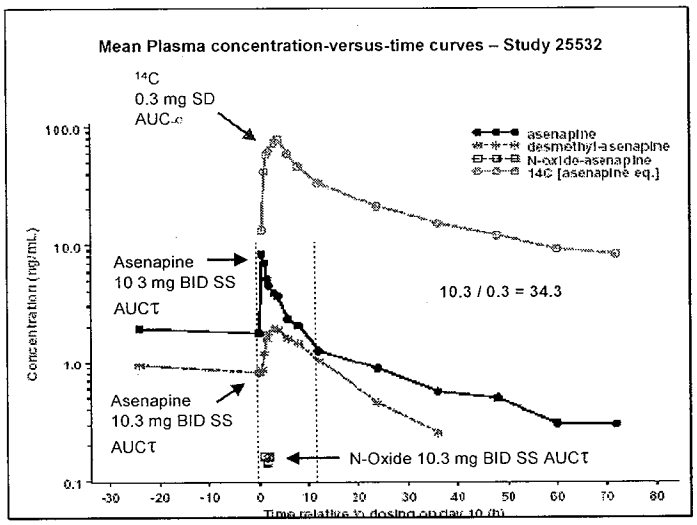
Slide 10



Slide 11



Slide 12



Slide 13

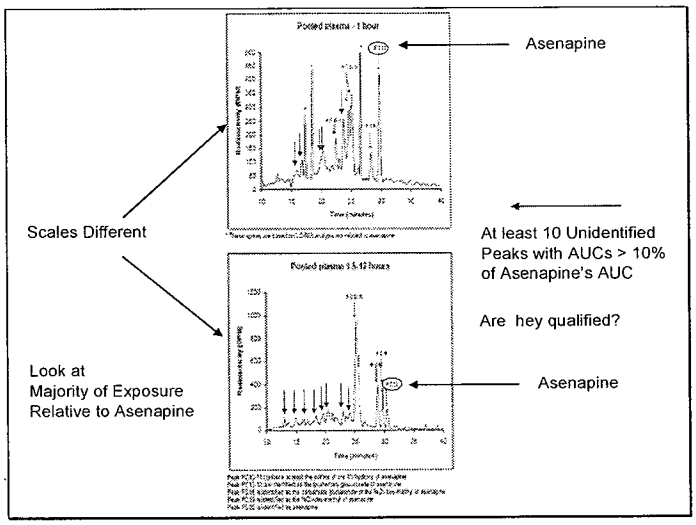
Table 1 Plasma Exposures to Asenapine and Selected Metabolites Relative to Total ^{14}C Radioactivity after Asenapine 10 mg and 0.3 mg ^{14}C-Asenapine at Steady-State - Study 25532

Dose		10.3 mg			0.3 mg	10.3 mg	
Metric	Subject	Asenapine	Desmethyl - Asenapine	Asenapine N-oxide	^{14}C [asenapine equivalents]	Dose Normalized ^{14}C [asenapine equivalents]	% extrap
AUC_{τ}[a] (ng/mL x hr^{-1})	1	33.3	12.8	0.2	1523.2	52297	11.5
	2	27.8	13.6	0.9	1282.6	44036	25.6
	3	50.6	27.7	0.7	1952.9	67046	15.5
	4	35.7	17.7	0.6	1470.0	50476	9.5
Fraction of ^{14}C (%)	1	2.2	0.8	0.01	–	–	–
	2	2.2	1.1	0.07	–	–	–
	3	2.6	1.4	0.04	–	–	–
	4	2.4	1.2	0.04	–	–	–
	Mean[b]	2.3	1.1	0.04	–	–	–
Fraction of Dose Normalized ^{14}C (%)	1	0.06	0.02	0.000	–	–	–
	2	0.05	0.03	0.002	–	–	–
	3	0.08	0.04	0.001	–	–	–
	4	0.07	0.04	0.001	–	–	–
	Mean[b]	0.067	0.032	0.001	–	–	–

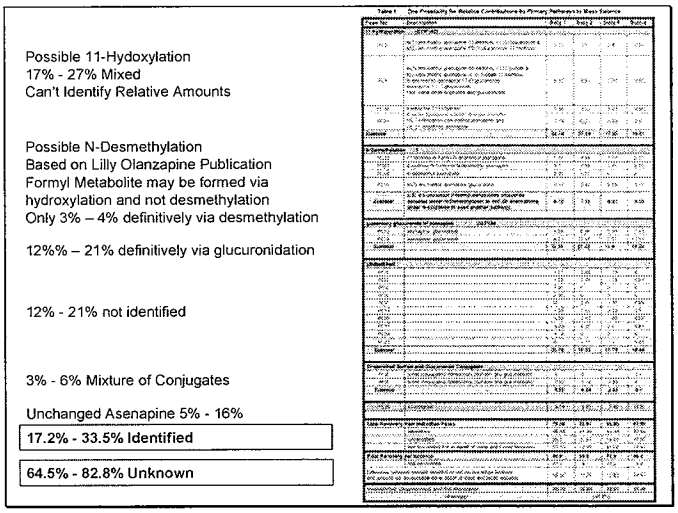
Total 0.1% 99.9% of Circulating Radioactivity Unidentified

Even if only look at unnormalized data 96.6% unidentified

Slide 14



Slide 15



Slide 16

Dose and Time Dependent Drug Induced Liver Injury*

***Oral* Multiple Rising Dose PK S/T Study – Feb 1988**

Group No.	Subject No & Initials	Dose	Abnormal Tests	Day of Onset of rise	Time of Peak of rise	Day of 1st subsequent normal value	Severity	
II	14	3 mg bd	ALT	10	10	14	++	1/ 4
III	18	10 mg bd	ALT	10	11	21	++	1/ 4
			AST	10	11	13	+	
IIIA	101.	20 mg bd	T.bili	2 & 10	2 & 10	5 & 14	+ & +	
	102.	Placebo	Alk Phos	Raised at screening and throughout			+	1-2 / 6
			ALT	14	14	21	+	
	104.	20 mg bd	ALT	10	15	-	++	
			AST	0	2 & 14	5 & 21	+	
IV	28.	30 mg bd	ALT	9	9	-	+++	
			AST	9	9	- 3.75x ULN	+++	
	29.	30 mg bd	ALT	0	12	15	+++	3 / 6
			AST	10	12	14 2x ULN	+	
			GGT	0	6	15	+	
	30.	30 mg bd	ALT	6	11	-	+++	
			AST	6	9	17 8.33x ULN	+++	

b(6)

9 of 20 given asenapine had elevated LFTs

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

PK included in study design but not reported.

* D LI – differentiated from hepatotoxicity by increase in bilirubin indicating end-stage injury

Slide 17

Other Signals - DILI

- BE study 41026 – [redacted] (b) (4) Tab
  - Inc LFTs star ing day 2 (synopsis)
  - Study Report Available only on request
- Paroxetine Interaction Study
  - (Asenapine 5 mg BID)
  - 4 subjects Inc. LFTs
    - 2 after single dose of paroxetine added
    - 1 after 3 days of asenapine
    - 1 inc AST after 6 days Rx; ALT Max 9.5 x ULN; declined to WNL 8 days after d/c
- BE Study – Different [redacted] (b) (4)
- TQT Study
  - Pop PK study reported 6 subjects wi h Total Bilirubin ≥ 10 mg/dL
  - CSR only reports summary statistics for labs prior to & after Rx (how long?)
  - Labs during Rx note reported

Slide 18

Asystole with 0.7 mg IV over 30 minutes

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

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

Dec 1991

Secondly, this almost certainly has to be classed as a drug induced effect with a serious adverse effect on the conducting system of the heart.

If you require any further report or details from me please let me know.

Kind regards,

Yours sincerely,

[redacted]

CONSULTANT CARDIOLOGIST

b(4)

$Fabs^{SL} \approx 0.35$
0.7 mg IV ≈ 2.1 mg SL

Slide 19

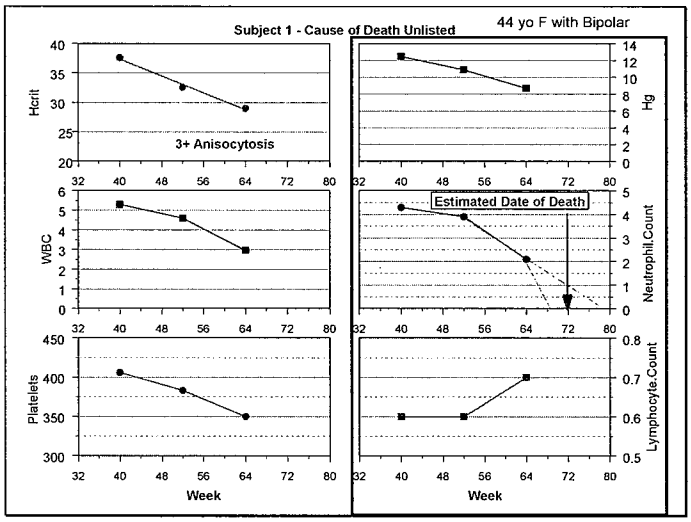
Other Cardiac Safety Signals

- Study 25509
  - sponsor indicates that the asenapine is unsafe at drug exposures obtained with clinical dosages and due to cardiotoxicity and direct hepatotoxicity and should not be dosed chronically at greater than 4 mg daily
- PO MRD Study
  - 1 subj with asystole for 8.7 seconds with a junctional escape rhythm with single 30 mg dose (~ 3 – 10 mg SL)
- 5 mg SD Pivotal BE Study – (b) (4)
  - *20 of 35 healthy subjects had observed cardiac effects on telemetry*
  - 10 subjects experienced bradycardia, 8 tachycardia, 7 sinus pause, 3 junctional escape rhythms, and 1 bradycardia with junctional rhythm
- 5 mg SD Pivotal BE Study –
  - *"One subject (Subject 20) had a neurally mediated reflex bradyca without sciousness) in supine position after treatment with the (b) t (b) (4) n tablet."*
- Paroxetine nteraction Study (5 mg BID)
  - Afib 1 5 hr post dose requiring sotalol for cardioversion 24 hours later
  - Subject 09 dropped out due to ECG changes (negative T in II, III and AVF, main reason), "non-cardiac" chest pain, pain between scapulae and shortness of breath at Day 7. (Day 2 of asenapine)
- MI in Safety Database
- Study 246021
  - Death due to cardiac failure 2 months after maprotiline was added.

b(4)

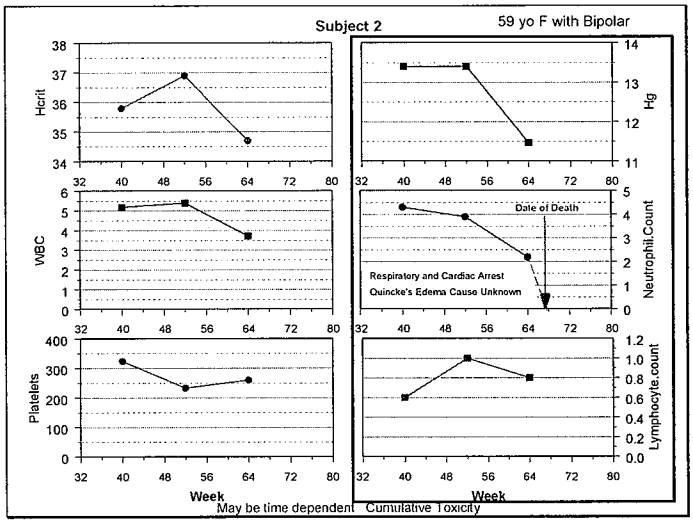
This does not include the cases of cardiac effects in the safety data base from the phase III trials and vica versa (except for MI as noted).

Slide 20



Based on initial lab sheets thought that might be aplastic anemia, however after plotting it appears platelets might not have been dropping fast enough, however microhemorrhages were noted in the brain on autopsy. Consequently this is definitely neutropenia with RBC anemia, with presumptive death due to agranulocytosis and possible aplastic anemia.

Slide 21



Slide 22

Suicidality in Acute Psychosis in Schizophrentics

Week	1	2	3	4	5	6	Total
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)
Suicidal ideation	1 (0.2)	--	1 (0.3)	2 (0.7)	--	--	4 (0.8)
Suicide attempt	--	--	--	--	--	2 (0.9)	2 (0.4)
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)
Suicidal ideation	--	--	--	--	1 (0.6)	--	1 (0.36)
Suicide attempt	--	--	--	--	1 (0.6)	1 (0.6)	2 (1.2)
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)
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)
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)
Suicidal ideation	--	--	--	1 (0.8)	--	--	1 (0.8)
Total	--	--	--	2 (1.6)	1 (0.9)	--	3 (1.5)

Slide 23

Prevalence of AEs Indicative of Suicidality over Time by Treatment in Acute Bipolar I Trials During Inpatient Period

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

Slide 24

Safety Summary

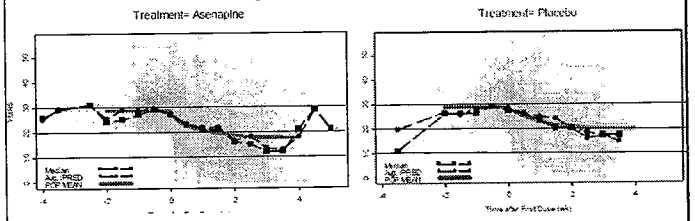
- Death due to Presumptive Agranulocytosis
  - 1 / 313 to 1 / 156 with 1 - 1.2 years of Rx (0.32% - 0.65%)
- Death due to Suicide in Acute Bipolar
  - 1 / 317 (0.32%)
- Deaths due to Cardiotoxicity
  - MI, CHF, Arrhythmias (?)
- Potential Total Incidence in Similar Population
  - > 1 / 117 – 1 / 158 – 1 / (~ 1%)
- Deaths in Actual Population of Use
  - (Greater exposures, DDIs, Comorbid Disorders, less intensive monitoring)
  - Expected to be higher (< 1%)

The higher range for death due to agranulocytosis is based on assuming that at least 2 other cases of death due to respiratory arrest are due to infection secondary to agranulocytosis.

Slide 25

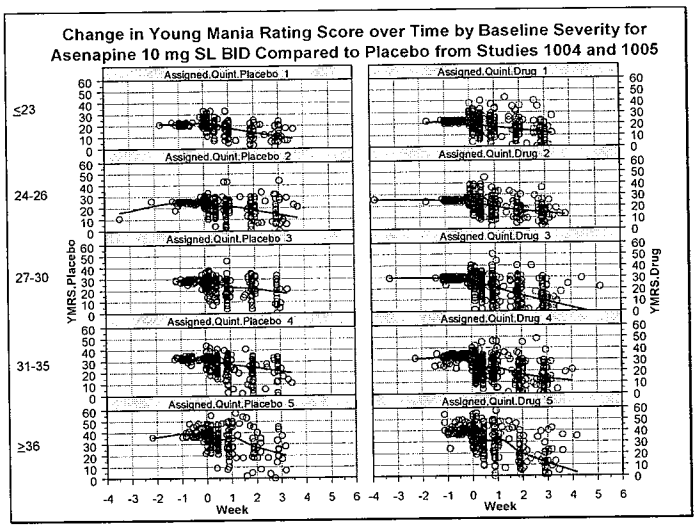
Sponsor's Exposure Response Analysis

Bipolar Disorder



YMRS	0 – 60
Moderate – Severe	≥20
Mild (Hypomania)	~12 – 20
BSD	4 – ~10

Slide 26



Only works with YMRS > 27

Similar results with active control ziprasidone

Information from other reviews and submissions (olanzapine, paliperidone) indicate similar findings

Slide 27

Racial and Ethnic Characteristics by Treatment and Disease Severity - Study A7501004

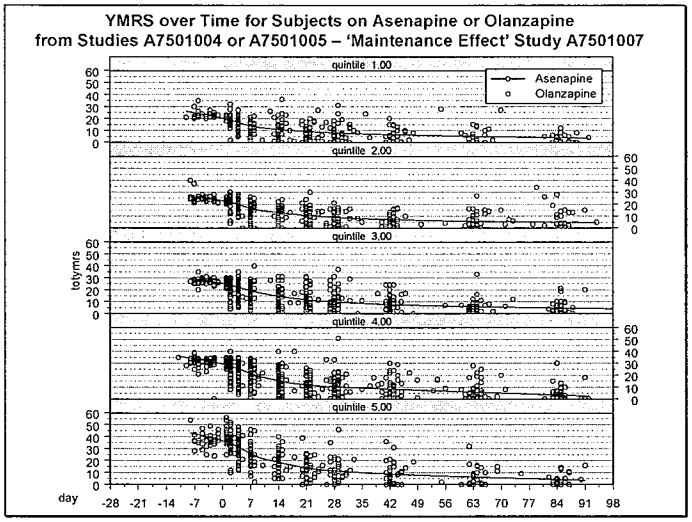
Treatment	Group Quintile	% of Subjects					
		Asian	Black	Caucasian	Ethiopian	Hispanic	Puerto Rican
Placebo	1	12.5	3.1	78.1	0.0	6.3	0.0
	2	18.8	18.8	50.0	0.0	12.5	0.0
	3	15.8	26.3	57.9	0.0	0.0	0.0
	4	38.5	7.7	46.2	0.0	7.7	0.0
	5	43.8	31.3	25.0	0.0	0.0	0.0
	Total	22.9	15.6	56.3	0.0	5.2	0.0
Asenapine	1	15.2	10.9	73.9	0.0	0.0	0.0
	2	15.6	15.6	65.6	0.0	3.1	0.0
	3	15.9	25.0	56.8	0.0	2.3	0.0
	4	28.6	28.6	39.3	0.0	3.6	0.0
	5	38.2	26.5	35.3	0.0	0.0	0.0
	Total	21.7	20.7	56.0	0.0	1.6	0.0
Olanzapine	1	15.9	18.2	59.1	0.0	6.8	0.0
	2	6.1	3.0	81.8	0.0	9.1	0.0
	3	18.0	24.0	56.0	0.0	0.0	2.0
	4	34.2	21.1	42.1	0.0	2.6	0.0
	5	35.1	24.3	35.1	2.7	2.7	0.0
	Total	21.8	18.8	54.5	0.5	4.0	0.5

Slide 28

Ethnic Characteristics by Treatment and Disease Severity Study A7501005

Treatment	Group Quintile	% of Subjects						
		Asian & Oriental	Asian Indian	Black	Caucasian	Hispanic	Latino	NA & American Indian
Placebo	1	0.0	0.0	15.0	70.0	15.0	0.0	0.0
	2	0.0	0.0	33.3	55.6	0.0	5.6	5.6
	3	5.0	0.0	20.0	75.0	0.0	0.0	0.0
	4	25.0	0.0	20.0	55.0	0.0	0.0	0.0
	5	50.0	3.8	7.7	38.5	0.0	0.0	0.0
	Total	18.3	1.0	18.3	57.7	2.9	1.0	1.0
Asenapine	1	8.5	0.0	19.1	68.1	4.3	0.0	0.0
	2	11.4	0.0	17.1	71.4	0.0	0.0	0.0
	3	11.6	0.0	16.3	65.1	2.3	2.3	2.3
	4	17.5	0.0	12.5	70.0	0.0	0.0	0.0
	5	51.9	3.7	14.8	29.6	0.0	0.0	0.0
	Total	17.7	0.5	16.1	63.0	1.6	0.5	0.5
Olanzapine	1	11.8	0.0	15.7	64.7	5.9	2.0	0.0
	2	15.4	2.6	20.5	53.8	5.1	0.0	2.6
	3	12.5	0.0	17.5	67.5	2.5	0.0	0.0
	4	28.0	0.0	16.0	56.0	0.0	0.0	0.0
	5	30.3	3.0	12.1	51.5	3.0	0.0	0.0
	Total	18.1	1.1	16.5	59.6	3.7	0.5	0.5

Slide 29



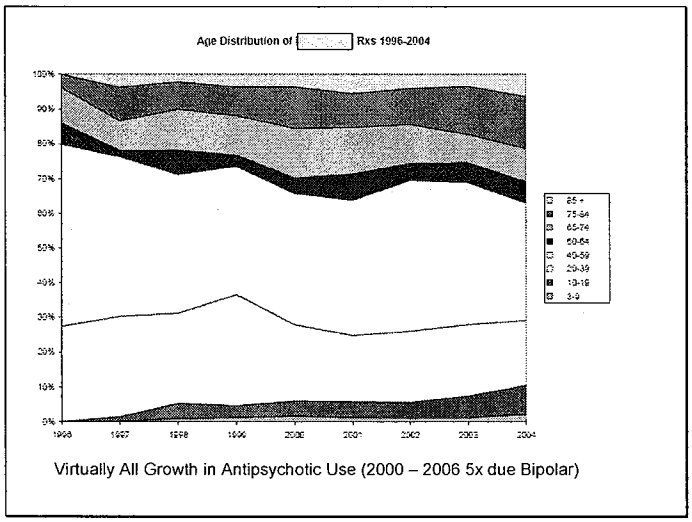
Not placebo controlled.

Noninferiority inappropriate.

Even Olanzapine with Placebo Control only had median time to release a few days longer as compare to placebo.

Question. If continue Rx and inpatient stay for 4 – 6 weeks would there be any diff with maint Rx

Slide 30



Slide 31

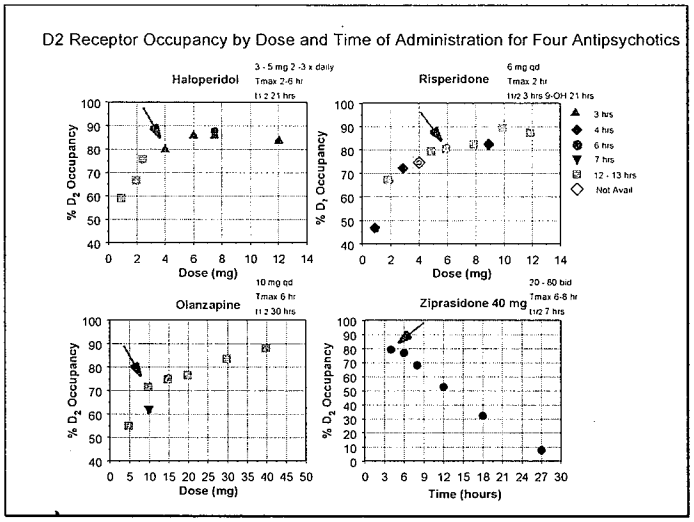
- BSD
  - NIMH May 2007
  - 2.5%
  - Rec. Rx with antipsychotics
- Pediatric Bipolar
  - Full DSM IV criteria
  - Bipolar vs. ADHD
  - Easy to Misdiagnose
- APA – Washington DC; May 2007
  - 43% of Patients Coming to NYU Hospital with Dx Bipolar did not have Bipolar per DSM-IV
  - Overdiagnosed
- Concerns
  - Misuse (inappropriate use)
  - High Risk to Benefit even with appropriate use

Slide 32

Exposure Response

Schizophrenia

Slide 33

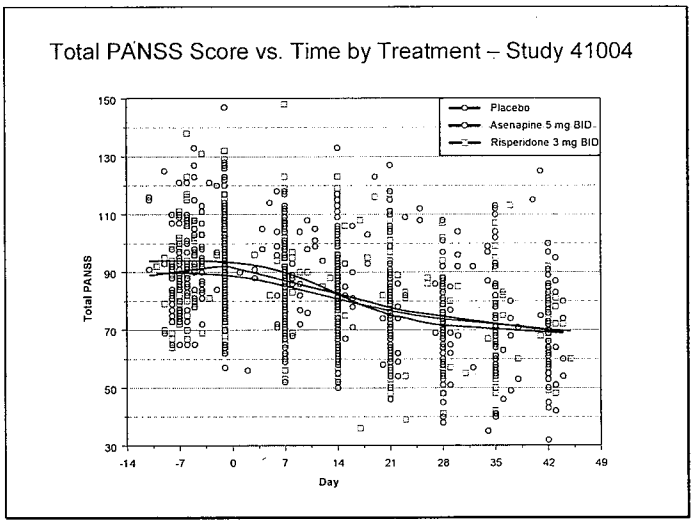


Slide 34

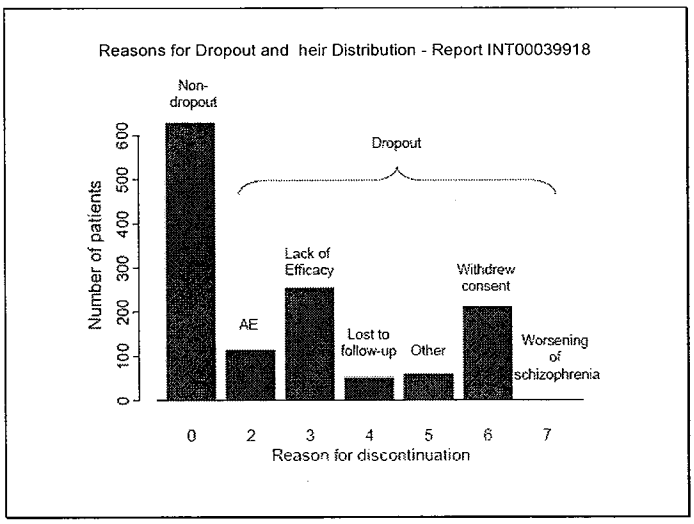
Study		041004			041021			
Treatments		Placebo	Asenapine 5 mg BID	Risperidone 3 mg BID	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Olanzapine 15 mg QD
Rx Arm (tcaf)		3	2	1	1			
N		69	58	6	93	102	96	95
Baseline		92.4 (1.9)	96.3 (2.2)	92.2 (2.1)	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
Δ to:	Day 4				-5.9 (.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)	-10.6 (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)	-10.9 (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)	-10.0 (2.6)*	-10.5 (2.7)	-10.2 (1.6)	-14.5 (1.6)*	-13.1 (1.6)	-15.8 (1.6)*
	Day 42	-5.3 (2.3)	-13.5 (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)	-5.4 (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)*

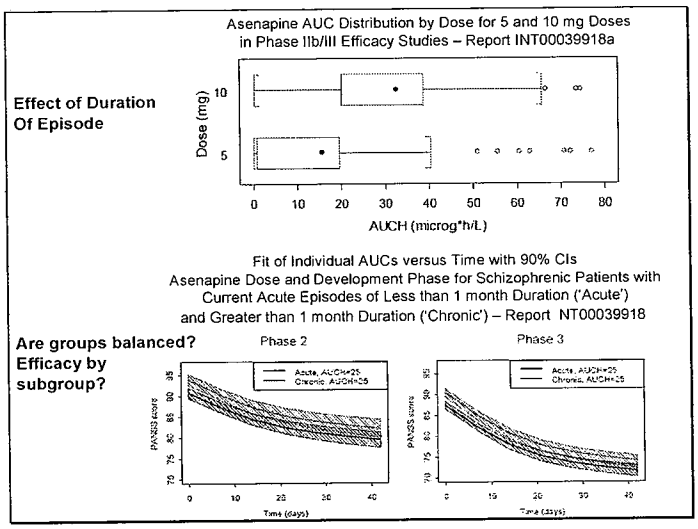
Slide 35



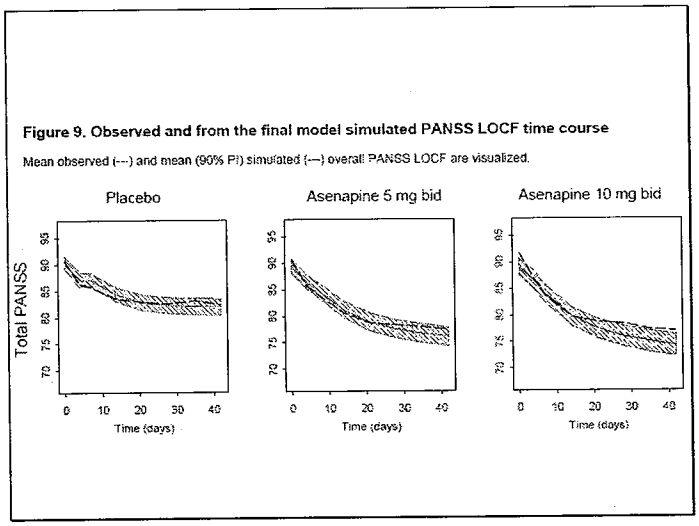
Slide 36



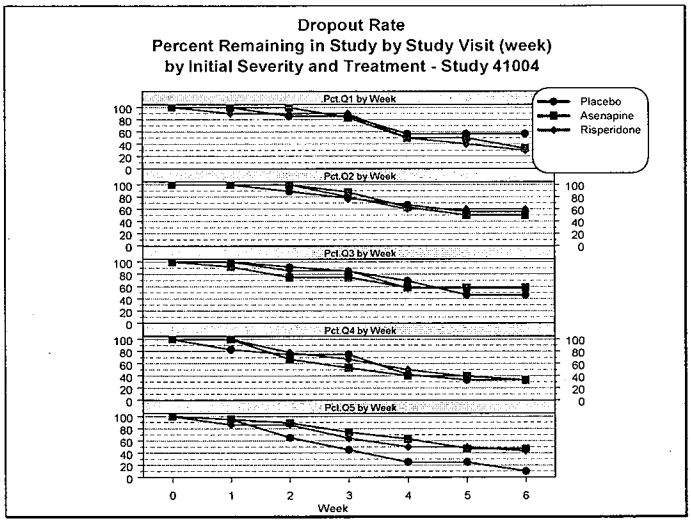
Slide 37



Slide 38



Slide 39



Slide 40

Drop out Rates and Odds Ratio by Treatment and Initial Disease Severity – Study 41004

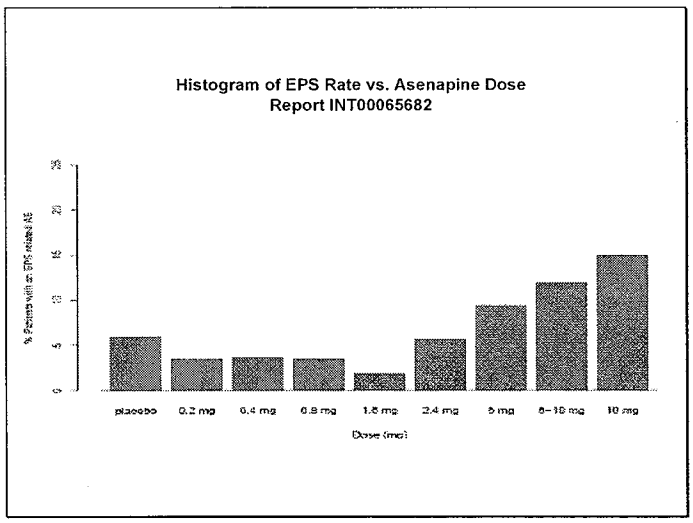
Treatment	Duration of Rx	Odds Ratio of Remaining on Active Drug Treatment Compared to Placebo					
		Q1	Q2	Q3	Q4	Q5	Total
Asenapine	Baseline	1.0	1.0	1.0	1.0	1.0	1.0
	Screen	1.0	1.0	1.0	1.0	1.0	1.0
	Visit 1	1.0	1.0	0.92	1.20	1.0	1.02
	Visit 2	1.17	1.13	0.81	0.89	1.38	1.06
	Visit 3	0.97	1.13	0.89	0.71	1.64	1.04
	Visit 4	0.88	0.94	0.84	0.96	2.53	1.16
	Visit 5	0.88	0.90	1.26	1.20	1.89	1.23
	Visit 6	0.58	0.90	1.26	1.00	4.74	1.31
Risperidone	Baseline	1.0	1.0	1.0	1.0	1.0	1.0
	Screen	1.0	1.0	1.0	1.0	1.0	1.0
	Visit 1	0.90	1.0	1.0	1.2	0.90	1.00
	Visit 2	1.05	1.13	0.93	1.04	1.32	1.10
	Visit 3	1.05	1.03	1.01	0.89	1.43	1.08
	Visit 4	0.88	0.90	0.83	1.20	2.00	1.11
	Visit 5	0.70	1.08	1.24	1.17	2.00	1.21
	Visit 6	0.53	1.08	1.24	1.00	4.29	1.23

Slide 41

Drop out Rates and Odds Ratio by Treatment and Initial Disease Severity – Study 41023

Treatment	Duration of Rx	Odds Ratio of Remaining on Active Drug Treatment Compared to Placebo					
		Q1	Q2	Q3	Q4	Q5	Total
Asenapine 5 mg BID	Baseline	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	1.04	0.93	0.88	1.00	1.00	0.96
	Visit 2	1.08	1.01	0.86	0.97	0.97	0.98
	Visit 3	0.90	1.06	0.76	1.02	0.73	0.91
	Visit 4	1.04	0.97	0.73	1.18	0.70	0.93
	Visit 5	1.04	1.03	0.77	1.60	0.67	1.01
	Visit 6	1.04	1.03	0.91	1.50	0.74	1.06
Asenapine 10 mg BID	Baseline	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	1.04	1.00	0.96	0.91	0.96	0.98
	Visit 2	1.23	1.09	0.97	0.99	0.96	1.03
	Visit 3	1.46	1.07	0.89	0.93	1.03	1.04
	Visit 4	1.78	0.99	0.80	0.96	1.03	1.04
	Visit 5	1.70	0.86	0.85	1.30	0.98	1.07
	Visit 6	1.70	0.90	1.00	1.30	1.08	1.14
Haloperidol 4 mg BID	Baseline	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	1.01	0.81	1.00	0.95	1.00	0.96
	Visit 2	1.10	0.78	1.02	0.94	0.99	0.95
	Visit 3	1.18	0.76	0.87	0.88	1.01	0.91
	Visit 4	1.43	0.70	0.81	1.02	0.86	0.91
	Visit 5	1.35	0.71	0.85	1.38	0.81	0.96
	Visit 6	1.28	0.69	1.01	1.22	1.03	1.00

Slide 42



Slide 43

Psychometric Testing in Healthy Young Adults
PO MRD PK S/T Study

a) Immediate Recall (Session 1)

Change 0-13	II	3	0.5	(0.71)	0.3	(3.40)	2.6	>0.2
	III	10	0.0	(0.00)	1.8	(0.96)	0.8	0.072
	IIIa	20	-1.0	(1.41)	2.0	(1.55)	1.2	0.053
	+P value		>0.2		>0.2			

b) Delayed Recall (Sessions 2 & 3)

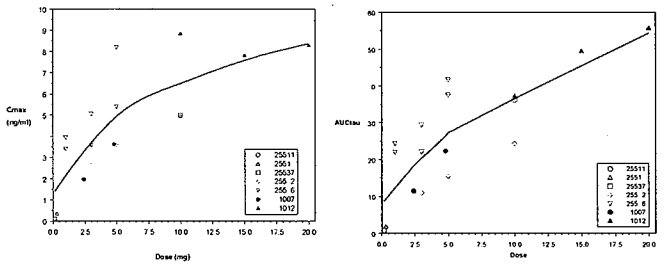
Change 0-13	II	3	0.8	(1.06)	-0.9	(3.20)	2.4	>0.2
	III	10	0.5	(1.41)	2.5	(2.12)	1.7	>0.2
	IIIa	20	-1.8	(1.06)	1.6	(1.83)	1.4	0.056
	+P value		>0.2		0.15			

- Significance in Dementia Associated Psychosis (particularly Alzheimer's)? Class Effect?

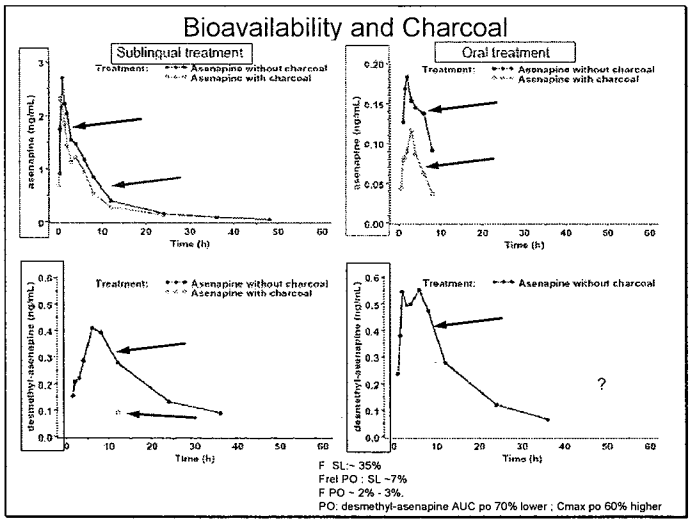
This is in contrast to a recent publication from the sponsor in on effect on neurotransmitters in brains of rats that they claim indicates it might improve cognition. This would be significant for demented patients and could be used for promotion of off-label claims.

Slide 44

MD Linearity



Slide 45



Slide 46

Intrinsic Factors

- Race and Ethnicity
  - Caucasian vs. Japanese (n = 6 / group)
    - Higher Desme hyl-asenapine in caucasians
      - Likely due to swallowing
- Gender
  - Not studied
  - Data might be extractable
  - 1A2 substrate
    - Exposures likely higher in women
- Elderly
  - Not studied
  - Found abbreviated study report hidden in 4 mo safety update
- Adolescents
  - Abbreviated study report
  - NDA not for adolescents
  - Risk Management Strategy (REMS) for Off Label Use

Slide 47

Asenapine BID Pharmacokinetics in Adolescents receiving Antipsychotics - Study A7501022

Asenapine

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

Desmethyl-Asenapine

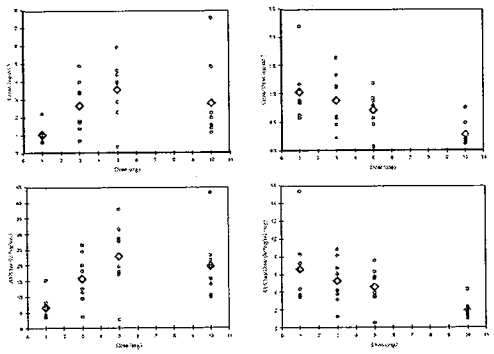
N (n)	8 (5)	8 (5)	8 (8)	8 (6)
Tmax (hr)	3.04 (0.50 - 12)	1.82 (0.28 - 6.0)	4.00 (0.0 - 11)	3.59 (0.78 - 4.0)
Cmax (ng/mL)	0.430 (67.7)	1.04 (63.2)	1.40 (37.4)	2.96 (74.5)
Cmin (ng/mL)	0.219 (57.5)	0.621 (67.8)	0.800 (37.6)	1.07 (83.5)
AUC(0 τ) (ng/mL x hr ^{1})	4.03 (60.2)	10.1 (72.9)	13.3 (38.2)	25.8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

N = Number of subjects
n = N for t½ and Vd/F

Slide 48

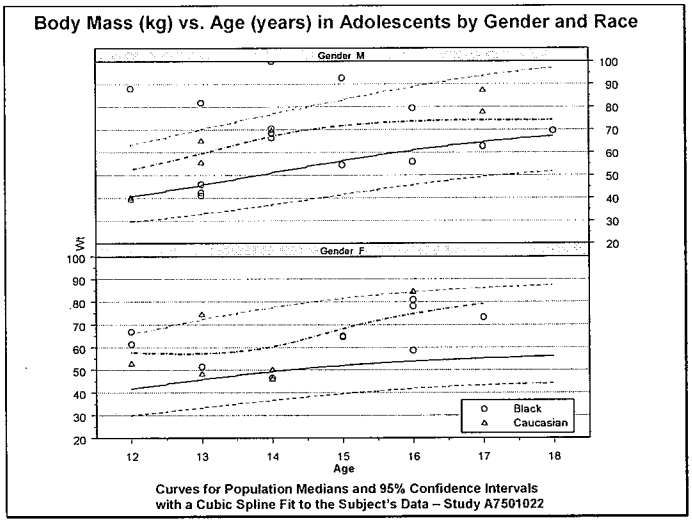
Unnormalized and Dose-normalized Asenapine Cmax and AUCs by Dose in Adolescent Subjects – Study A7501022

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

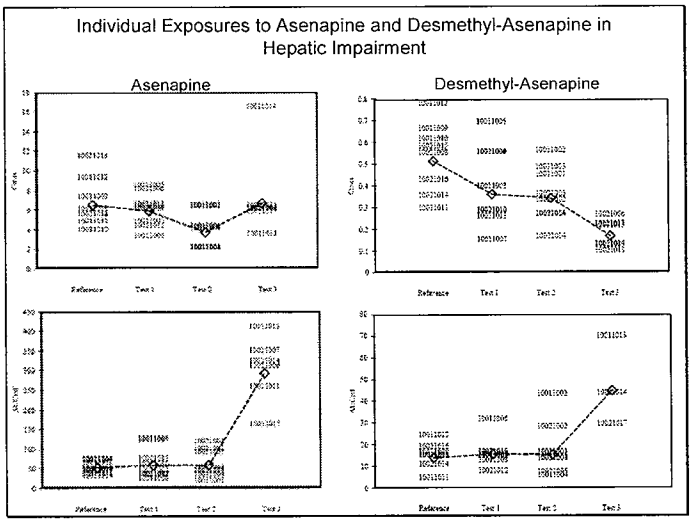


Left panels show observed values; right panels show dose-normalized values. Circles are individual subjects, diamonds are arithmetic means.

Slide 49

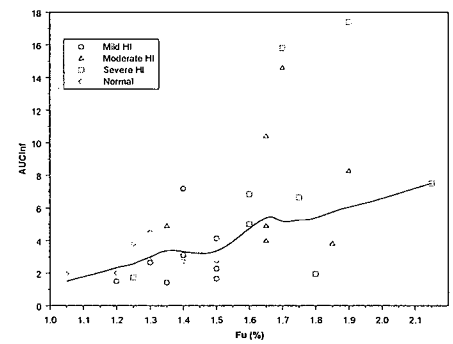


Slide 50



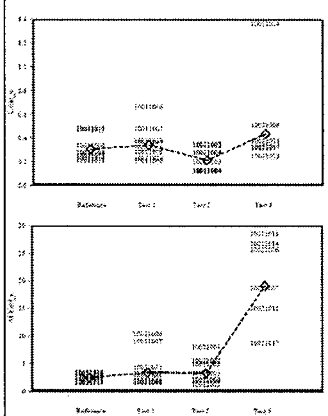
Slide 51

AUC vs. Free Fraction in Subjects with Hepatic Impairment



Slide 52

Unbound Asenapine following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018



	Normal	Mild	Moderate	Severe
N	6	[illegible]	6/7	6
Cmaxu (ng/mL)	0.317 ± 0.106 (33.[illegible]) 0.2[illegible]-0.4[illegible] [illegible]	0.364 ± 0.148 (40.6) 0.206-0.6[illegible] [0.3[illegible]]	0.229 ± 0.0046 (43.6) 0.110-0.347 [0.238]	0.524 ± 0.41[illegible] (80.1) 0.248-1.36 [0.35[illegible]]
AUCu(0-tlqc) (ng/mL x hr)	2.38 ± 0.626 (26.[illegible]) 1.55-3.87 [2.38]	3.05 ± 2.45 (67.3) 1.02-6.3[illegible] [2.7[illegible]]	3.64 ± 2.18 (5[illegible]) 1.20-7.[illegible] [3.0[illegible]]	18.[illegible] ± 5.06 (30.[illegible]) 8.44-2[illegible] [16.[illegible]]
AUCu(0-∞) (ng/mL x hr)	[illegible]	[illegible]	[illegible]	[illegible]
CL/Fu (mL/min)	[illegible]	[illegible]	[illegible]	[illegible]
fu (%)	0.047 ± 0.00[illegible] [illegible]	0.0[illegible] ± 0.012 [illegible]	0.057 ± 0.007 [illegible]	0.0[illegible] ± 0.013 [illegible]

Slide 53

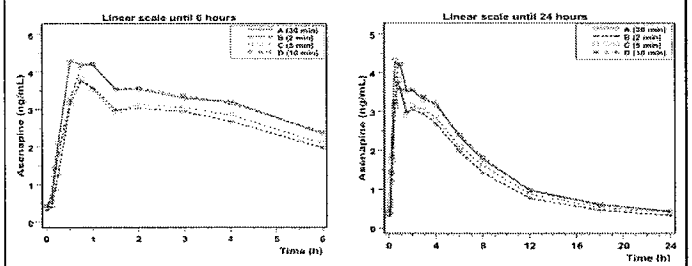
Renal Insufficiency

- No clear effect on Asenapine or Desmethyl-asenapine kinetics
- CYP2D6 and Transporters Effected in Severe Renal Failure
- Other metabolites not examined
  - Expected that conjugates and possibly N-oxides and may be effected

Slide 54

Extrinsic Factors

Effect of Water at Various Times after Drug Administration – Study 25537



Desmethyl-asenapine 90% CI for Cmax Indicates Higher Peaks in some subjects at 2 min

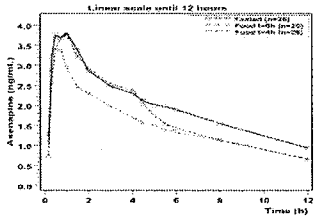
Slide 55

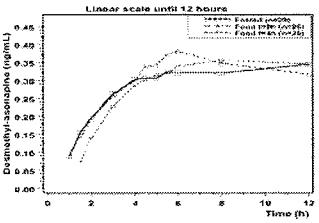
Smoking

- CYP1A2 Substrate
  - smoking should induce
- Study conducted in Smokers
  - Effect of a single cigarette smoked concurrently
- Possibly applicable to schizophrenics Not other populations
  - Different Frequency of AEs?
  - Different Risk : Benefit Ratios?
- No clear effect on asenapine or desmethyl-asenapine
- Other metabolites not studied
- Applicable

Slide 56

Effect of Food Administration at Various Times on Asenapine Mean Concentration vs. Time Profiles – Study 41029





NOT Truly Fasted
High Energy Supplement

Analyte (N)	Metric	Summary Statistics (A) Fasted	(B) Fed 2h-0h	(C) Fed 1h-0h	Geometric Mean Ratios (90% CI) B : A	C : A
Asenapine (n=26)	Tmax (h)	0.00 (0.00 - 3.00)	0.75 (0.50 - 4.00)	0.75 (0.50 - 4.00)	--	--
	Cmax (ng/mL)	4.46 ± 2.57	3.86 ± 2.24	4.27 ± 2.19	0.90 (0.73 - 1.11)	1.02 (0.83 - 1.26)
	AUC∞ (ng/mL x hr-1)	36.5 ± 15.6	33.6 ± 14.1	32.6 ± 11.7	0.79 (0.69 - 0.94)	0.87 (0.73 - 1.05)
N - Desmethyl - Asenapine (n=26)	Tmax (h)	7.00 (4.00 - 12.0)	7.0 (3.00 - 12.0)	6.00 (3.00 - 12.0)	--	--
	Cmax (ng/mL)	0.395 ± 0.167	0.402 ± 0.139	0.401 ± 0.192	--	--
	AUC∞ (ng/mL x hr-1)	10.6 ± 3.68	11.0 ± 3.36	10.9 ± 4.23	--	--

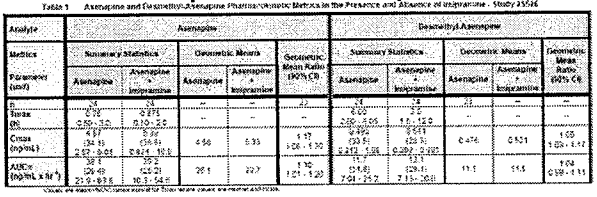
Slide 57

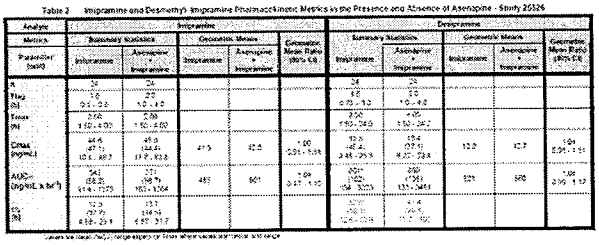
Drug-Drug Interactions

- Studied
  - CYP2D6 – noncompetitive inhibitor
    - Single Dose Asenapine 5 mg & Imipramine 75 mg
    - Multiple Dose Asenapine & Paroxetine
    - Single and Multiple Dose Dextromethorphan
  - CYP1A2
  - UDPGT1A4
- Expected - Not Studied - Likely Clinically Significant
  - CYP2C9 ?
  - COMT
- Possible - Significance?
  - PST
  - FMO

Slide 58

Asenapine and Imipramine





75 mg SD first followed by 5 mg SL SD

Slide 59

DDI Study

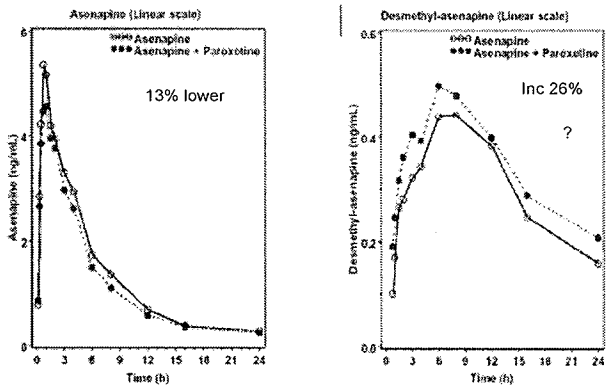
Asenapine / Paroxetine / DM

Table 1 Study Design for Paroxetine / Asenapine Drug-Drug Interaction Study - Study 25525

Objective		Effect of Asenapine on Paroxetine & Dextromethorphan		Effect of Paroxetine on Asenapine & Dextromethorphan	
Nominal Designations Used	Treatment Sequence	A		B	
	CSR Statistical Analysis Arm	B		A	
	PK Report SAS Analysis Arm	A		B	
	Treatment Arm	A		A	
	Pharmacokinetic Arm	A		A	
Treatments	Screening	DM 30 mg PO to determine 8 hour DX:DM UMR		DM 30 mg PO to determine 8 hour DX:DM UMR	
	Day 1		Paroxetine 20 mg SD		Placebo
	Day 2				Asenapine 5 mg SL
	Day 3		Placebo		
	Day 4	Asenapine 1 mg SL BID			
	Day 5	Asenapine 3 mg SL BID			
	Day 6				
	Day 7				
	Day 8				
	Day 9				
	Day 10				
	Day 11	Asenapine 5 mg SL BID		Paroxetine 20 mg PO QD	DM 30 mg PO to determine 8 hour DX:DM UMR
	Day 12		DM 30 mg PO to determine 8 hour DX:DM UMR		
	Day 13		Placebo-Paroxetine		Placebo-Asenapine
	Day 14		Paroxetine 20 mg SD		Asenapine 5 mg SL
	Day 15				
	Day 16				

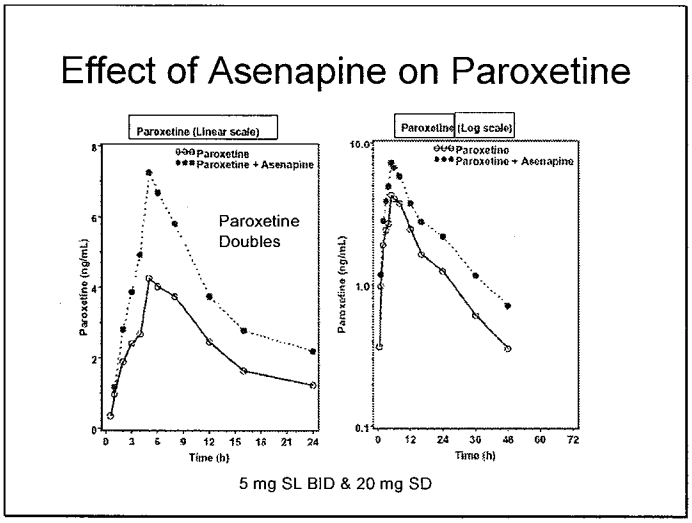
Slide 60

Effect of Paroxetine on Asenapine

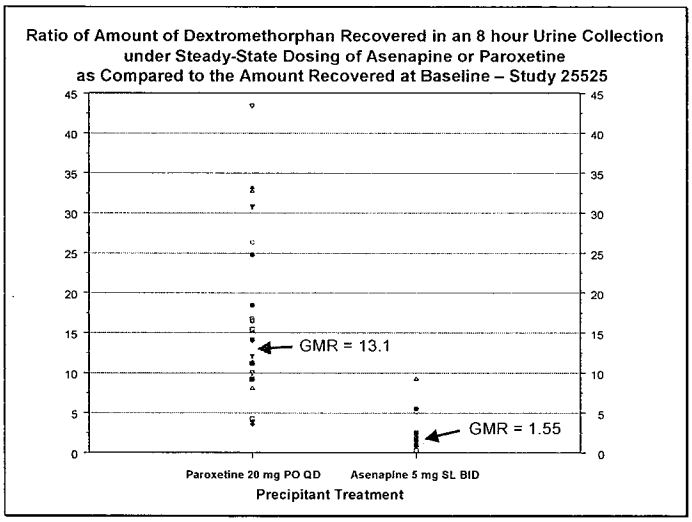


20 mg QD & 5 mg SL SD

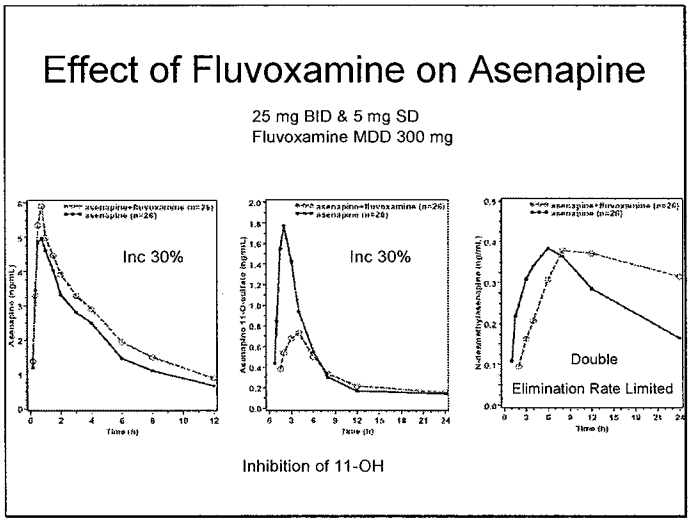
Slide 61



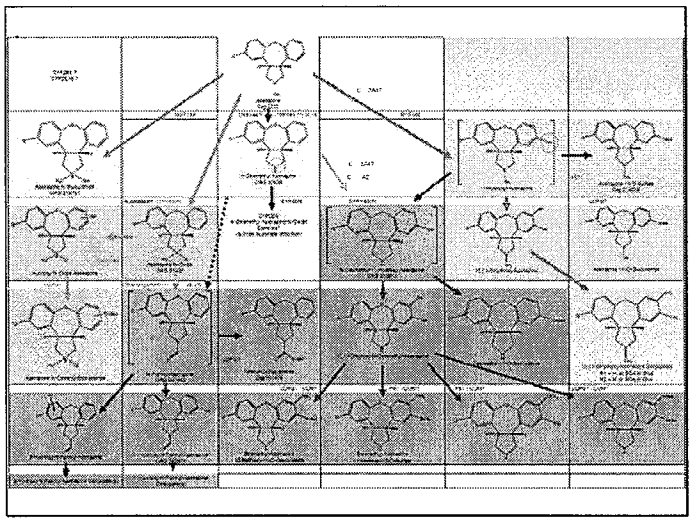
Slide 62



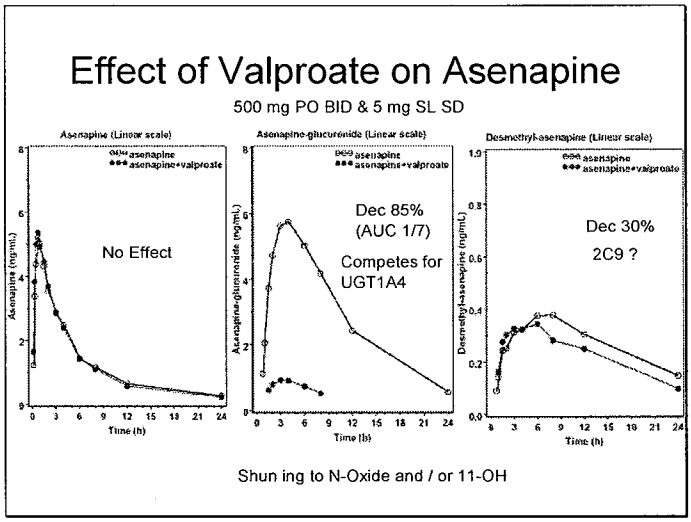
Slide 63



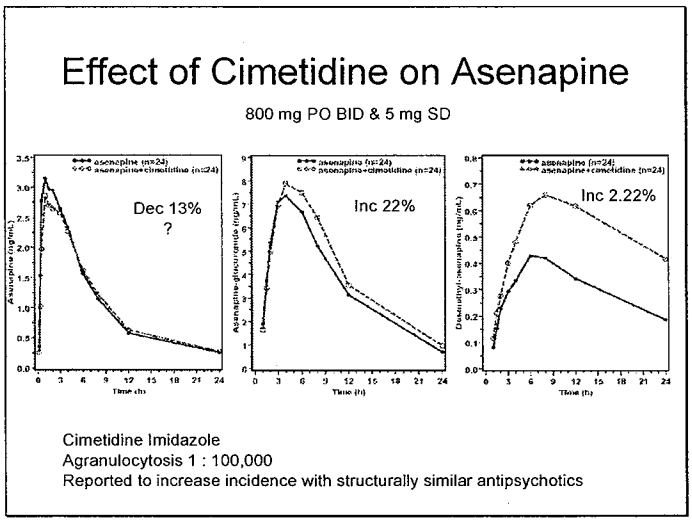
Slide 64



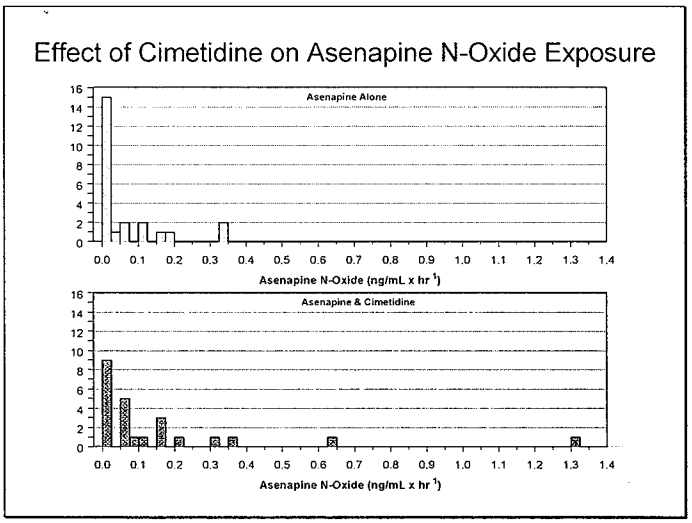
Slide 65



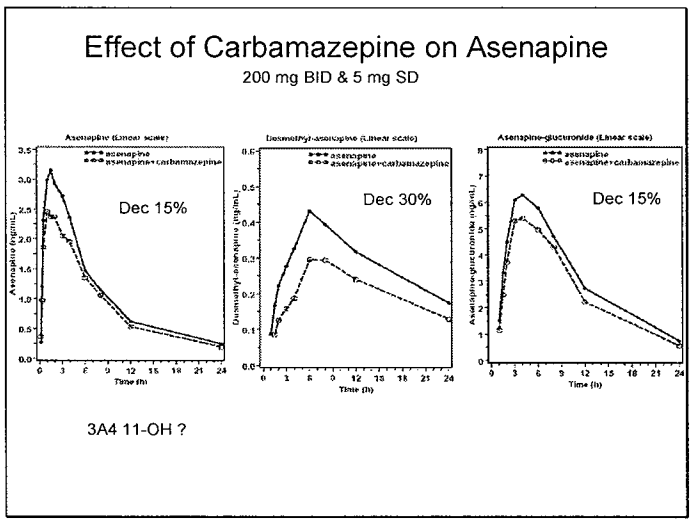
Slide 66



Slide 67



Slide 68



Slide 69

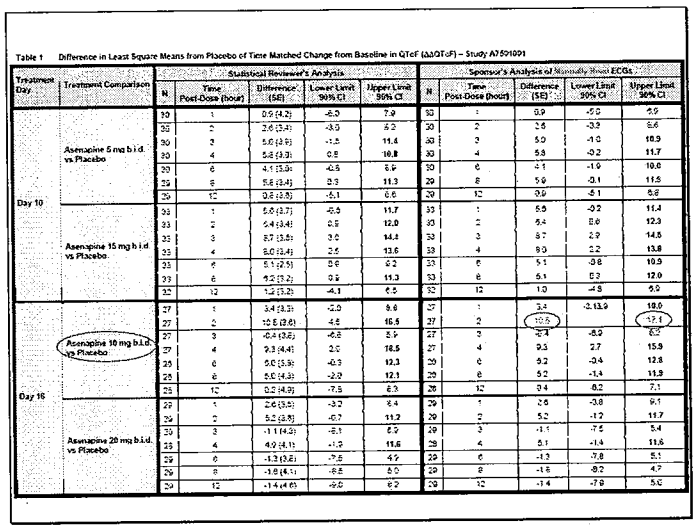


Table 1 Difference in Least Square Means from Placebo of Time Matched Change from Baseline in QTcF (ΔΔQTcF) – Study A7591091

Treatment Day	Treatment Comparison	Statistical Reviewer's Analysis N	Time Post-Dose (hour)	Difference* (SE)	Lower Limit 90% CI	Upper Limit 90% CI	Sponsor's Analysis of Manually Read ECGs 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	-3.2	8.6
		30	3	5.0 (2.9)	-1.5	11.4	30	3	5.0	-1.0	10.9
		30	4	5.8 (2.9)	0.8	10.8	30	4	5.8	-0.2	11.7
		29	6	4.1 (3.0)	-0.8	8.9	30	6	4.1	-1.9	10.0
		29	8	5.6 (3.4)	0.3	11.3	29	8	5.9	-0.1	11.5
		29	12	0.8 (3.5)	-5.1	6.6	29	12	0.9	-5.1	6.8
	Asenapine 15 mg b.i.d. vs Placebo	33	1	5.0 (2.7)	-0.5	11.7	33	1	5.5	-0.2	11.4
		33	2	5.4 (3.4)	0.5	12.0	33	2	5.4	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)	0.6	9.2	33	6	5.1	-0.8	10.9
		33	8	6.2 (3.2)	0.6	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	9.0	27	1	3.4	-2.13.9	19.0
		27	2	10.5 (3.6)	4.6	16.5	27	2	10.5		17.1
		27	3	-0.4 (3.6)	-6.5	5.7	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	5.0 (3.9)	-0.3	12.3	29	6	5.2	-0.4	12.8
		26	8	5.0 (4.3)	-2.0	12.1	29	8	5.2	-1.4	11.9
		25	12	0.2 (4.0)	-7.5	6.3	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 (2.8)	-0.7	11.2	29	2	5.2	-1.2	11.7
		29	3	-1.1 (4.3)	-8.1	6.0	29	3	-1.1	-7.5	5.4
		28	4	4.9 (4.1)	-1.9	11.6	29	4	5.1	-1.4	11.6
		29	6	-1.3 (3.6)	-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

Slide 70

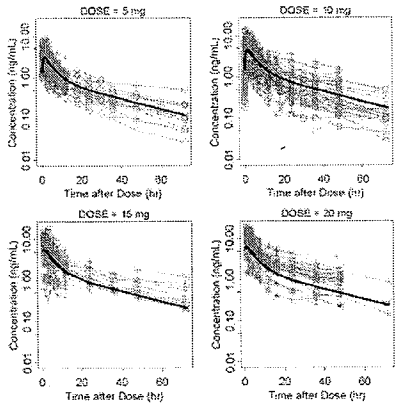
Sponsor's Table of Categorical QTcF by Gender and Treatment

		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	26	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* through Day 10										
Placebo	26	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
* Post dose

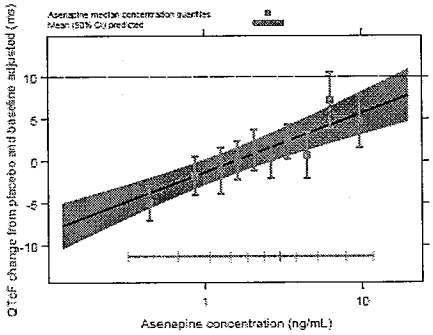
Slide 71

Phase I/II Pop PK Predicted Asenapine Steady State Concentration-Time Profiles
(Base Model) for Selected Doses with Overlaid Observed Concentra ions

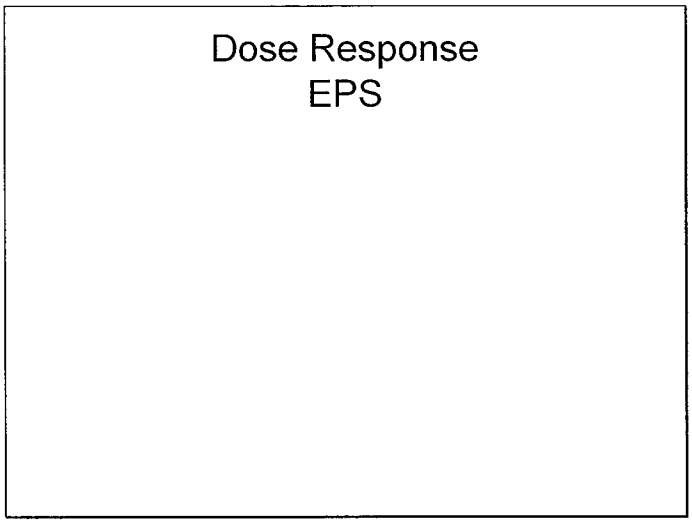


Slide 72

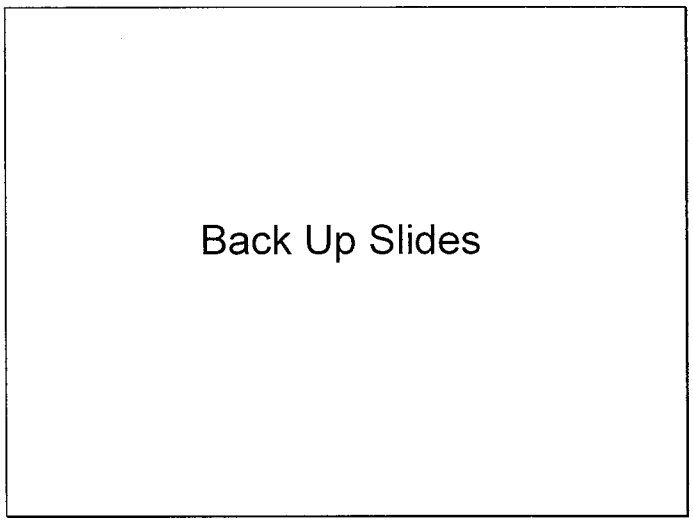
**Linear Model of ΔΔQTcF vs. Asenapine Concentration
Overlaid with Mean QT Prolongation with 90% CIs
at the Median-of the 10% Quantiles for Asenapine Concentration**



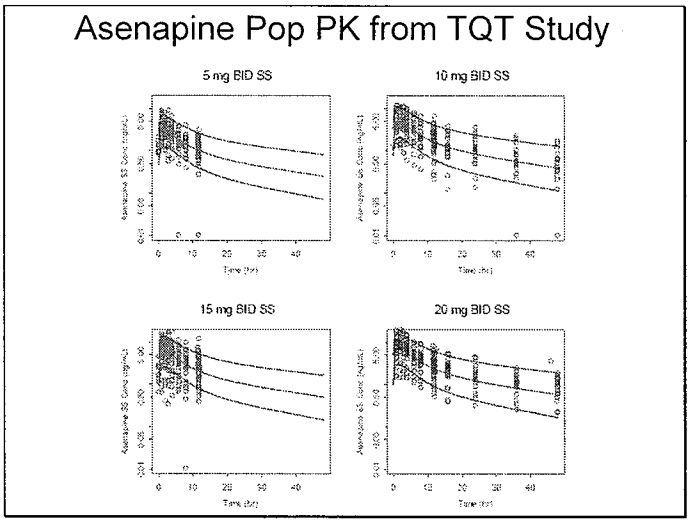
Slide 73



Slide 74



Slide 75



Slide 76

Medians of the Typical Individual Model Predictions of the YMRS Response, Median Differences in the Typical Individual YMRS Response (ΔYMRS) and 90% CIs

	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	
		Median[b]	90%CI	Median[b]	90%CI	Median[b]	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).

Slide 77

b(4)

Table 1 Summary of Asenapine Pharmacokinetic Parameter Values Following Administration of Asenapine 5 mg (b)(4) Tablets (Reference) and 5 mg (b)(4) Tablets (Test) (Study A7501016)

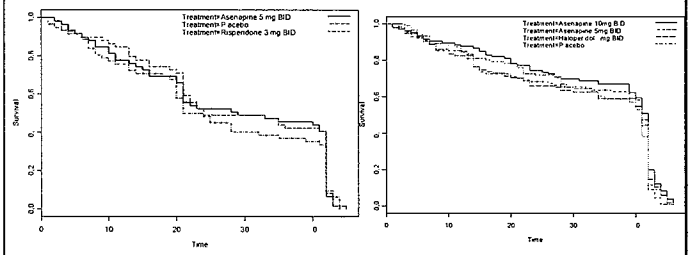
Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	(b)(4) Tablet (Test)	(b)(4) Tablet (Reference)		
N	35	34		
Cmax ng/mL	2.95	3.25	90.6	80.80 to 101.65
AUC(0-tlqc) ng*hr/mL	21.2	23.0	92.1	83.62 to 101.45
AUC(0-∞) ng*hr/mL	23.1a	25.1b	92.0	83.69 to 101.18
Tmax hr	1.13	1.12	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

a N=33;
b N = 32 (t½ could not be determined for all subjects)
Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference). 90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

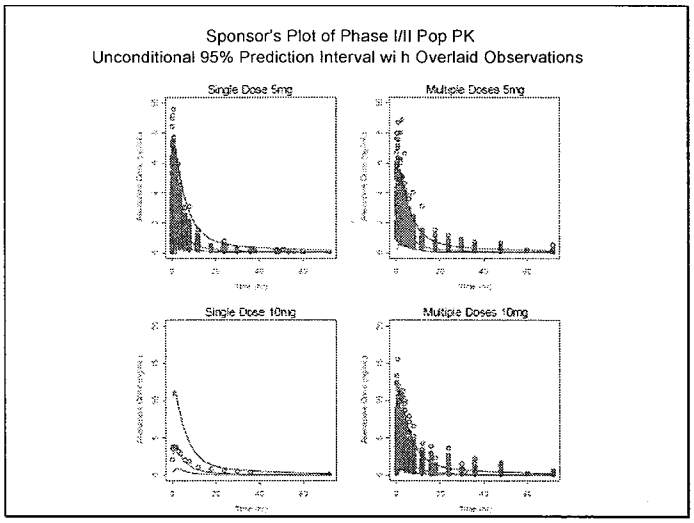
AEs

Slide 78

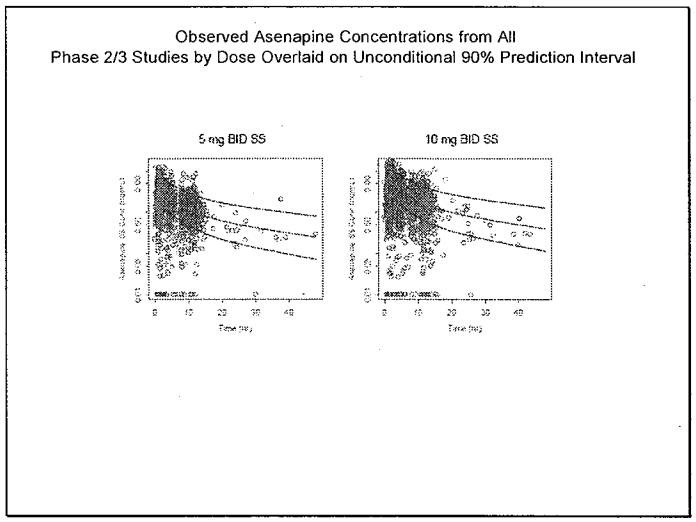
Kaplan-Meir Plots
Survival over Time by Treatment Group - Study 41023



Slide 79

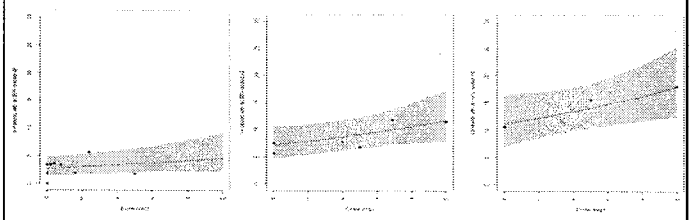


Slide 80



Slide 81

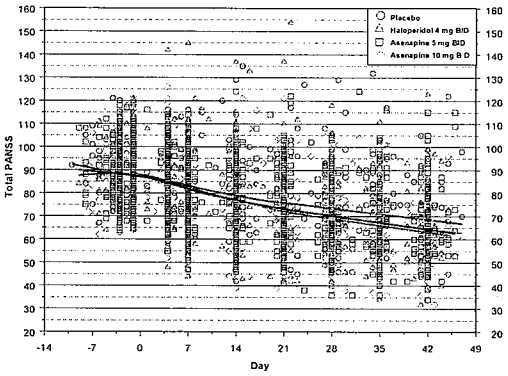
Proportion of Subjects with an EPS-Related Adverse Event in the Different Acute Schizophrenia Trials vs. Dose in Milligrams Report INT00065682



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

Slide 82

Total PANSS Score vs. Time by Treatment - Study 41023



b(4)

6.9 Submission Quality

This will be provided as an amendment to this review.

6.10 Good Review Management Practice – Pilot Program - Critique

This will be provided as an amendment to this review.

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

/s/

Ron Kavanagh
5/15/2008 11:32:55 AM
BIOPHARMACEUTICS
Please see amendment(s) for labeling and other comments per review

Raman Baweja
5/15/2008 03:53:55 PM
BIOPHARMACEUTICS
I plan to have a Memo to File as OCP TL.