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:	**X**	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	7		
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	X	5		
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**	

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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

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Revie...	Title	Type	Status	Submitted In	File E...	Pages	Size (KB)
	DEFINE	File	Current	0000 (Origi...	.pdf	0	885

Preview

Bookmarks | Pages | Attachments | Comments

Options

- 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 *)
drgendd	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
durlszp	Duration of schizophrenia symptoms (yrs)	num			
durepic	Duration of present episode	char			
durepif	Duration of present episode	num			Format=DURATN 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 possibilites, see CRF.

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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		
(b) (4)		4 months		

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

(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
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
	(b) (4)	4 months

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	(b) (4)
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	Claimed no interference in 6 samples. (Inadequate description.)
Internal Standard	No interference.
Metabolites	No interference with N-oxide. Others not tested.
Incurred Samples	Not Tested.
OTC Drugs	
Dietary – e.g. Caffeine	
Drugs – Rx	
Stability - Blood	
Stability - Plasma	
RT	
Refrigerated	
Long Term (-20 °C)	Stable 2 weeks. Not Stable at 1 month. Contrary to Claims.
Stability Freeze/Thaw	
Stability - Extracted	
RT	
Refrigerated	
On Machine	

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	(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	(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	(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**	

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

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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 [^{11}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

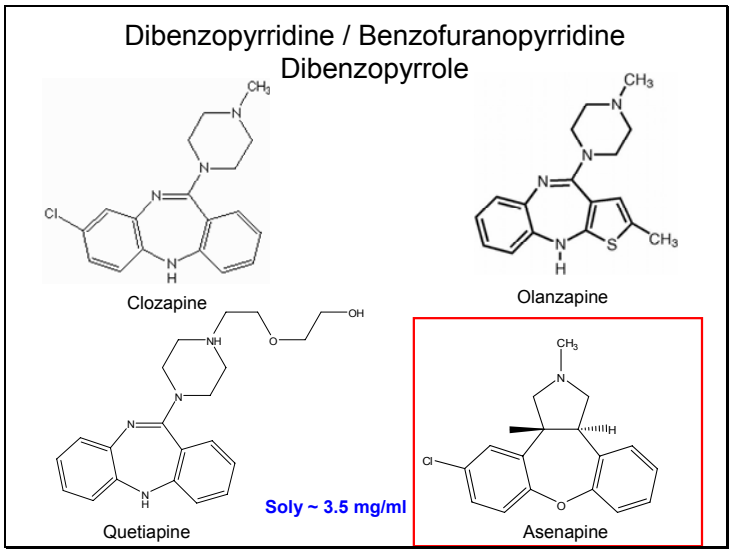
OCP Briefing
Ron Kavanagh, B.S.Pharm,. Pharm.D., Ph.D.
May 12, 2008

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								

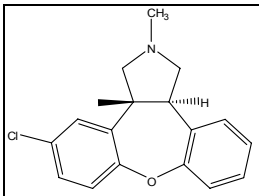
	Approx Conc / IC50	
Red	≥10	Only Binding
Pink	1 to 10	Virtually NO Information on agonism / antagonism
Maroon	0.5 - 1	

5HT2B – Agonists associated with Phen-fen cardiac valvulopathy

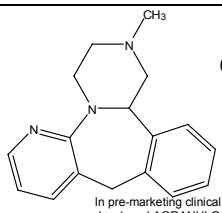
5HT2A and 5HT5A associate with appetitie

D4 associated with akathesia

Slide 6



Asenapine



Mirtazapine

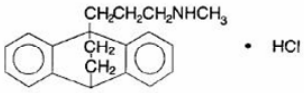
(Remeron – Organon 1994)

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

In pre-marketing clinical trials of mirtazapine, 2 out of 2796 patients developed AGRANULOCYTOSIS (absolute neutrophil count (ANC) less than 500 cells/cubic millimeters with symptoms) and 1 patient developed severe NEUTROPENIA (ANC less than 500 cells/cubic millimeters without symptoms).
All 3 patients recovered after mirtazapine was discontinued.
The incidence based on these 3 cases was approximately 1.1 per 1000 patients.

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

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

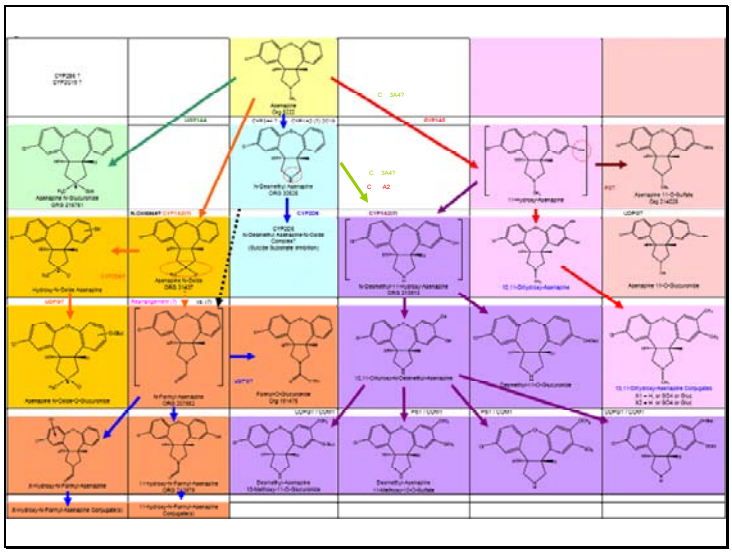


Maprotiline - Ludiomil – Ciba Geigy

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

Ludiomil because of case of possible DDI with CHF

Slide 7



Olanapine formyl metabolite via hydroxyl intermediate

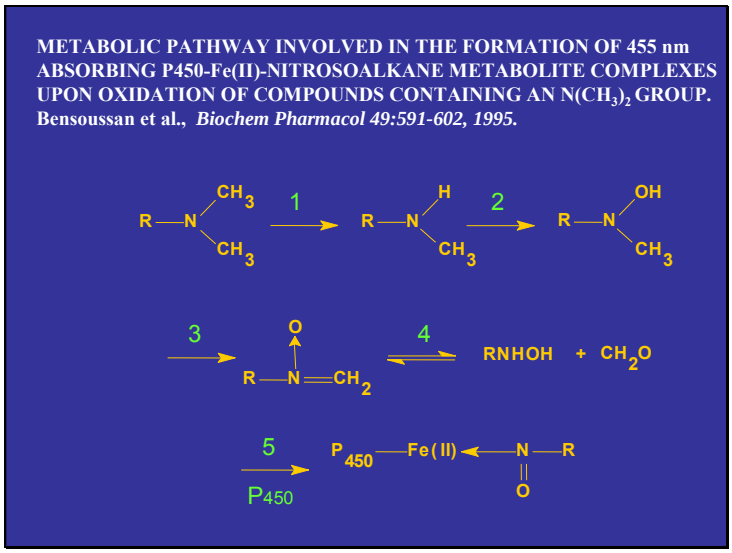
Slide 8

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

Study	Date	Test System	Isozyme	Inhibitor	Ki	Claimed Type of Inhibition
NL0017588	Dec 1999	Supersomes	1A2	Asenapine	2.8 µMol	Competitive
			2D6		6.76 nMol	Competitive
NL0013163	April 1999	Supersomes	2C19	Asenapine	25.16	uncompetitive
			3A4 (a)		51.4	Mixed-competitive ?
			3A4 (b)		125.59	?
NL0048836	Aug 2003	Supersomes		Asenapine	15.2 nMol	Competitive
			2D6	30626 N-Desmethyl	62.08 nMol	Noncompetitive
				31437 N-Oxide	82.82 nMol	Competitive
NL0060059	Oct 2003	Supersomes	1A2	Asenapine (N.B. CYP2D6 not studied)	1.5 µMol	Competitive
			2A6		360.44 µMol	Noncompetitive
			2C8		105.10 µMol	Uncompetitive
			2C9		2.0 µMol	Competitive
			2C19		33.24 µMol	Noncompetitive
			3A4 (1)			
			1A2	30626 N-Desmethyl-Asenapine (N.B. CYP2D6 not studied)	1.4 µMol	Noncompetitive
			2A6		70.31 µMol	Competitive
			2C8		80.30 µMol	Noncompetitive
			2C9		172.34 µMol	Noncompetitive
			2C19		1.76 µMol	Competitive
			3A4 (1)		3.53 µMol	Competitive
			1A2	31437 N-oxide (N.B. CYP2D6 not studied)	No inhibition	
			2A6			
			2C8			
			2C9			
			2C19			
			3A4 (1)			
			3A4 (2)			
NL0060807	Oct 2003	Supersomes	2D6	100/50 N(2)-Oxide	28.72 nMol	Competitive
			2D6	100/50 N(2)-Oxide	12.40 nMol	Competitive
DM2006-005222-000	Dec 2006	Pooled Human Liver Microsomes (HLM)	CYP1A2	Asenapine	0.9 µMol*	
			CYP2B6		> 30 µMol*	
			CYP2C8		> 30 µMol*	
			CYP2C9		> 30 µMol*	
			CYP2C19		> 30 µMol*	
			CYP2D6		44 nMol*	
			CYP3A		> 30 µMol*	
			CYP3A		> 30 µMol*	

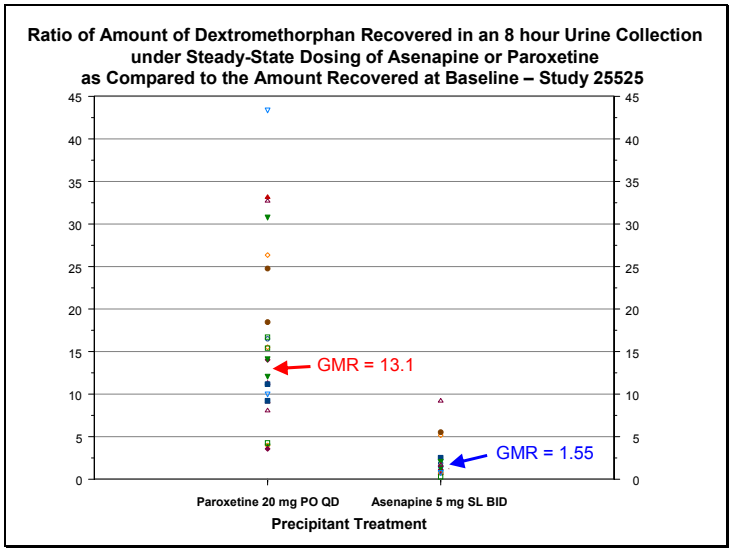
a IC50

Slide 9

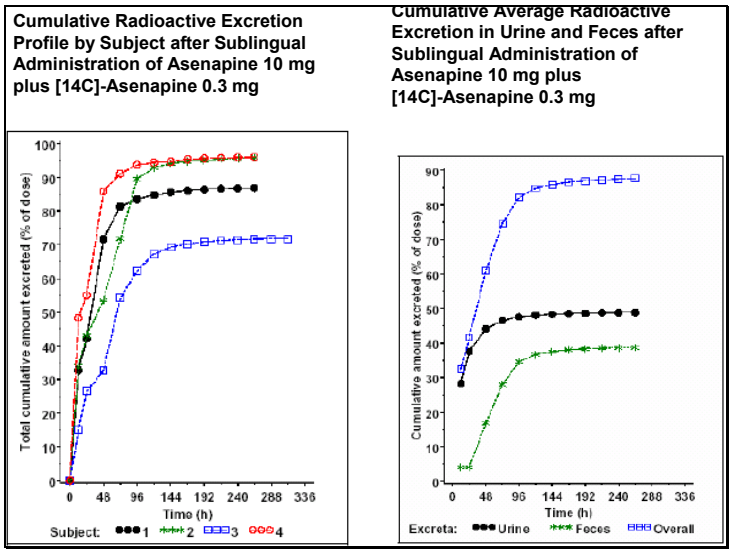


From FDA presentation 1999

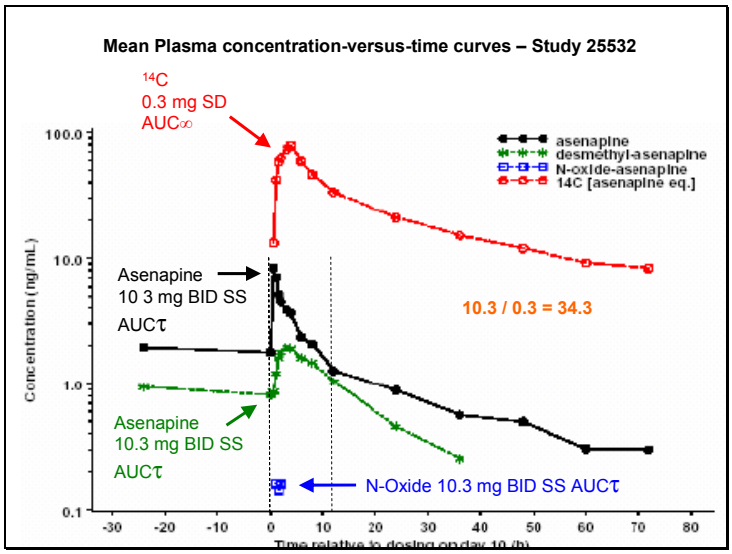
Slide 10



Slide 11



Slide 12



Slide 13

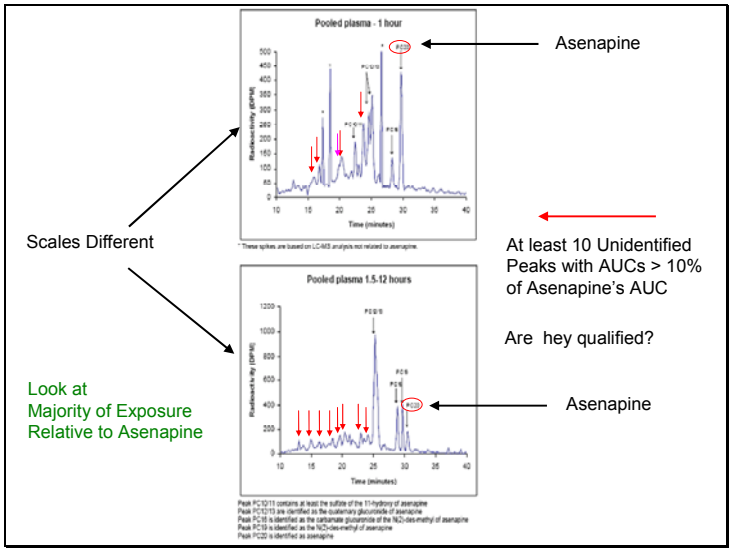
Table 1 Plasma Exposures to Asenapine and Selected Metabolites Relative to Total ^{14}C Radioactivity after Asenapine 10 mg and 0.3 mg 14-C-Asenapine at Steady-State - Study 25532

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	1952.8	67046	16.5
	4	35.7	17.7	0.6	1470.0	50470	8.5
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	0.06	0.03	0.002	–	–	–
	3	0.08	0.04	0.001	–	–	–
	4	0.07	0.04	0.001	–	–	–
	Mean[c]	0.067	0.032	0.001	–	–	–

Total 0.1% 99.9% of Circulating Radioactivity Unidentified

Even if only look at unnormalized data 96.6% unidentified

Slide 14



Slide 15

Possible 11-Hydoxylation
17% - 27% Mixed
Can't Identify Relative Amounts

Possible N-Desmethylation
Based on Lilly Olanzapine Publication
Formyl Metabolite may be formed via hydroxylation and not desmethylation
Only 3% – 4% definitively via desmethylation

12%% – 21% definitively via glucuronidation

12% - 21% not identified

3% - 6% Mixture of Conjugates

Unchanged Asenapine 5% - 16%

17.2% - 33.5% Identified

64.5% - 82.8% Unknown

Table 1 One Possibility for Relative Contributions by Primary Pathways to Mass Balance

Peak No.	Description	Subj 1	Subj 2	Subj 4	Subj 6
11-Hydroxylation	2CYP1A2;				
PC2	N(2)-des-methyl asenapine 10-Methoxy 11-O-Glucuronide & N(2)-des-methyl asenapine 10-O-Glucuronide 11-Methoxy	2.51	2.7	2.8	2.61
PC6	N(2)-des-methyl asenapine 10-methoxy 11-O-Sulfate & N(2)-des-methyl asenapine 10-O-Sulfate 11-Methoxy N-des-methyl asenapine 11-O-glucuronide Asenapine 11-O-glucuronide Plus some other sulphates and glucuronides	6.17	6.91	2.75	3.90
PC10	Asenapine 11-O-Sulfate	7.36	5.53	3.52	4.85
PC11	N-oxide asenapine sulfate and glucuronides 10, 11-dihydroxy-des-methyl asenapine and 10, 11-dihydroxy asenapine	7.74	15.21	6.05	2.8
Subtotal		23.78	27.25	17.28	19.21
N-Demethylation	?				
PC22	11-hydroxy N-formyl N-desmethyl asenapine	1.97	1.44	1.34	2.31
PC23	8-hydroxy N-formyl of N-desmethyl asenapine	2.7	1.66	1.71	2.82
PC15	N-desmethyl-asenapine	0.92	1.65	0	0
PC16	N(2)-des-methyl asenapine glucuronide	3.13	2.42	2.79	3.16
Subtotal	N.B. it's uncertain if formyl metabolites should be included under N-Demethylation or not. Or alternatively under N-oxidation or even another pathway.	8.72	7.39	6.01	8.29
quaternary glucuronide of asenapine	UGT1A4				
PC12	asenapine glucuronide	3.58	9.36	5.99	7.42
PC13	asenapine glucuronide	8.51	11.97	7.51	11.91
Subtotal		12.09	21.33	13.5	19.34
Unidentified					
PC1		2.71	2.29	1.19	0
PC3		1.93	1.93	1.14	1.67
PC4		2.95	0	0	0
PC5		2.35	0	0	0
PC7		0	2.39	1.38	1.96
PC14		2.87	1.62	2.32	2.3
PC15		3.55	3.12	1.65	3.02
PC17		3.79	4.05	2.4	2.91
PC18		1.13	0	0	0
PC21		0	1.17	1.1	1.39
Subtotal		20.78	16.53	11.78	15.45
Unidentified Sulfate and Glucuronide Conjugates					
PC8	some conjugated metabolites (sulfates and glucuronides)	2	0	0	3.1
PC9	some conjugated metabolites (sulfates and glucuronides)	3.92	4.34	2.85	0
Subtotal		5.92	4.34	2.85	3.1
PC20	Asenapine	4.75	6.87	7.42	19.2
Total Recovery from Individual Peaks		76.26	82.91	58.56	81.59
	Identified	48.68	61.64	44.28	63.64
	Unidentified	26.7	20.67	14.28	18.02
	Not Accounted For in report of (Jiba and Fazes Recovery	23.52	17.39	41.32	18.41
Total Recovery per Sponsor		86.9	93.3	71.8	99.6
	Not Recovered	13.1	6.1	28.2	0.3
Difference between amount reported as not recovered by sponsor and amount not accountable for in report of Jiba and Nzas recovery		10.52	11.29	12.92	14.41
Unidentified, Unaccounted, and Not Recovered (Average)		36.22	28.06	55.61	34.06
			(48.7%)		

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. (b) (6)	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	- 8.33x ULN	+++	
			AST	6	9	17	+++	

9 of 20 given asenapine had elevated LFTs

PK included in study design but not reported.

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

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

Slide 17

Other Signals - DILI

- BE study 41026 – (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 (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

Dec 1991

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.

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

$Fabs^{SL} \approx 0.35$

0.7 mg IV ≈ 2.1 mg SL

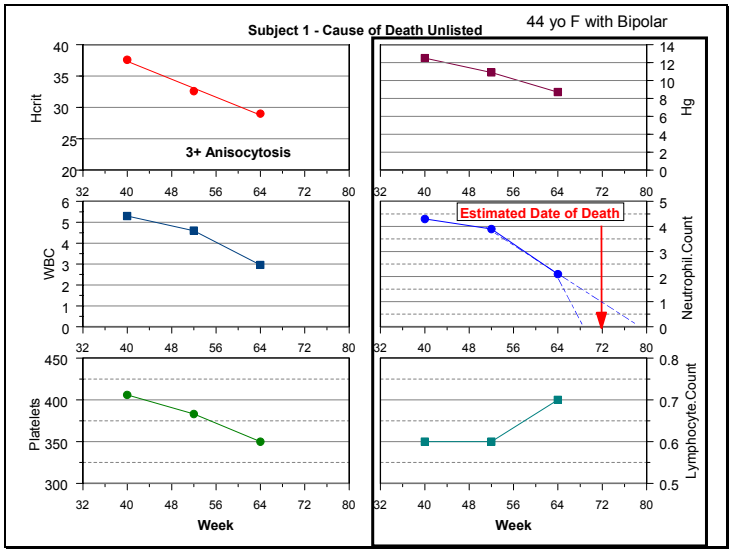
Slide 19

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 – (b) (4) vs. (b) (4)
  - *"One subject (Subject 20) had a neurally mediated reflex bradyca without iousness) in supine position after treatment with the (b) (4) 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.

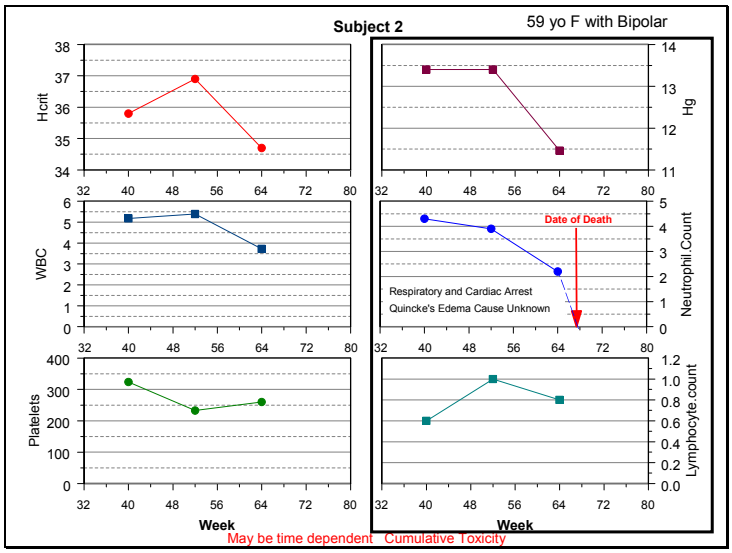
This does not include the cases of cardiac effects in the safety data base from the phase III trials and vica versa (except for MI as noted).

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)
Se f–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%)
Se f–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)
Se f–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				
Se f-injurious ideation				
Intentional self-injury				
Suicidal ideation				
Suicide a tempt				
Completed Suicide				
Total				0 (0.0)
All Asenapine 5-10 mg BID (fixed and flexiible)	N 379	N 317	N 260	379
Suicidal and self-injurious behaviours NEC				
Se f-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%)
Se f-injurious ideation				
Intentional self-injury				
Suicidal ideation				
Suicide a tempt		1 (0.3)		
Completed Suicide		1 (0.3)		
Total		4		4 (1.02%)

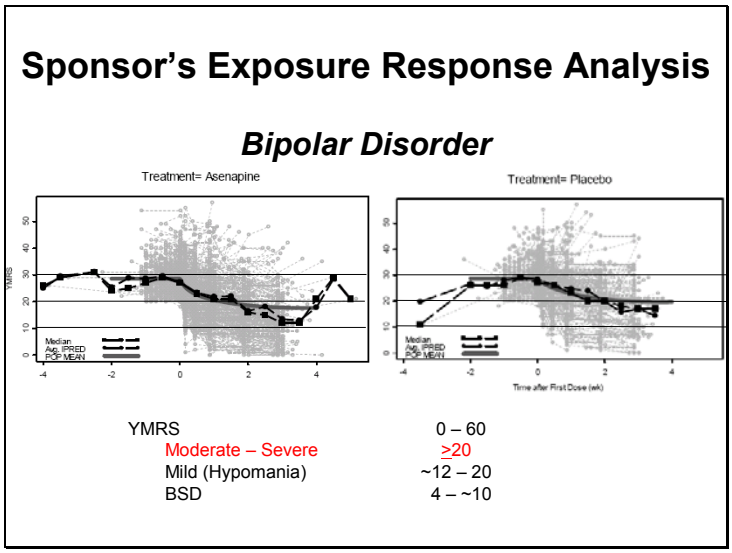
Slide 24

Safety Summary

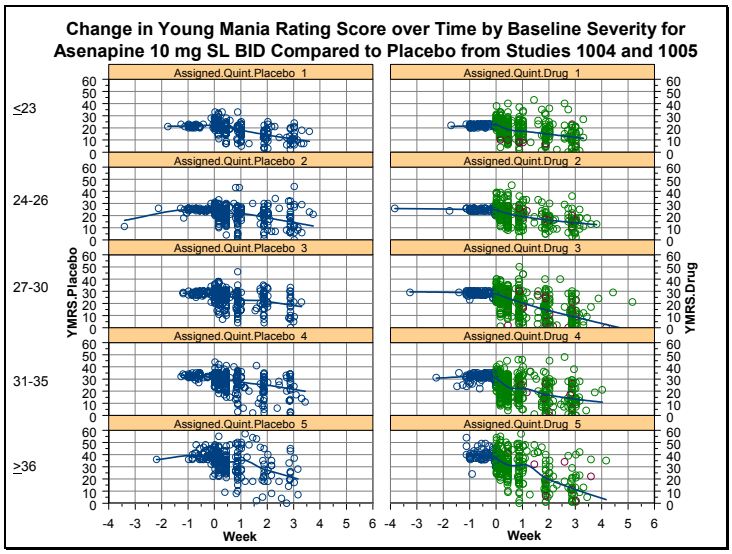
- Death due to Presumptive Agranulocytosis
  - 1 / 313 to 1 / 156 with 1 - 1.2 years of Rx (0.32% - 0.65%)
- Death due to Suicide in Acute Bipolar
  - 1 / 317 (0.32%)
- Deaths due to Cardiotoxicity
  - MI, CHF, Arrhythmias (?)
- Potential Total Incidence in Similar Population
  - > 1 / 117 – 1 / 158 – 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



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	% of Subjects					
	Quintile	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

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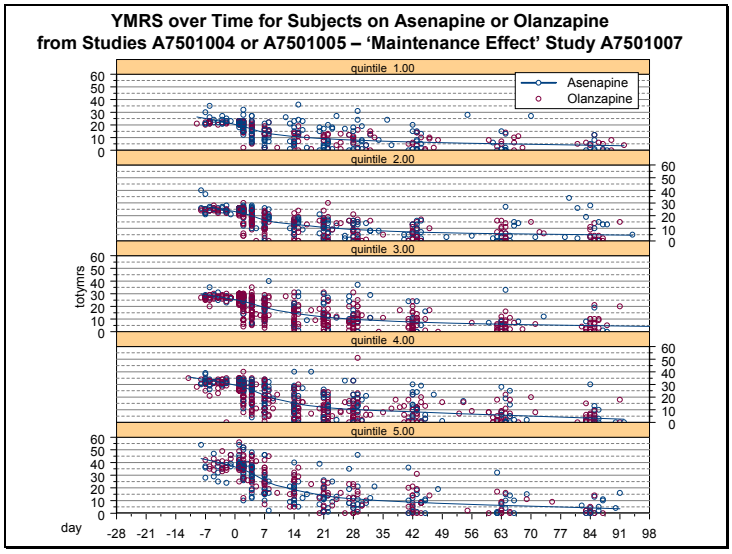
Ethnic Characteristics by Treatment and Disease Severity Study A7501005

Treatment	Group	% of Subjects						
	Quintile	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



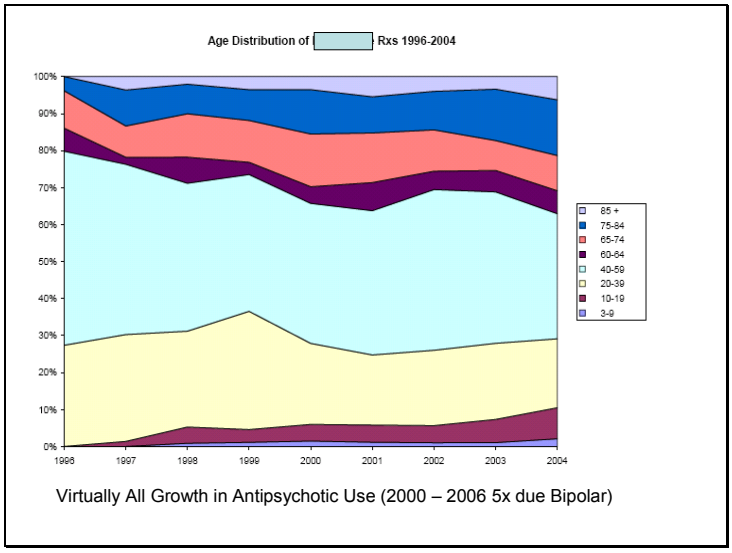
Not placebo controlled.

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

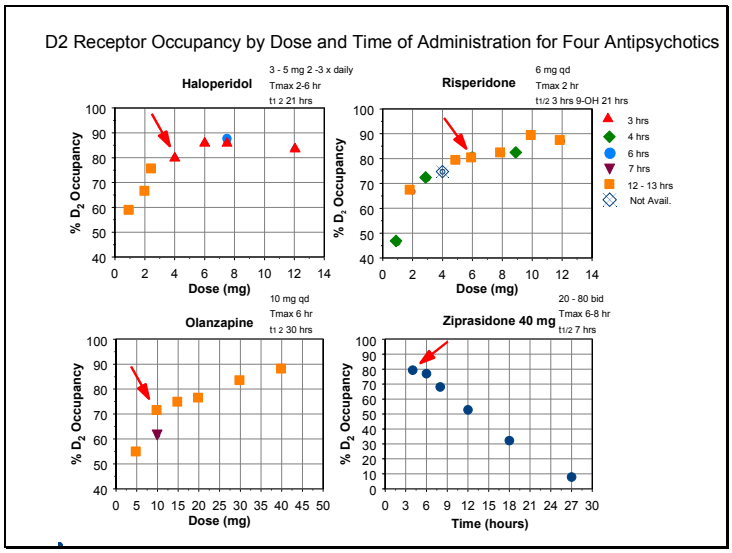
- BSD
  - NIMH May 2007
  - 2.5%
  - Rec. Rx with antipsychotics
- Pediatric Bipolar
  - Full DSM IV criteria
  - Bipolar vs. ADHD
  - Easy to Misdiagnose
- APA – Washington DC; May 2007
  - 43% of Patients Coming to NYU Hospital with Dx Bipolar did not have Bipolar per DSM-IV
  - Overdiagnosed
- Concerns
  - 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		60	58	56	93	102	96	95
Baseline		92.4 (1 9)	96.5 (2.2)	92.2 (2.1)	93.7 (1 1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
Δ to:	Day 4				-3.9 (.8)	-4.0 (0.8)	-5.5 (0.8)	-3.3 (0.8)
	Day 7	-3.9 (1.5)	-6.2 (1.7)	-5.6 (1.8)	-6.5 (1.0)	-7.8 (1.0)	-8.8 (1.0)	-7.1 (1.0)
	Day 14	-5.5 (1.6)	-11.3 (2.0)*	-8.3 (2.4)	-9.8 (1.3)	-13.1 (1.3)	-11.5 (1.3)	-11.6 (1.3)
	Day 21	-6.4 (2.1)	-16.9 (2.4)*	-10.8 (2.8)	-10.5 (1.4)	-12.9 (1.4)	-11.9 (1.4)	-12.8 (1.4)
	Day 28	-6.6 (2.3)	-16.9 (2.5)*	-10.3 (2.7)	-10.7 (1.5)	-14.0 (1.)	-12.0 (1.)	-14.6 (1.5)
	Day 35	-4.7 (2.2)	-16.0 (2.6)*	-10.5 (2.7)	-10.2 (1.6)	-14.5 (1.)*	-13.1 (1.6)	-15.8 (1.6)*
	Day 42	-5.3 (2.3)	-15.9 (2.6)*	-10.9 (2.7)	-11.1 (1.6)	-14.4 (1.6)	-13.5 (1.6)	-16.5 (1.6)*
	Endpoint	–	–	–	-11.1 (1.6)	-14.5 (1.6)	-13.4 (1.6)	-16.5 (1.6)*

Study		041022			041023			
Treatments		Placebo	Asenapine 5/10 mg BID	Olanzapine 10-20 mg QD	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Haloperidol 4 mg BID
Rx Arm (tcaf)								
N		89	85	85	122	109	105	112
Baseline		84.7 (1 1)	86.8 (1.1)	86.5 (1.1)	89.0(0.9)	88.9 (1.0)	89.4 (1.0)	88.5 (1.0)
Δ to:	Day 4	-2.9 (0.7)	-4.2 (0.7)	-3.7 (0.7)	-3.4 (0.7)	-2.9 (0.8)	-4.4 (0.8)	-3.4 (0.8)
	Day 7	-4.8 (1.2)	-4.9 (1.2)	-5.0 (1.1)	-5.9 (0.9)	-7.2 (1.0)	-7.7 (1.0)	-7.3 (1.0)
	Day 14	-7.1 (1.5)	-8.7 (1.5)	-9.2 (1.5)	-8.3 (1.1)	-10.5 (1.2)	-10.4 (1.2)	-11.0 (1.2)
	Day 21	-8.8 (1.6)	-9.5 (1.6)	-9.9 (1.6)	-9.1 (1.3)	-13.2 (1.4)*	-11.6 (1.4)	-13.8 (1.4)*
	Day 28	-8.9 (1.6)	-10.0 (1.6)	-10.7 (1.6)	-9.4 (1.4)	-14.2 (1.)*	-11.7 (1.)	-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)*

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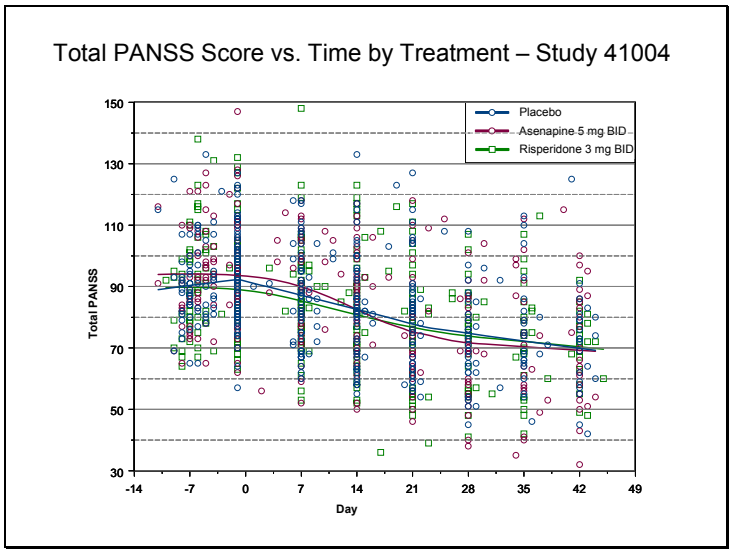
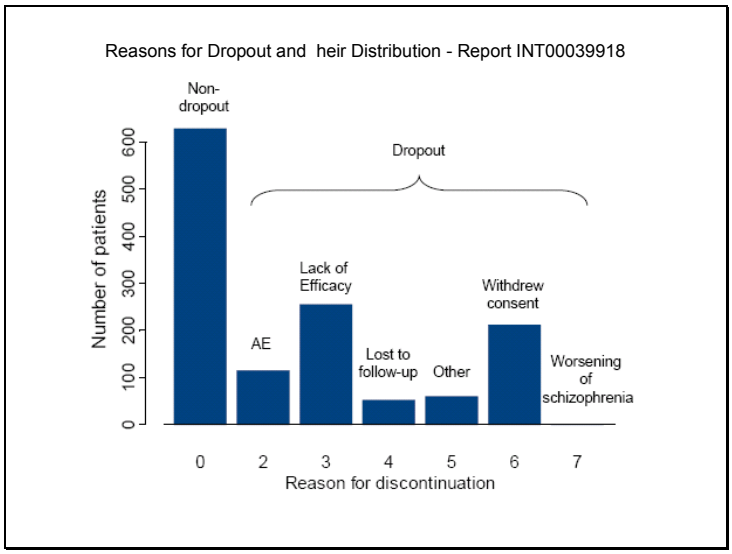


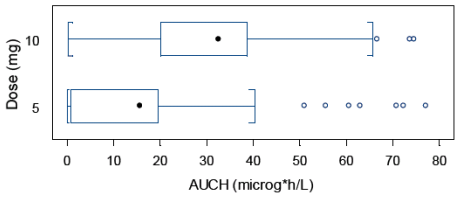
Slide 36



Slide 37

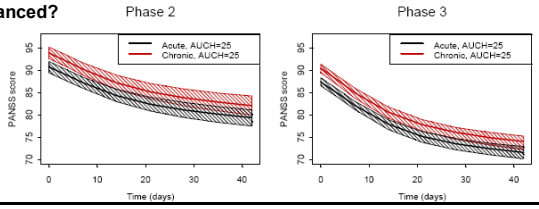
Effect of Duration Of Episode

Asenapine AUC Distribution by Dose for 5 and 10 mg Doses in Phase IIb/III Efficacy Studies – Report INT00039918a



Are groups balanced? Efficacy by subgroup?

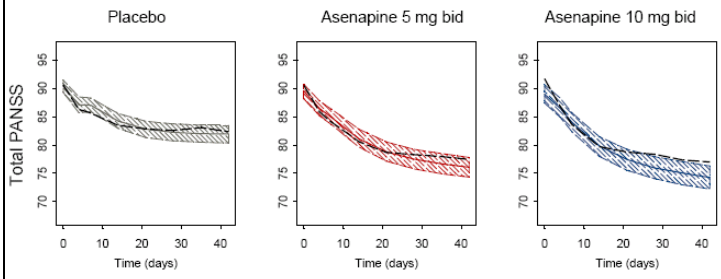
Fit of Individual AUCs versus Time with 90% CIs
Asenapine Dose and Development Phase for Schizophrenic Patients with Current Acute Episodes of Less than 1 month Duration ('Acute') and Greater than 1 month Duration ('Chronic') – Report NT00039918



Slide 38

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

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



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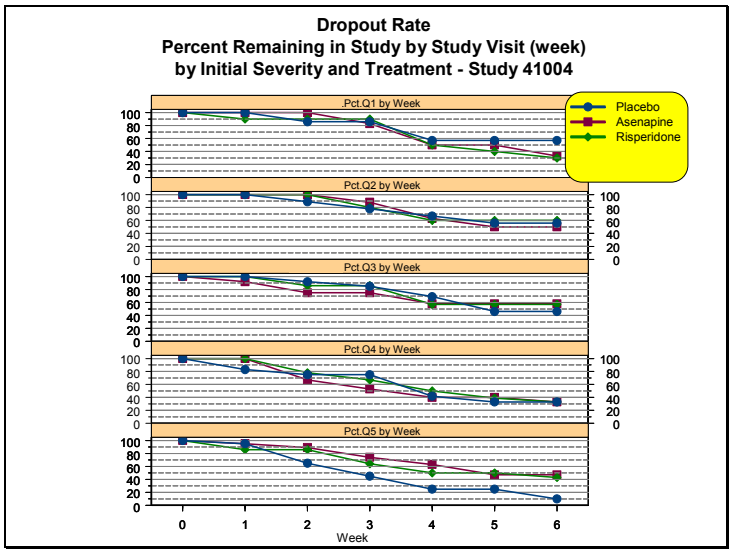

Slide 40

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

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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

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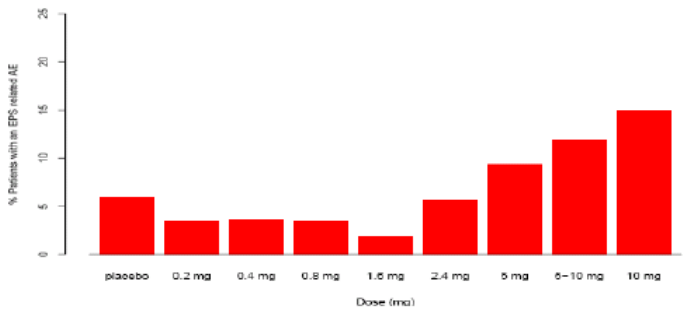
Histogram of EPS Rate vs. Asenapine Dose
Report INT00065682



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)

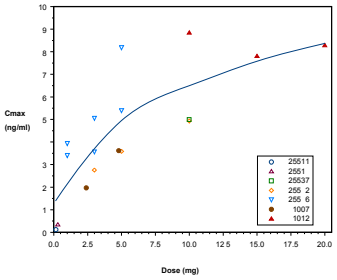
Change 0-13	II	3	0.8	(1.06)	-0.9	(3.20)	2.4	>0.2
	III	10	0.5	(1.41)	2.5	(2.12)	1.7	>0.2
	IIIa	20	-1.8	(1.06)	1.6	(1.83)	1.4	0.056
	+P value		>0.2		0.15			

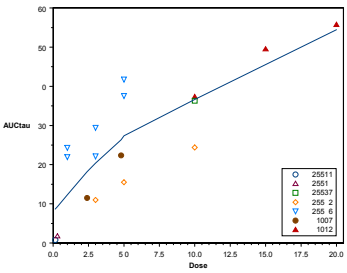
- Significance in Dementia Associated Psychosis (particularly Alzheimer's)? Class Effect?

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





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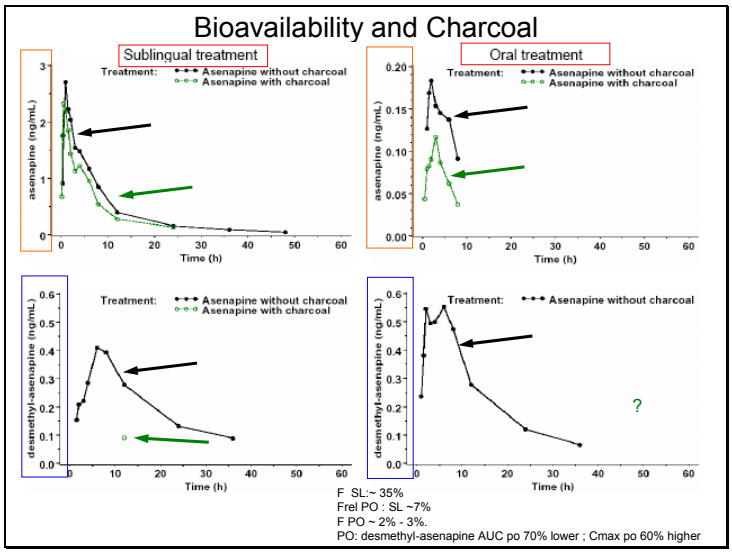

Slide 46

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

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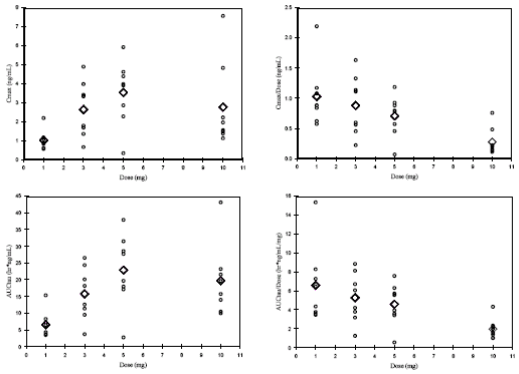
Unnormalized and Dose-normalized Asenapine Cmax and AUCs by Dose in Adolescent Subjects – Study A7501022

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.

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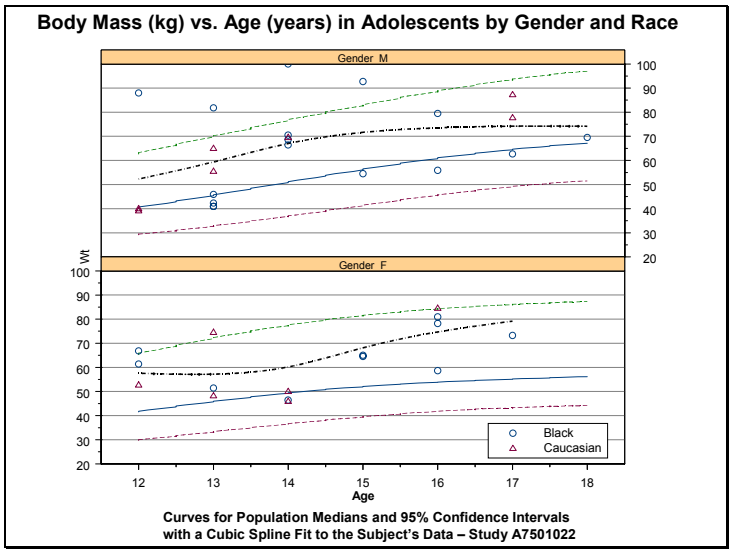

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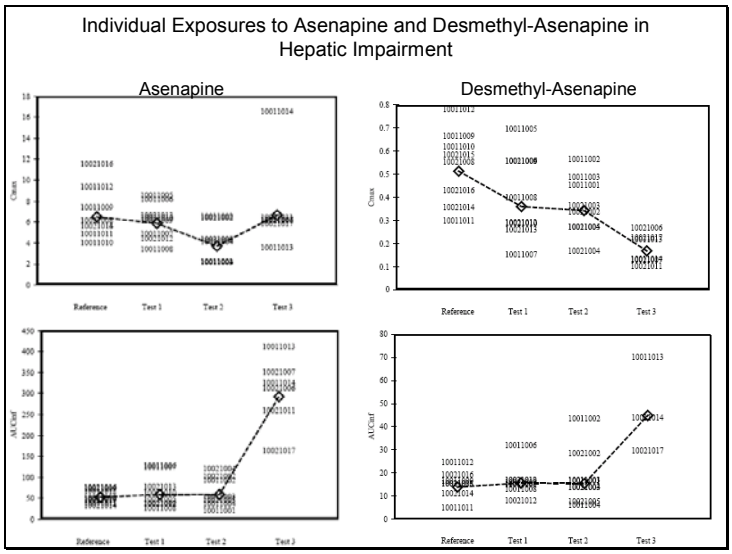

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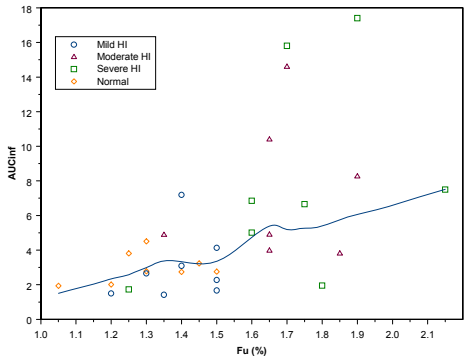
AUC vs. Free Fraction in Subjects with Hepatic Impairment



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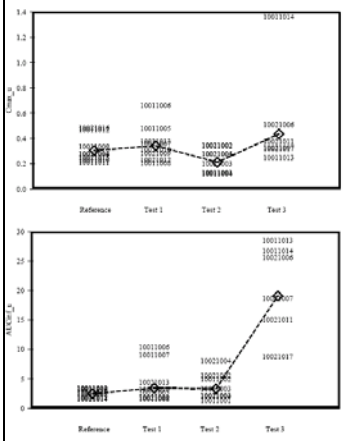
Unbound Asenapine following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018



	Normal	Mild	Moderate	Severe
N	8		8/7	6
Cmaxu (ng/mL)	0.317 ± 0.105 (33.1) 0.217-0.487 [0.278]	0.364 ± 0.148 (40.6) 0.206 - 0.659 [0.330]	0.229 ± 0.0948 (41.4) 0.119 - 0.347 [0.238]	0.524 ± 0.419 (80.1) 0.248 - 1.36 [0.353]
AUCu(0 - tlqc) (ng/mL x hr^{-1})	2.38 ± 0.686 (20.6) 1.55-3.17 [2.38]	3.65 ± 2.45 (67.1) 1.52 - 8.38 [2.78]	3.64 ± 2.16 (59.5) 1.20 - 7.69 [3.00]	16.5 ± 5.06 (30.7) 8.44 - 22.5 [16.4]
AUCu(0-∞) (ng/mL x hr^{-1})	2.57 ± 0.717 (27.9) 1.65-3.42 [2.61]	4.38 ± 3.44 (78.6) 1.61 - 10.4 [2.93]	3.93 ± 2.41 (61.2) 1.30 - 8.09 [3.34]	20.6 ± 7.71 (37.5) 8.83 - 28.4 [22.1]
CL/Fu (mL/min)	35000 ± 10400 (29.9) 24300-50600 [32200]	29400 ± 16900 (57.3) 8020 - 51600 [26600]	29900 ± 18900 (63.2) 10300 - 64100 [25000]	4790 ± 2480 (51.9) 2030 - 9430 [3860]
fu (%)	0.047 ± 0.006 0.040 - 0.057	0.059 ± 0.012 0.046 - 0.080	0.057 ± 0.007 0.046 - 0.067	0.066 ± 0.013 0.053 - 0.092

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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

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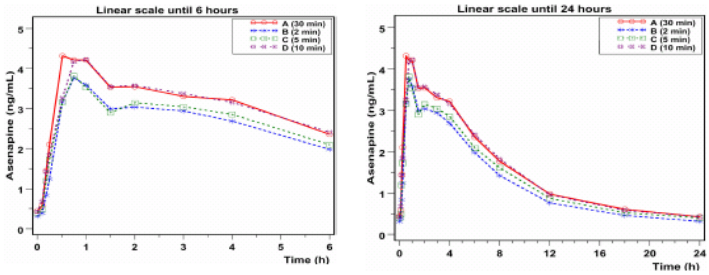
Extrinsic Factors

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

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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

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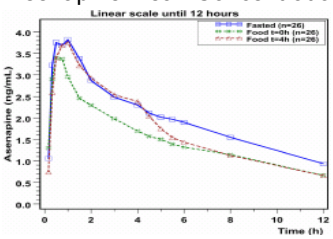
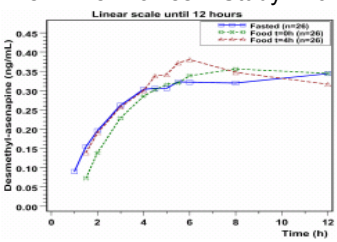
Effect of Food Administration at Various Times on Asenapine Mean Concentration vs. Time Profiles – Study 41029





NOT Truly Fasted
High Energy Supplement

Analyte (n)	Metric	Summary Statistics (A) Fasted	(B) Fed t=0h	(C) Fed t=4h	Geometric Mean Ratios (90% CI) B : A	C : A
Asenapine (n=26)	Tmax (h)	0.98 0.38 - 3.00	0.75 0.32 - 4.00	0.76 0.33 - 4.00	–	–
	Cmax (ng/mL)	4.46 ± 2.57	3.89 ± 2.24	4.27 ± 2.10	0.90 0.73 - 1.11	1.02 0.83 - 1.26
	AUC∞ (ng/mL x hr^{-1})†	38.5 ± 15.6	30.8 ± 14.1	32.6 ± 11.7	0.79 0.66 - 0.94	0.87 0.73 - 1.03
N - Desmethyl - Asenapine (n=26)	Tmax (h)	7.00 4.00 - 12.0	7.9 8.00 - 12.0	6.00 3.00 - 12.0	–	–
	Cmax (ng/mL)	0.395 0.167	0.402 ± 0.139	0.407 ± 0.192	–	–
	AUC∞ (ng/mL x hr^{-1})†	10.9 ± 3.68	11.0 ± 3.30	10.9 ± 4.23	–	–

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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

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Asenapine and Imipramine

Table 1 Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics in the Presence and Absence of Imipramine - Study 25526

Analyte	Asenapine					Desmethyl-Asenapine				
Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)
Parameter (unit)	Asenapine	Asenapine + Imipramine	Asenapine	Asenapine + Imipramine		Asenapine	Asenapine + Imipramine	Asenapine	Asenapine + Imipramine	
n	24	24	–	–	23	24	24	23	–	–
Tmax (h)	0.75 0.50 - 3.0	0.975 0.50 - 2.0	–	–	–	6.00 2.00 - 8.05	3.0 1.5 - 12.0	–	–	–
Cmax (ng/mL)	4.87 (34.1) 2.67 - 9.01	5.39 (36.6) 0.974 - 10.6	4.56	5.33	1.17 1.05 - 1.30	0.490 (33.5) 0.212 - 1.09	0.641 (28.3) 0.299 - 0.981	0.476	0.521	1.09 1.03 - 1.17
AUC∞ (ng/mL x hr^{-1})	38.1 (29.4) 21.9 - 63.8	39.2 (25.2) 10.3 - 54.6	36.1	39.7	1.10 1.01 - 1.20	11.7 (34.8) 7.04 - 25.2	12.1 (29.1) 7.13 - 20.0	11.1	11.6	1.04 0.98 - 1.11

Values are mean (%CV) range except for Tmax where values are median and range.

Table 2 Imipramine and Desmethyl- Imipramine Pharmacokinetic Metrics in the Presence and Absence of Asenapine - Study 25526

Analyte	Imipramine					Desipramine				
Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)
Parameter (unit)	Imipramine	Asenapine + Imipramine	Imipramine	Asenapine + Imipramine		Imipramine	Asenapine + Imipramine	Imipramine	Asenapine + Imipramine	
n	24	24				24	24			
Tlag (h)	1.0 0.5 – 2.0	2.0 1.0 – 4.0				1.5 0.75 – 3.0	2.0 1.0 – 4.0			
Tmax (h)	2.50 1.50 - 4.00	2.00 1.50 - 4.00				3.00 1.50 - 24.0	4.00 1.50 - 24.2			
Cmax (ng/mL)	44.6 (47.1) 10.4 - 98.7	45.0 (44.4) 17.7 - 83.8	41.9	42.0	1.00 0.91 - 1.11	12.6 (45.4) 3.45 - 29.3	13.4 (37.1) 6.22 - 23.4	12.2	12.7	1.04 0.98 - 1.11
AUC∞ (ng/mL x hr^{-1})	542 (58.2) 91.4 - 1175	571 (58.7) 103 - 1364	483	501	1.04 0.97 - 1.10	801* (102) 154 - 3223	869 (105) 133 - 3461	521	560	1.06 0.99 - 1.17
t½ (h)	12.3 (37.7) 4.68 - 23.1	13.7 (44.5) 6.87 - 31.7				32.9* (58.1) 12.6 - 82.8	41.4 (96.1) 13.7 - 190			

Values are mean (%CV) range except for Tmax where values are median and range.

75 mg SD first followed by 5 mg SL SD

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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	Asenapine 5 mg SL BID		Paroxetine 20 mg PO QD	
	Day 7				
	Day 8				
	Day 9				
	Day 10				
	Day 11				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				

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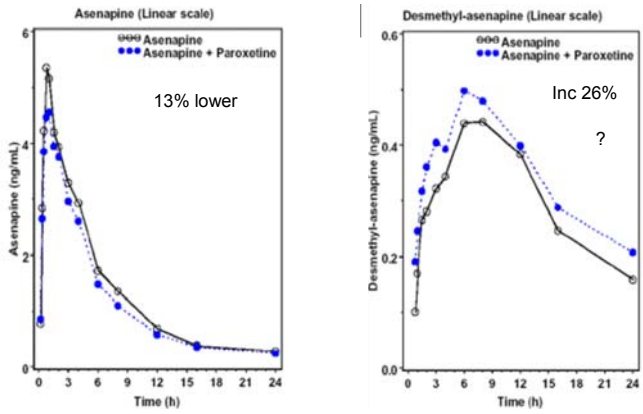
Effect of Paroxetine on Asenapine



20 mg QD & 5 mg SL SD

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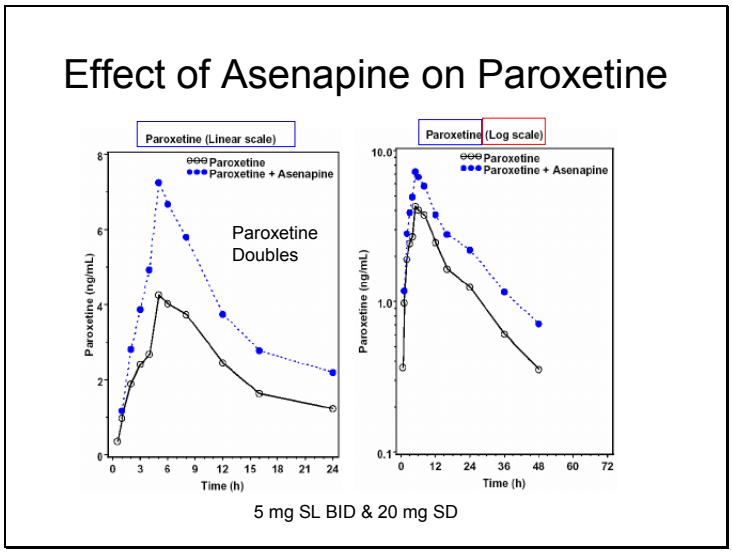

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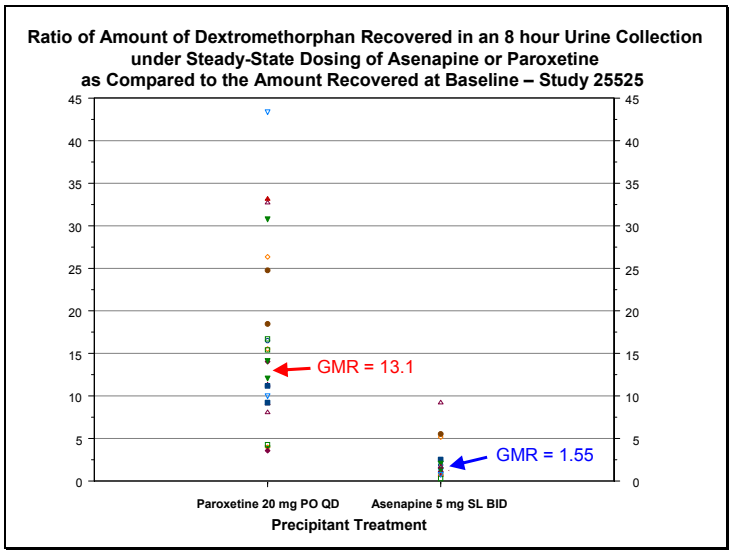

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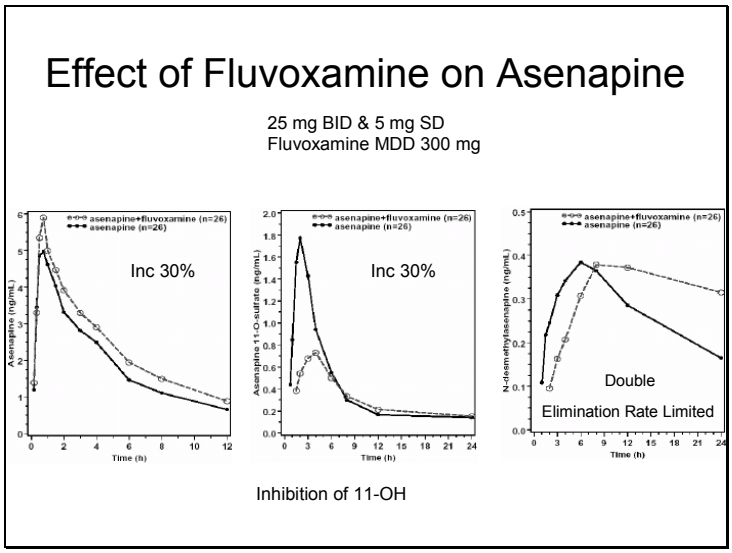

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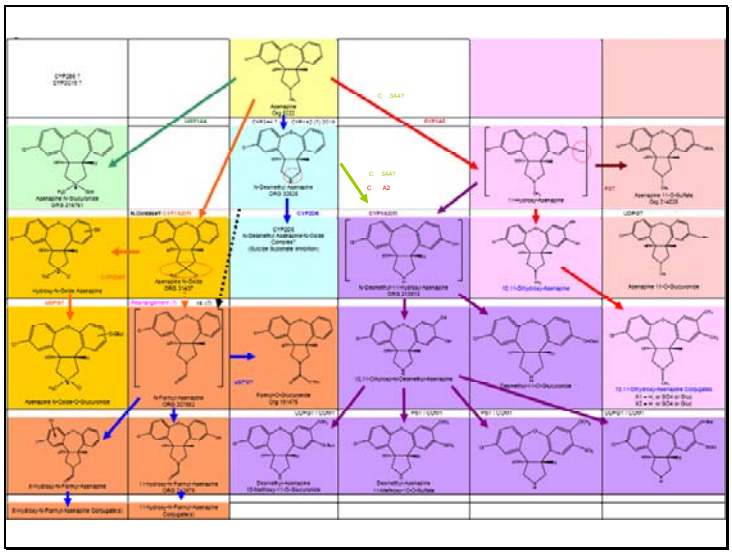

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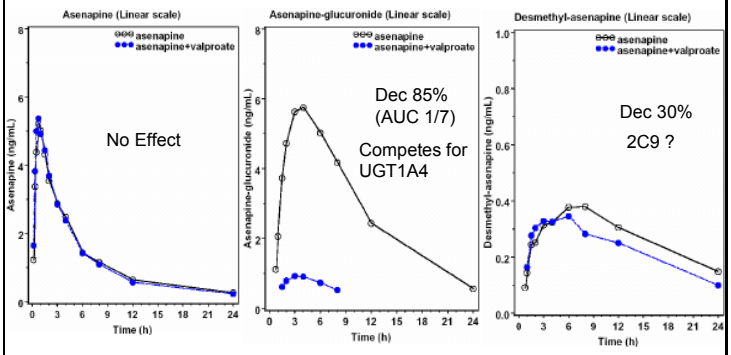
Effect of Valproate on Asenapine

500 mg PO BID & 5 mg SL SD



Shun ing to N-Oxide and / or 11-OH

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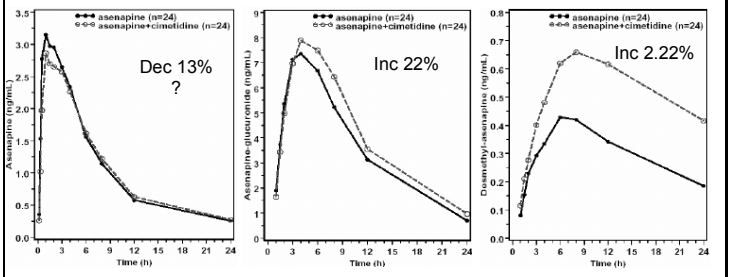
Effect of Cimetidine on Asenapine

800 mg PO BID & 5 mg SD



Cimetidine Imidazole
Agranulocytosis 1 : 100,000
Reported to increase incidence with structurally similar antipsychotics

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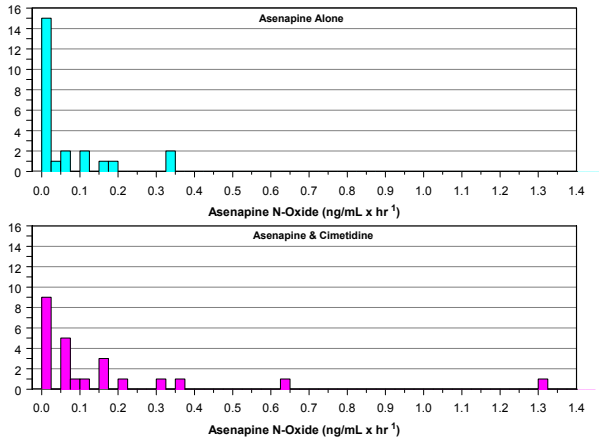
Effect of Cimetidine on Asenapine N-Oxide Exposure



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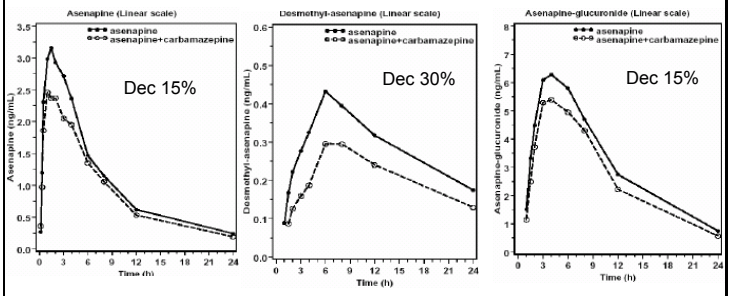
Effect of Carbamazepine on Asenapine

200 mg BID & 5 mg SD



3A4 11-OH ?

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Table 1 Difference in Least Square Means from Placebo of Time Matched Change from Baseline in QTcF (ΔΔQTcF) – Study A7501001

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

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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	28	27 (96.4)	1 (3.6)	0 (0.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 5 mg	33	33 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	26 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	12	12 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quetiapine 375 mg	27	27 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 1[a] through Day 10										
Placebo	28	27 (96.4)	0 (0.0)	1 (3.6)	0 (0.0)	7	6 (85.7)	0 (0.0)	1 (14.3)	0 (0.0)
Asenapine 5 mg	33	29 (87.9)	4 (12.1)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	24 (92.3)	1 (3.8)	1 (3.8)	0 (0.0)	12	9 (75.0)	2 (16.7)	1 (8.3)	0 (0.0)
Quetiapine 375 mg	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	10	9 (90.0)	1 (10.0)	0 (0.0)	0 (0.0)
Day 11 through Day 16										
Placebo	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 10 mg	24	21 (87.5)	3 (12.5)	0 (0.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 20 mg	20	20 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	8 (80.0)	1 (10.0)	1 (10.0)	0 (0.0)
Quetiapine 375 mg	22	22 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)

Source: 11.1.2.01.01.05
[a] Post dose

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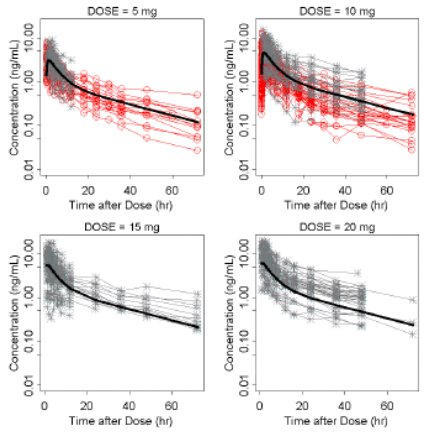
Phase I/II Pop PK Predicted Asenapine Steady State Concentration-Time Profiles
(Base Model) for Selected Doses with Overlaid Observed Concentra ions



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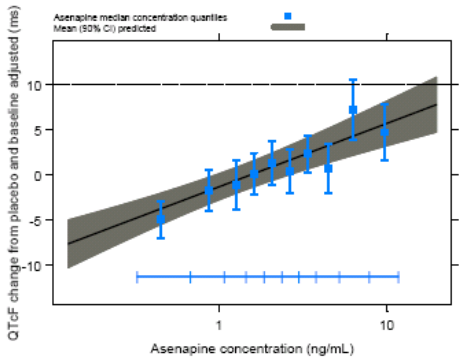
Linear Model of ΔΔQTcF vs. Asenapine Concentration
Overlaid with Mean QT Prolongation with 90% CIs
at the Median-of the 10% Quantiles for Asenapine Concentration



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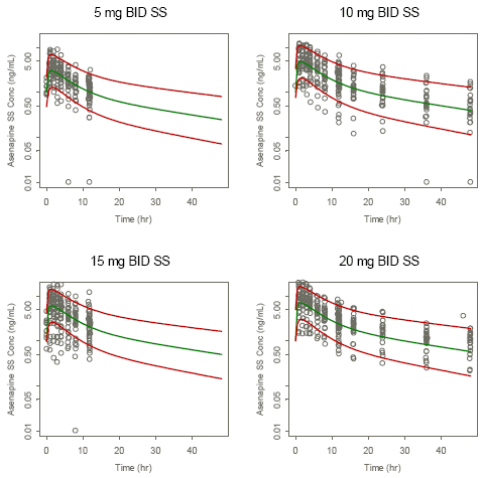
Dose Response
EPS

Slide 74

Back Up Slides

Slide 75

Asenapine Pop PK from TQT Study



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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	
		Medianb	90%CI	Medianb	90%CI	Medianb	90%CI
ΔYMRS[b c]	0	0 [0]	--	0 [0]	--	0 [0]	--
	0.5	-0.8 [-3.7]	(-1.1,-0.4)	-1.5 [-6.3]	(-2.1, -0.7)	**2.4 [9.7]**	(-3.2, -1.2)
	1	-0.8 [-4.1]	(-1.2,-0.4)	-1.5 [-7.0]	(-2.3, -0.7)	**2.4 [10.8]**	(-3.5, -1.1)
	1.5	-0.8 [-4.2]	(-1.2,-0.4)	-1.4 [-7.0]	(-2.2, -0.7)	**2.2 [10.9]**	(-3.4, -1.0)
	2	-0.7 [-4.2]	(-1.1,-0.3)	-1.3 [-7.0]	(-2.1, -0.6)	**2.0 [10.9]**	(-3.2, -1.0)
	2.5	-0.6 [-4.2]	(-1.1,-0.3)	-1.2 [-7.0]	(-2.0, -0.6)	**1.8 [10.9]**	(-3.1, -0.9)
	3	-0.6 [-4.2]	(-1.0,-0.3)	-1.1 [-7.0]	(-1.9, -0.5)	**1.7 [10.9]**	(-2.9, -0.8)

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

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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

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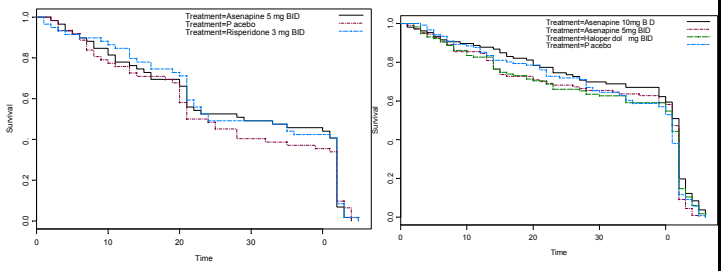
Kaplan-Meir Plots
Survival over Time by Treatment Group - Study 41023



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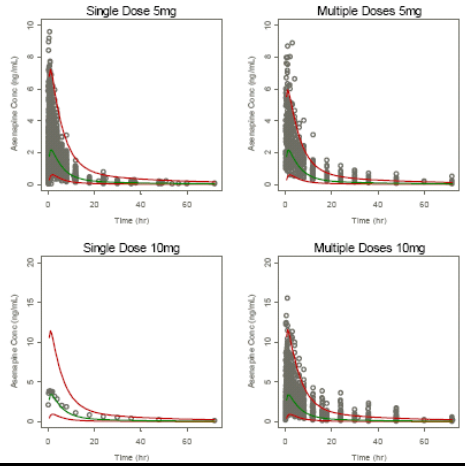
Sponsor's Plot of Phase I/II Pop PK
Unconditional 95% Prediction Interval wi h Overlaid Observations



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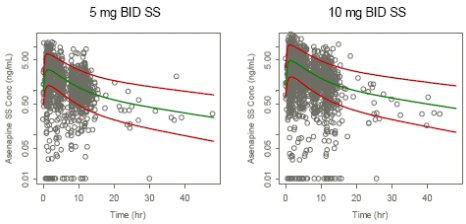
Observed Asenapine Concentrations from All
Phase 2/3 Studies by Dose Overlaid on Unconditional 90% Prediction Interval



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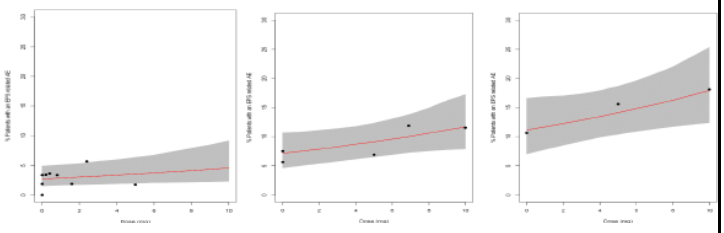
Proportion of Subjects with an EPS-Related Adverse Event in the Different Acute Schizophrenia Trials vs. Dose in Milligrams Report INT00065682



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

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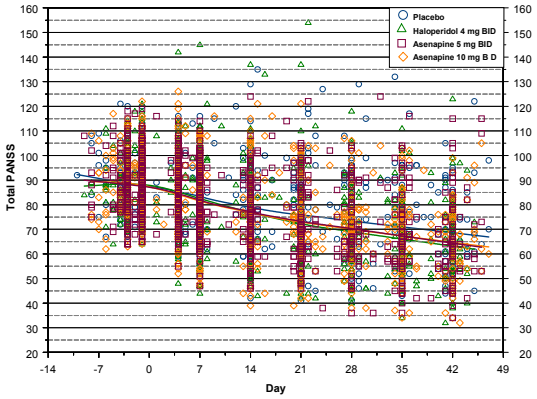
Total PANSS Score vs. Time by Treatment - Study 41023



(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.