APPENDIX VI-24: DEMOGRAPHIC CHARACTERISTICS STUDY 97202 (ALL RANDOMIZED PATIENTS)							
	Age (years)		Gender (%)		Race (%)		
	Mean	Range	Male	Female	White	Black	Other
Ari 20mg	38.1	18-57	72%	28%	60%	32%	8%
Ari 30mg	40.2	20-65	65%	35%	61%	34%	5%
Placebo	38.8	18-62	71%	29%	58%	35%	7%
Risp 6mg	38.6	18-64	72%	28%	55%	39%	6%

APPENDIX VI-25 STUDY 97202 BASELINE SEVERITY OF ILLNESS (ALL RANDOMIZED PATIENTS)			
TX Group	N	Mean PANSS Total Score	Mean CGI-Severity Score
Ari 20mg	101	94.4	4.8
Ari 30mg	101	92.6	4.8
Placebo	103	95.7	4.8
Risperidone	99	94.9	4.8

APPENDIX VI-26 STUDY 97202 ENUMERATION OF ALL PATIENTS BY DISPOSITION				
	Treatment Group			
	Ari 20mg	Ari 30mg	Plac	Risp
Randomized	101	101	103	99
Completed	61	67	52	62
Dropouts by Reason				
-adverse event	11	8	17	8
-lost to follow-up	0	2	0	2
-withdrew consent	18	9	11	12
-protocol violation	0	1	1	1
-noncompliance	1	2	0	1
-poor clinical response	10	12	22	13

APPENDIX VI-27 STUDY 97202 ENUMERATION OF ITT PATIENTS IN-STUDY BY WEEK[54] (N(% OF ITT))				
Week	Ari 20mg	Ari 30mg	Placebo	Risperidone
Baseline (ITT)	98	96	103	95
1	96(98%)	95(99%)	102(99%)	95(100%)
2	77(79%)	79(82%)	77(75%)	84(88%)
3	68(69%)	73(76%)	56(54%)	68(72%)
4	61(62%)	68(71%)	52(50%)	61(64%)

[54] Based on patients with PANSS total score data.

APPENDIX VI-28
STUDY 97202
MEAN CHANGE FROM BASELINE IN THE PANSS TOTAL SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 20mg	98	94.0	77	-15.5	68	-18.6	61	-23.4	98	-14.5
Ari 30mg	96	92.3	79	-13.8	73	-19.0	68	-20.2	96	-13.9
Risperidone	95	93.6	84	-14.2	68	-18.3	61	-22.7	95	-15.7
Placebo	103	95.0	77	-8.9	56	-15.4	52	-18.2	103	-5.0
2-sided p-values										
20mg vs. Plac	0.670		0.023		0.348		0.132		0.001	
30mg vs. Plac	0.270		0.089		0.288		0.552		0.003	
Risp vs. Plac	0.557		0.062		0.394		0.191		<0.001	

APPENDIX VI-29
STUDY 97202
MEAN CHANGE FROM BASELINE IN THE PANSS POSITIVE SUBSCALE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 20mg	98	24.8	77	-5.1	68	-6.2	61	-7.5	98	-4.9
Ari 30mg	96	24.0	79	-3.9	73	-5.1	68	-5.7	96	-3.9
Risperidone	95	23.9	84	-5.0	68	-5.8	61	-7.3	95	-5.2
Placebo	103	24.5	77	-2.5	56	-4.7	52	-5.3	103	-1.8
2-sided p-values										
20mg vs. Plac	0.710		0.002		0.167		0.045		0.001	
30mg vs. Plac	0.433		0.111		0.721		0.700		0.018	
Risp vs. Plac	0.401		0.003		0.277		0.073		<0.001	

APPENDIX VI-30
STUDY 97202
MEAN CHANGE FROM BASELINE IN THE CGI-SEVERITY OF ILLNESS SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 20mg	98	4.8	77	-0.6	69	-0.8	61	-1.0	98	-0.5
Ari 30mg	96	4.7	79	-0.6	73	-0.8	68	-0.9	96	-0.6
Risperidone	95	4.8	84	-0.7	68	-0.8	61	-1.1	95	-0.7
Placebo	103	4.8	77	-0.3	56	-0.6	52	-0.7	103	-0.2
2-sided p-values										
20mg vs. Plac	0.926		0.003		0.200		0.165		0.030	
30mg vs. Plac	0.538		0.011		0.328		0.335		0.006	
Risp vs. Plac	0.737		0.001		0.167		0.043		<0.001	

APPENDIX VI-31: STUDY 138001 PRINCIPAL INVESTIGATORS			
Center	Investigator	Center	Investigator
001	David Adson, M.D.	033	David Daniel, M.D.
002	Mohammed Bari, M.D.	035	Marshall R. Thomas, M.D.
003	Joseph Bona, M.D., Ph.D.	037	Adam Lowy, M.D.
004	David L. Garner, M.D.	038	Bijan Bastani, M.D.
005	Hisham Hafez, M.D.	040	Jose Canive, M.D.
007	Philip G. Janicak, M.D.	041	Andrew Cutler, M.D.
008	Richard P. Johnson, M.D.	043	Alan I. Green, M.D.
009	Richard Josiassen, Ph.D.	045	Eduardo Dunayevich, M.D.
010	Mary Ann Knesevich, M.D.	046	Joseph Fanelli, M.D.
011	Gunnar Larson, M.D.	047	Mark R. Bloch, M.D.
012	Mark Lerman, M.D.	050	Naveed Iqbal, M.D.
013	Joseph P. McEvoy, M.D.	051	Jeffrey A. Lieberman, M.D.
014	Richard Pearlman, M.D.	054	Rudra Prakash, M.D.
015	William Petrie, M.D.	055	Jeffrey L. Rausch, M.D.
016	Robert Moreines, M.D.	056	Neil Richtand, M.D., Ph.D.
017	Valerie Smith-Gamble, M.D.	057	Adam Wolkins, M.D.
020	Seeth Vivek, M.D.	062	Craig Wronski, D.O.
021	Jesse Carr, M.D.	064	Osvaldo Caro, M.D.
022	Louise Beckett, M.D.	066	S. Craig Risch, M.D.
023	Harold Harsch, M.D.	068	Michael Woodbury, M.D.
024	Patricia Solbach, Ph.D.	069	Evagelos Coskinas, M.D.
025	Samuel Shillcutt, Pharm.D., Ph.D.	070	Kathleen Degen, M.D.
026	Richard Jaffe, M.D.	072	Roberto Gill, M.D.
027	Cherian Verghese, M.D.	073	Sean Flynn, M.D.
028	Tram K. Tran-Johnson, Pharm.D., Psy.D.	074	Alain Labelle, M.D.
029	Alexander L. Miller, M.D.	075	Wilson Lit, M.D.
030	Harold D. Udelman, M.D.	076	Bill Macewan, M.D.
031	David W. Brown, M.D.	082	Carlos Figueroa, M.D.
032	Timothy Reid, M.D.		

APPENDIX VI-32: DEMOGRAPHIC CHARACTERISTICS STUDY 138001 (ALL RANDOMIZED PATIENTS)							
	Age (years)		Gender (%)		Race (%)		
	Mean	Range	Male	Female	White	Black	Other
Ari 10mg	40.0	18-73	77%	23%	50%	27%	23%
Ari 15mg	40.0	19-68	75%	25%	54%	26%	20%
Ari 20mg	40.4	19-69	82%	18%	52%	29%	19%
Placebo	41.2	19-76	77%	23%	45%	34%	21%

APPENDIX VI-33 STUDY 138001 BASELINE SEVERITY OF ILLNESS (ALL RANDOMIZED PATIENTS)			
TX Group	N	Mean PANSS Total Score	Mean CGI-Severity Score
Ari 10mg	106	92.7	4.8
Ari 15mg	106	93.2	4.8
Ari 20mg	100	92.5	4.7
Placebo	108	92.3	4.6

APPENDIX VI-34
STUDY 138001
ENUMERATION OF ALL PATIENTS BY DISPOSITION

	Treatment Group			
	Ari 10mg	**Ari 15mg**	**Ari 20mg**	**Plac**
Randomized	106	106	100	108
Completed DB Treatment	43	32	37	30
Dropouts from DB TX by Reason				
-entered OL rescue after wk 3	28	37	22	44
-lack of efficacy	5	8	11	11
-adverse event	11	3	5	6
-withdrew consent	18	24	18	13
-patient unreliability	1	1	1	0
-lost to follow-up	0	0	4	0
-other cause	0	1	2	4

APPENDIX VI-35 STUDY 138001 ENUMERATION OF ITT PATIENTS IN-STUDY BY WEEK[55] (N(% OF EFFICACY SAMPLE))				
Week	Ari 10mg	Ari 15mg	Ari 20mg	Plac
N-Efficacy Sample	103	103	97	107
1	89(86%)	95(92%)	87(90%)	100(93%)
2	86(83%)	89(86%)	81(84%)	88(82%)
3	78(76%)	82(80%)	68(70%)	82(77%)
4	51(50%)	41(40%)	49(51%)	42(39%)
5	45(44%)	37(36%)	40(41%)	31(29%)
6	42(41%)	34(33%)	39(40%)	30(28%)

[55] Based on patients with PANSS total score data.

APPENDIX VI-36
STUDY 138001
MEAN CHANGE FROM BASELINE IN THE PANSS TOTAL SCORE

	Observed Cases								LOCF	
	Baseline		Week 3		Week 4		Week 6		Week 6	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 10mg	103	92.76	78	-15.69	51	-23.69	42	-33.42	103	-15.04
Ari 15mg	103	93.27	82	-10.59	41	-22.51	34	-31.92	103	-11.73
Ari 20mg	97	92.29	68	-14.99	49	-20.86	39	-28.91	97	-14.44
Placebo	107	92.40	82	-7.45	42	-18.96	30	-26.86	107	-2.33
2-sided p-values										
10mg vs. Plac	0.902		0.008		0.212		0.113		<0.001	
15mg vs. Plac	0.763		0.300		0.373		0.242		0.004	
20mg vs. Plac	0.969		0.018		0.619		0.624		<0.001	

APPENDIX VI-37
STUDY 138001
MEAN CHANGE FROM BASELINE IN THE PANSS-DERIVED BPRS CORE SCORE

	Observed Cases								LOCF	
	Baseline		Week 3		Week 4		Week 6		Week 6	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 10mg	103	16.87	78	-4.04	51	-5.56	42	-7.53	103	-3.91
Ari 15mg	103	16.78	82	-2.49	41	-5.28	34	-7.18	103	-2.88
Ari 20mg	97	16.69	68	-3.65	49	-4.63	39	-6.40	97	-3.56
Placebo	107	16.78	82	-2.21	42	-4.56	30	-5.77	107	-1.37
2-sided p-values										
10mg vs. Plac	0.825		0.003		0.183		0.037		<0.001	
15mg vs. Plac	0.998		0.648		0.366		0.110		0.014	
20mg vs. Plac	0.851		0.025		0.924		0.465		<0.001	

APPENDIX VI-38
STUDY 138001
MEAN CHANGE FROM BASELINE IN THE PANSS NEGATIVE SUBSCALE

	Observed Cases								LOCF	
	Baseline		Week 3		Week 4		Week 6		Week 6	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 10mg	103	23.39	78	-3.58	51	-5.29	42	-7.37	103	-3.52
Ari 15mg	103	23.37	82	-2.06	41	-4.91	34	-7.28	103	-2.65
Ari 20mg	97	23.31	68	-3.53	49	-5.02	39	-6.89	97	-3.33
Placebo	107	22.65	82	-1.13	42	-3.99	30	-5.21	107	+0.08
2-sided p-values										
10mg vs. Plac	0.455		0.006		0.247		0.075		<0.001	
15mg vs. Plac	0.467		0.287		0.437		0.102		0.002	
20mg vs. Plac	0.511		0.010		0.362		0.170		<0.001	

APPENDIX VI-39

MODEL-BASED MEAN CHANGE FROM BASELINE IN THE PANSS TOTAL SCORE (LOCF) FOR DEMOGRAPHIC AND BASELINE SCORE SUBGROUPS

POOL OF FIVE SHORT-TERM, PLACEBO-CONTROLLED STUDIES IN SCHIZOPHRENIA

		PANSS Total Score at Endpoint							
Subgroup		N	Placebo	N	Haloperidol	N	Risperidone	N	Aripiprazole
Gender	Men	301	-2.8	137	-13.4	67	-14.1	661	-12.6
	Women	103	-3.2	49	-14.1	28	-15.3	224	-13.9
Age (years)	< 50	351	-1.8	162	-14.2	87	-14.2	743	-13.3
	≥ 50	53	-9.8	24	-9.4	8	-17.6	142	-10.8
Race	White	204	-2.0	115	-14.4	53	-15.0	492	-12.7
	Black	140	-2.4	51	-11.5	36	-15.8	260	-13.7
	Hispanic	42	-10.9	14	-14.1	4	-1.8	91	-9.0
	Asian	10	14.1	1	-14.0	1	11.4	21	-22.5
Baseline PANSS Total	Above Median (> 91)	196	-5.7	105	-18.1	49	-17.1	433	-17.9
	Below Median (≤ 91)	208	0.1	81	-9.4	46	-11.4	452	-8.0

APPENDIX VI-40
SUMMARY OF EFFICACY RESULTS AT STUDY ENDPOINT

Study	Treatment	Variable	Observed Cases		LOCF	
			p-value	Superiority[56]	p-value	Superiority
93202	Aripiprazole	BPRS Total	Not Reported by Sponsor		0.173	ns
		CGI-severity			0.045	
	Haloperidol	BPRS Total			0.010	*
		CGI-severity			0.003	
94202	Ari 2mg	BPRS Core	0.8521	ns	0.7034	ns
		CGI-improvement	0.9639		0.5860	
	Ari 10mg	BPRS Core	0.0881	ns	0.8939	ns
		CGI-improvement	0.4416		0.2260	
	Ari 30mg	BPRS Core	0.4901	ns	0.1165	ns
		CGI-improvement	0.4731		0.0055	
	Haloperidol	BPRS Core	0.7817	ns	0.0495	ns
		CGI-improvement	0.9537		0.0811	
97201	Ari 15mg	PANSS total	<0.001	*	<0.001	*
		PANSS positive	<0.001		<0.001	
		CGI-severity	0.001		<0.001	
	Ari 30mg	PANSS total	0.040	*	0.009	*
		PANSS positive	0.001		0.001	
		CGI-severity	0.053		0.019	
	Haloperidol	PANSS total	0.163	ns	0.001	*
		PANSS positive	0.023		<0.001	
		CGI-severity	0.147		0.002	

[56] *=treatment is statistically superior to placebo after multiplicity adjustment; ns=not superior.

APPENDIX VI-40
SUMMARY OF EFFICACY RESULTS AT STUDY ENDPOINT

Study	Treatment	Variable	Observed Cases		LOCF	
			p-value	Superiority[56]	p-value	Superiority
97202	Ari 20mg	PANSS total	0.132	ns	0.001	*
		PANSS positive	0.045		0.001	
		CGI-severity	0.165		0.030	
	Ari 30mg	PANSS total	0.552	ns	0.003	*
		PANSS positive	0.700		0.018	
		CGI-severity	0.335		0.006	
	Risperidone	PANSS total	0.191	ns	<0.001	*
		PANSS positive	0.073		<0.001	
		CGI-severity	0.043		<0.001	
138001	Ari 10mg	PANSS total	0.113	ns	<0.001	*
	Ari 15mg	PANSS total	0.242		0.004	
	Ari 20mg	PANSS total	0.624		<0.001	
	Ari 10mg	PANSS/BPRS core	0.037	*	<0.001	*
		PANSS negative	0.075		<0.001	
	Ari 15mg	PANSS/BPRS core	0.110	ns	0.014	*
		PANSS negative	0.102		0.002	
	Ari 20mg	PANSS/BPRS core	0.465	ns	<0.001	*
		PANSS negative	0.170		<0.001	

APPENDIX VI-41
SUMMARY OF MULTIPLICITY ADJUSTMENT METHODOLOGIES FOR P-VALUE INTERPRETATION

Study	TX Arm	Criteria for Statistical Superiority over Placebo
93202	Aripiprazole	$p \leq 0.05$ on BOTH primary variables
	Haloperidol	$p \leq 0.05$ on BOTH primary variables
94202	Ari 2mg	$p \leq 0.017$ on BOTH primary variables
	Ari 10mg	$p \leq 0.017$ on BOTH primary variables
	Ari 30mg	$p \leq 0.017$ on BOTH primary variables
	Haloperidol	$p \leq 0.05$ on BOTH primary variables
97201	Ari 15mg	If 30mg superior, $p \leq 0.05$ on ALL 3 primary variables. If 30mg not superior, 15mg not tested.
	Ari 30mg	$p \leq 0.05$ on ALL 3 primary variables
	Haloperidol	$p \leq 0.05$ on ALL 3 primary variables
97202	Ari 20mg	If 30mg superior, $p \leq 0.05$ on ALL 3 primary variables. If 30mg not superior, 15mg not tested.
	Ari 30mg	$p \leq 0.05$ on ALL 3 primary variables
	Risperidone	$p \leq 0.05$ on ALL 3 primary variables
138001 (1°variable)	Ari 10/15/20	$p \leq 0.05$ for all 3 doses <u>OR</u> $p \leq 0.025$ for any 2 doses <u>OR</u> $p \leq 0.0167$ for any 1 dose.
138001 (2°variables)	Ari 10mg	For BPRS core score, $p \leq 0.05$. For PANSS negative subscale, $p \leq 0.05$ <u>AND</u> $p \leq 0.05$ for BPRS core.
	Ari 15mg	For BPRS core score, $p \leq 0.05$. For PANSS negative subscale, $p \leq 0.05$ <u>AND</u> $p \leq 0.05$ for BPRS core.
	Ari 20mg	For BPRS core score, $p \leq 0.05$. For PANSS negative subscale, $p \leq 0.05$ <u>AND</u> $p \leq 0.05$ for BPRS core.

SAFETY

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Body as a Whole	
Psychosocial support	48(1.02%)
Accidental injury	37(0.79%)
Suicide attempt	26(0.55%)
Overdose	23(0.49%)
Chest pain	18(0.38%)
Asthenia	8(0.17%)
Fever	7(0.15%)
Sepsis	7(0.15%)
Hernia	6(0.13%)

[57] Events are listed by preferred (coded) term. The incidence is corrected for gender as approporiate. In addition, the following events were reported as SAE's in only one patient each: abscess, AIDS, allergic reaction, craving alcohol, adjustment disorder, food poisoning, hyperplastic polyp, multisystem failure, back pain, rigidity, arrhythmia, arteriosclerosis, dissecting artery, AV block, bigeminy, bradycardia, congestive heart failure, coronary artery disorder, peripheral vascular disorder, ventricular extrasystoles, orthostatic hypotension, palpitation, phlebitis, tachycardia, supraventricular tachycardia, thrombosis, varicose vein, anorexia, appendicitis, gastrointestinal carcinoma, gastrointestinal disorder, dysphagia, hepatitis, fecal impaction, jaundice, nausea and vomiting, esophgeal stenosis, hypothyroidism, macrocytic anemia, coagulation time decreased, leukocytosis, thrombocytopenic purpura, thrombocythemia, electrolyte abnormality, hypokalemia, hyponatremia, LDH increased, malnourished, hypoglycemic reaction, arthritis, bone disorder, rhabdomyolysis, abnormal gait, coma, dysarthria, dyskinesia, dystonia, hypertonia, cerebral ischemia, CNS neoplasm, nervousness, neuralgia, salivation increased, somnolence, stress, subdural hematoma, tremor, asphyxia, lung carcinoma, cough increased, respiratory disorder, pulmonary embolism, hemoptysis, pleural effusion, basal cell carcinoma, psoriasis, rash, cataract, retinal disorder, vestibular disorder, eardrum rupture, hip fracture, menstrual disorder, ovarian disorder, vaginal disorder, dysmenorrhea, uterine hemorrhage, menorrhagia, prostate carcinoma, prostatic disorder, abnormal kidney function, urinary tract infection, pyelonephritis, and urinary retention.

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Abdominal pain	6(0.13%)
Cellulitis	5(0.11%)
Infection	5(0.11%)
Carcinoma	3(0.06%)
Gangrene	3(0.06%)
Neoplasm	3(0.06%)
Intentional injury	2(0.04%)
Mendelson's syndrome	2(0.04%)
Neuroleptic malignant syndrome	2(0.04%)
Cardiovascular	
Myocardial infarction	10(0.21%)
Syncope	8(0.17%)
Cardiac arrest	5(0.11%)
Hypertension	4(0.08%)
Abnormal ECG	3(0.06%)
Heart failure	3(0.06%)
Deep vein thrombosis	3(0.06%)
Hypotension	2(0.04%)
Myocardial ischemia	2(0.04%)
Shock	2(0.04%)
Digestive	
Vomiting	7(0.15%)
Cholecystitis	5(0.11%)
Cholelithiasis	3(0.06%)
Gastritis	3(0.06%)

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Gastroenteritis	3(0.06%)
Nausea	3(0.06%)
Intestinal obstruction	3(0.06%)
Pancreatitis	3(0.06%)
Abnormal liver function tests	2(0.04%)
Diarrhea	2(0.04%)
Rectal disorder	2(0.04%)
Dyspepsia	2(0.04%)
Gastrointestinal hemorrhage	2(0.04%)
Liver damage	2(0.04%)
Hematologic	
Anemia	5(0.11%)
Leukopenia	3(0.06%)
Metabolic/Nutritional	
Dehydration	8(0.17%)
CPK increased	5(0.11%)
Diabetes mellitus	4(0.08%)
Alcohol intolerance	3(0.06%)
Hyperglycemia	3(0.06%)
Cachexia	2(0.04%)
Hypoglycemia	2(0.04%)
Weight loss	2(0.04%)
Musculoskeletal	
Myasthenia	2(0.04%)
Nervous	

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Psychosis	382(8.11%)
Schizophrenic reaction	130(2.76%)
Suicidal thoughts	58(1.23%)
Depression	41(0.87%)
Agitation	24(0.51%)
Hallucination	24(0.51%)
Manic reaction	23(0.49%)
Paranoid reaction	22(0.47%)
Anxiety	21(0.45%)
Hostility	18(0.38%)
Psychiatric decompensation	15(0.32%)
Seizure	13(0.28%)
Manic depressive reaction	12(0.25%)
Delusions	10(0.21%)
Drug dependence	10(0.21%)
Confusion	7(0.15%)
Insomnia	7(0.15%)
Abnormal behavior	6(0.13%)
Mental disorder	5(0.11%)
Extrapyramidal syndrome	5(0.11%)
Akathisia	4(0.08%)
Abnormal thinking	3(0.06%)
Cerebrovascular accident	3(0.06%)
Grand mal seizure	3(0.06%)
Withdrawal syndrome	3(0.06%)

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Delirium	2(0.04%)
Personality disorder	2(0.04%)
Lightheadedness	2(0.04%)
Respiratory	
Pneumonia	22(0.47%)
Lung disorder	10(0.21%)
Dyspnea	6(0.13%)
Asthma	4(0.08%)
Bronchitis	3(0.06%)
Pulmonary edema	2(0.04%)
Aspiration pneumonia	2(0.04%)
Respiratory failure	2(0.04%)
Skin	
Skin Ulcer	3(0.06%)
Skin melanoma	2(0.04%)
Urogenital	
Pregnancy	3(0.16%)
Breast carcinoma	2(0.04%)
Kidney failure	2(0.04%)

APPENDIX VII-2: DEATH LINE LISTING NON-JAPANESE PHASE 2/3 STUDIES[58]					
Patient Unique ID Number	Age	Sex	Day of Onset/ Day of Last Dose	Last Dose (mg/day)	Cause of Death (as determined from Narrative Summary review)
TREATMENT=ARIPIPRAZOLE					
97201-7-8	38	M	96/83	30	Overdose (EtOH/fluoxetine)
97201-8-11	47	M	36/35	30	Asphyxia (house fire)
97201-18-10	68	F	54/53	5	Suicide (hanging)
97201-22-4	47	M	57/57	30	Myocardial infarction
97301-120-1	60	F	11/11	30	Suicide (hanging)
98213-602-5	60	M	313/312	15	Myocardial infarction
98304-437-59	59	F	553/553	15	Suicide (stabbing)
98304-438-57	30	M	129/128	30	Heart failure (congenital defect)
98304-439-60	45	F	126/126	30	Suicide (drowning)
98304-440-63	40	F	45/44	30	Unknown (underlying cardiomegaly/CAD)
98304-485-66	27	M	18/18	30	Suicide (hanging)
98304-509-50	28	M	10/4	30	Suicide (hanging)
98304-558-58	27	M	7/7	30	Suicide (hanging)
98304-559-50	30	M	525/616	30	Metastatic melanoma
98304-568-53	28	F	44/43	20	Suicide (jumping)

[58] Days were counted relative to the start of dosing with the designated treatment. Onset refers to the start of the adverse event deemed to be causally related to death when such a premorbid event was identified; otherwise, it is the day of death. Dose at onset equals zero when the designated treatment was discontinued prior to onset.

APPENDIX VII-2:
DEATH LINE LISTING
NON-JAPANESE PHASE 2/3 STUDIES[58]

Patient Unique ID Number	Age	Sex	Day of Onset/ Day of Last Dose	Last Dose (mg/day)	Cause of Death (as determined from Narrative Summary review)
138001-12-492	54	M	95/52	20	Suicide (wrist laceration)
138001-13-151	41	M	57/54	Unknown	Suicide
138001-68-275	62	F	107/103	20	Respiratory distress synd. assoc. w/pancreatitis
138001-68-454	57	F	95/93	10	Skull fracture assoc. w/seizure
138002-75-339	46	M	61/60	Unknown	Murder (strangulation)
138004-3-25	86	F	271/270	15	Unknown (H/O CHF)
138004-11-31	80	M	163/163	10	Cerebrovascular accident
138004-11-211	85	M	69/68	10	Unknown (unspecified complication of surgery)
138004-11-213	82	F	3/3	2	Unknown
138004-20-17	87	F	332/332	10	Unknown
138004-20-208	89	F	151/151	5	Sepsis
138004-42-119	84	F	215/201	2	Volvulus
138004-59-135	90	F	76/75	2	Respiratory infection
138004-83-125	78	M	19/18	5	Pneumonia
138004-84-107	80	F	104/104	10	Cancer (colon)
138004-98-196	74	M	175/169	2	Aspiration pneumonia
138004-105-195	69	M	37/13	2	Cachexia assoc. with Alzheimer's disease
138005-3-16	76	M	92/86	15	Pneumonia, H/O GERD
138005-9-42	78	F	176/140	10	Cachexia assoc. with Alzheimer's disease

APPENDIX VII-2: DEATH LINE LISTING NON-JAPANESE PHASE 2/3 STUDIES[58]					
Patient Unique ID Number	Age	Sex	Day of Onset/ Day of Last Dose	Last Dose (mg/day)	Cause of Death (as determined from Narrative Summary review)
138005-11-22	88	M	182/162	10	Aspiration pneumonia
138005-12-49	93	F	244/242	5	Unspecified respiratory infection
138005-20-65	89	F	136/137	5	Pneumonia
138005-43-96	86	F	220/214	5	Unknown (underlying arteriosclerosis)
138005-43-103	82	M	127/126	Unknown	Heart failure
138006-8-18	79	M	145/142	10	Heart failure
138006-8-36	86	F	122/119	5	Renal failure
138006-8-71	84	M	41/42	2	Aspiration pneumonia D/T incorrect alimentation
138006-8-98	83	F	138/138	2	Pulmonary embolism
138006-8-138	92	F	48/42	Unknown	Pneumonia
138006-8-139	91	F	72/67	Unknown	Heart failure
138006-8-167	87	F	84/84	2	Unknown
138006-20-30	77	M	241/241	5	Aspiration pneumonia
138006-20-34	86	M	324/324	5	Aspiration pneumonia D/T incorrect alimentation
138006-20-35	94	M	307/297	Unknown	Pneumonia
138006-20-75	87	F	61/61	10	Sepsis
138006-20-78	97	M	178/178	5	Cardiac arrest
138006-20-79	96	F	149/147	5	Unknown
138006-20-221	78	F	50/50	10	Unknown
138006-21-7	89	F	163/162	5	Unknown (sudden death)

APPENDIX VII-2: DEATH LINE LISTING NON-JAPANESE PHASE 2/3 STUDIES[58]					
Patient Unique ID Number	**Age**	**Sex**	**Day of Onset/ Day of Last Dose**	**Last Dose (mg/day)**	**Cause of Death (as determined from Narrative Summary review)**
138006-21-176	96	M	79/76	5	Myocardial infarction
138006-36-66	76	F	272/271	10	Myocardial infarction
138006-71-120	82	F	202/204	10	Bronchitis
138006-71-159	82	F	113/110	5	Unknown
138006-73-188	93	F	109/109	7	Sepsis
138007-108-470	39	M	42/41	30	Overdose (heroin)
138047-7-117	30	M	1/1	15	Accident (struck by cars)
TREATMENT=HALOPERIDOL					
97301-130-1	43	M	43/42	7	Suicide (hanging)
98304-447-55	34	M	156/155	10	Suicide (jumping)
TREATMENT=BLINDED					
138003-26-411	62	M	95/92	Unknown	Asphyxia (self-induced)
138003-45-475	24	M	5/4	Unknown	Asphyxia (aspirated vomit)
138004-11-10	89	F	56/48	Unknown	Shock (probable UGI bleed)
138004-28-35	83	F	11/10	Unknown	Aortic aneurysm
138004-28-114	91	M	22/15	Unknown	Pneumonia
138004-42-87	79	F	38/36	Unknown	Unknown
138004-75-161	78	F	36/35	Unknown	Cerebral hemorrhage
138004-76-223	92	F	48/47	Unknown	Myocardial infarction
138004-83-231	85	F	70/70	Unknown	Heart failure
138004-102-248	82	M	6/6	Unknown	Unknown
138005-15-56	92	F	15/4	Unknown	Cardiopulmonary arrest
138005-46-141	95	F	20/8	Unknown	Pneumonia
138007-47-103	52	M	341/280	Unknown	Unknown

APPENDIX VII-3: DEATH LINE LISTING FOR ARIPIPRAZOLE-TREATED PATIENTS JAPANESE PHASE 2/3 STUDIES					
Protocol/Patient ID	**Age**	**Sex**	**Days on Drug (Post D/C)[59]**	**Last Dose (mg/day)**	**Cause of Death (as determined from Narrative Summary review)**
31-91-003/10702	51	M	30(1)	10	Unknown (sudden death)
31-95-003/06701	49	M	56(157)	6	Suicide (hanging)
31-95-003/08603	29	M	34(0)	9	Suicide (jumping)
31-95-004/F0701	64	F	80(2)	6	Diabetic ketoacidosis
31-95-005/H0202	36	M	260(0)	12	Suicide (jumping)
31-95-006/T1606	62	M	364(3)	3	Metastatic colon cancer
31-95-006/T1902	46	M	169(116)	6	Choking (misswallowing)

[59] The number of days between discontinuation of aripiprazole and death is provided in parentheses.

APPENDIX VII-4
ENUMERATION OF PATIENTS WITH SPECIFIC NON-FATAL SERIOUS ADVERSE EVENTS (N)
NON-JAPANESE PHASE 2/3 STUDY POOL

Body System/SAE	Alzheimer's Dementia			Schizophrenia/Bipolar		
	Ari N=504	Placebo N=102	p-value[60]	Ari N=4206	Placebo N=826	p-value
Body as a Whole						
Neoplasm	0	1	-	4	0	1.00
Carcinoma	4	0	1.00	8	0	0.37
AIDS	0	0	-	1	0	1.00
Sepsis	3	0	1.00	2	0	1.00
Cardiovascular						
Myocardial Infarction	1	0	1.00	5	0	1.00
Syncope	1	0	1.00	7	1	1.00
Deep Vein Thrombosis	1	0	1.00	2	0	1.00
Gangrene	1	0	1.00	3	0	1.00
Hypotension	0	0	-	1	0	1.00
Pulmonary Embolism	0	0	-	1	0	1.00
Digestive						
Cholelithiasis	1	0	1.00	3	1	0.51
Cholecystitis	1	0	1.00	2	0	1.00
Pancreatitis	0	0	-	3	0	1.00
UGI Bleed	1	0	1.00	1	1	0.30
Gastritis	0	0	-	2	0	1.00

[60] P-values are based on a 2-tailed Fisher's exact comparison of aripiprazole vs. placebo. Where no aripiprazole patients experienced an event, testing was not performed.

APPENDIX VII-4
ENUMERATION OF PATIENTS WITH SPECIFIC NON-FATAL SERIOUS ADVERSE EVENTS (N)
NON-JAPANESE PHASE 2/3 STUDY POOL

Body System/SAE	Alzheimer's Dementia			Schizophrenia/Bipolar		
	Ari N=504	Placebo N=102	p-value[60]	Ari N=4206	Placebo N=826	p-value
Appendicitis	0	0	-	1	0	1.00
Hepatitis	0	0	-	2	0	1.00
Esophageal Stenosis	0	0	-	1	0	1.00
Endocrine						
Diabetes Mellitus	0	0	-	3	0	1.00
Hematologic						
Leukopenia	1	0	1.00	0	0	-
Anemia	2	0	1.00	2	0	1.00
Thrombocytopenic Purpura	0	0	-	1	0	1.00
Metabolic/Nutritional						
Hyperglycemia	1	0	1.00	1	0	1.00
Hyponatremia	0	0	-	2	0	1.00
Hypoglycemia	1	0	1.00	1	0	1.00
Musculoskeletal						
Rhabdomyolysis	0	0	-	1	0	1.00
Nervous						
Seizure	6	1	1.00	12	0	0.24
Delirium	0	0	-	1	0	1.00
TIA	0	1	-	1	0	1.00
NMS	0	0	-	2	0	1.00
CVA	1	0	1.00	1	0	1.00
Subdural Hematoma	1	0	1.00	0	0	-
Respiratory						

APPENDIX VII-4
ENUMERATION OF PATIENTS WITH SPECIFIC NON-FATAL SERIOUS ADVERSE EVENTS (N)
NON-JAPANESE PHASE 2/3 STUDY POOL

Body System/SAE	Alzheimer's Dementia			Schizophrenia/Bipolar		
	Ari N=504	Placebo N=102	p-value[60]	Ari N=4206	Placebo N=826	p-value
Pneumonia (unspecified)	5	0	0.60	12	1	0.71
Respiratory Failure	0	0	-	1	0	1.00
Aspiration pneumonia	1	0	1.00	0	0	-
Pulmonary Edema	2	0	1.00	0	0	-
Hemoptysis	1	0	1.00	0	0	-
Special Senses						
Ruptured Eardrum	0	0	-	1	0	1.00
Cataract	1	1	0.31	0	0	-
Urogenital						
Kidney Failure	0	0	-	1	0	1.00

APPENDIX VII-5:
ENUMERATION OF ALL DROPOUTS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Number (%) of Patients			
	Placebo	Haloperidol	Risperidone	Aripiprazole
	N = 413	N = 200	N = 99	N = 926
Discontinued	232 (56)	84 (42)	37 (37)	424 (46)
AE[a]	41 (10)	17 (9)	8 (8)	65 (7)
Lack of efficacy	84 (20)	27 (14)	13 (13)	108 (12)
Lost to follow-up	1 (< 1)	0	2 (2)	6 (1)
Patient withdrew consent	50 (12)	38 (19)	12 (12)	140 (15)
Noncompliance	1 (< 1)	1 (1)	1 (1)	9 (1)
Other[b]	11 (3)	1 (1)	1 (1)	9 (1)
Entered open-label rescue[c]	44 (11)	n/a	n/a	87 (9)
Completed Study	181 (44)	116 (58)	62 (63)	502 (54)

[a] As recorded on the end-of-study status form.

[b] May include the following reasons for discontinuation: pregnancy, other known cause (other), study terminated by sponsor, protocol violation, patient met withdrawal criteria, patient did not satisfy one or more screening criteria, general inability to continue.

[c] Includes patients from Study CN138-001 who received open-label aripiprazole rescue treatment after Week 3 because of lack of response to double-blind treatment (lack of efficacy). Not applicable in studies involving haloperidol or risperidone controls.

APPENDIX VII-6
ENUMERATION OF DROPOUTS DUE TO ADVERSE EVENTS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Body System/ Primary Term[a]	Number (%) of Patients			
	Placebo	Haloperidol	Risperidone	Aripiprazole
	N = 413	N = 200	N = 99	N = 926
Any Treatment-Emergent AE Leading to Discontinuation of Study Therapy[b]	39 (9.4)	16 (8.0)	8 (8.1)	68 (7.3)
Body As A Whole				
Accidental Injury[c]	0	0	0	1 (0.1)
Intentional Injury	0	0	0	1 (0.1)
Pain Chest[d]	0	0	0	1 (0.1)
Suicide Attempt	0	0	0	1 (0.1)
Cardiovascular System				
Hemorrhage[e]	0	0	0	1 (0.1)
Hypertension	0	0	0	1 (0.1)
Syncope[f]	0	0	0	1 (0.1)
Tachycardia	0	0	1 (1.0)	0
Digestive System				
Nausea	1 (0.2)	1 (0.5)	0	3 (0.3)
Nausea And Vomiting	0	0	0	1 (0.1)
Vomiting	0	1 (0.5)	0	1 (0.1)
Abnormal Liver Function Test	0	1 (0.5)	1 (1.0)	0
Diarrhea	1 (0.2)	0	0	0
Metabolic/Nutritional System				
Creatine Phosphokinase Increased[g]	0	0	0	1 (0.1)
Musculoskeletal System				
Cramp Muscle	0	0	0	1 (0.1)

APPENDIX VII-6
ENUMERATION OF DROPOUTS DUE TO ADVERSE EVENTS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Body System/ Primary Term[a]	Number (%) of Patients			
	Placebo	Haloperidol	Risperidone	Aripiprazole
	N = 413	N = 200	N = 99	N = 926
Nervous System				
Psychosis	25 (6.1)	3 (1.5)	5 (5.1)	33 (3.6)
Agitation	8 (1.9)	0	0	6 (0.6)
Akathisia	0	3 (1.5)	0	6 (0.6)
Anxiety	1 (0.2)	0	0	5 (0.5)
Reaction Schizophrenic	2 (0.5)	0	0	3 (0.3)
Hostility	2 (0.5)	0	0	2 (0.2)
Insomnia	0	0	0	2 (0.2)
Lightheadedness	0	0	0	2 (0.2)
Depression	0	0	0	1 (0.1)
Dystonia	0	1 (0.5)	0	1 (0.1)
Extrapyramidal Syndrome	0	0	0	1 (0.1)
Paranoid Reaction	2 (0.5)	0	0	1 (0.1)
Seizure Grand Mal	0	0	0	1 (0.1)
Somnolence	1 (0.2)	1 (0.5)	0	1 (0.1)
Hyperactivity	1 (0.2)	0	0	0
Hypertonia	0	1 (0.5)	1 (1.0)	0
Libido Decreased	0	1 (0.5)	0	0
Rigidity Cogwheel	0	1 (0.5)	0	0
Seizure	0	1 (0.5)	0	0
Tremor Extremity	0	1 (0.5)	0	0
Respiratory System				
Hiccup	0	0	0	1 (0.1)

APPENDIX VII-6
ENUMERATION OF DROPOUTS DUE TO ADVERSE EVENTS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Body System/ Primary Term[a]	Number (%) of Patients			
	Placebo	Haloperidol	Risperidone	Aripiprazole
	N = 413	N = 200	N = 99	N = 926
Skin/Appendages				
Rash	0	0	0	1 (0.1)
Rash Maculopapular	1 (0.2)	0	0	0
Urogenital System				
Urinary Retention	0	1 (0.5)	0	0

a Modified COSTART term.

b AEs for which the "action taken" column on the AE form was marked "discontinue medication."

c Reported term was superficial laceration to left wrist as a result of suicide attempt.

d Myocardial infarction ruled out by cardiologist.

e Reported term was hematoma on the right occipital side of skull resulting from a fall during grand mal seizure.

f Syncope was reported to be mild and not related to aripiprazole.

g The event started at the end of Week 3, at which time the patient entered the open-label rescue phase. The CPK value remained elevated, which resulted in discontinuation of open-label treatment. (This patient is also noted in Section 6.4.1.)

APPEARS THIS WAY
ON ORIGINAL

APPENDIX VII-7
PRPORTIONS OF PATIENTS REPORTING ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 1% IN THE ARIPIPRAZOLE GROUP SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Number (%) of Patients							
Body System/	**Placebo**		**Haloperidol**		**Risperidone**		**Aripiprazole**	
Primary Term[a]	N = 413		N = 200		N = 99		N = 926	
Any Treatment-Emergent AE	362	(87.7)	183	(91.5)	92	(92.9)	844	(91.1)
Body As A Whole								
Headache	101	(24.5)	58	(29.0)	31	(31.3)	294	(31.7)
Asthenia	22	(5.3)	19	(9.5)	6	(6.1)	64	(6.9)
Pain Extremity	19	(4.6)	9	(4.5)	5	(5.1)	62	(6.7)
Pain Abdomen	20	(4.8)	8	(4.0)	4	(4.0)	48	(5.2)
Pain	13	(3.1)	10	(5.0)	2	(2.0)	46	(5.0)
Infection	13	(3.1)	4	(2.0)	2	(2.0)	40	(4.3)
Accidental Injury[b]	18	(4.4)	8	(4.0)	1	(1.0)	39	(4.2)
Pain Back	25	(6.1)	6	(3.0)	7	(7.1)	36	(3.9)
Fever	5	(1.2)	4	(2.0)	2	(2.0)	20	(2.2)
Edema Peripheral	2	(0.5)	4	(2.0)	0		17	(1.8)
Pain Chest	11	(2.7)	6	(3.0)	2	(2.0)	16	(1.7)
Rigidity Neck	6	(1.5)	3	(1.5)	4	(4.0)	15	(1.6)
Pain Neck	6	(1.5)	4	(2.0)	2	(2.0)	14	(1.5)
Stiffness	5	(1.2)	5	(2.5)	0		11	(1.2)
Cardiovascular System								
Hypotension Orthostatic	4	(1.0)	1	(0.5)	3	(3.0)	18	(1.9)
Tachycardia	4	(1.0)	0		15	(15.2)	18	(1.9)
Hypertension	4	(1.0)	2	(1.0)	1	(1.0)	17	(1.8)
Hypotension	4	(1.0)	1	(0.5)	0		10	(1.1)

APPENDIX VII-7
PRPORTIONS OF PATIENTS REPORTING ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 1% IN THE ARIPIPRAZOLE GROUP SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Number (%) of Patients			
Body System/ Primary Term[a]	Placebo N = 413	Haloperidol N = 200	Risperidone N = 99	Aripiprazole N = 926
Digestive System				
Dyspepsia	64 (15.5)	21 (10.5)	12 (12.1)	137 (14.8)
Nausea	40 (9.7)	22 (11.0)	11 (11.1)	130 (14.0)
Vomiting	29 (7.0)	23 (11.5)	7 (7.1)	111 (12.0)
Constipation	32 (7.7)	20 (10.0)	11 (11.1)	95 (10.3)
Diarrhea	27 (6.5)	9 (4.5)	8 (8.1)	55 (5.9)
Dry Mouth	17 (4.1)	7 (3.5)	7 (7.1)	40 (4.3)
Disorder Dental	13 (3.1)	3 (1.5)	7 (7.1)	28 (3.0)
Anorexia	13 (3.1)	2 (1.0)	2 (2.0)	15 (1.6)
Nausea And Vomiting	4 (1.0)	2 (1.0)	1 (1.0)	13 (1.4)
Musculoskeletal System				
Myalgia	15 (3.6)	5 (2.5)	2 (2.0)	39 (4.2)
Cramp Muscle	6 (1.5)	0	0	13 (1.4)
Disorder Joint	3 (0.7)	1 (0.5)	5 (5.1)	13 (1.4)
Nervous System				
Agitation	143 (34.6)	72 (36.0)	21 (21.2)	287 (31.0)
Anxiety	99 (24.0)	66 (33.0)	18 (18.2)	232 (25.1)
Insomnia	77 (18.6)	48 (24.0)	20 (20.2)	223 (24.1)
Lightheadedness	27 (6.5)	18 (9.0)	11 (11.1)	106 (11.4)
Somnolence	33 (8.0)	41 (20.5)	14 (14.1)	102 (11.0)
Akathisia	28 (6.8)	36 (18.0)	14 (14.1)	93 (10.0)
Psychosis	35 (8.5)	7 (3.5)	11 (11.1)	61 (6.6)
Extrapyramidal Syndrome	24 (5.8)	39 (19.5)	0	56 (6.0)
Tremor	8 (1.9)	7 (3.5)	2 (2.0)	28 (3.0)
Hypertonia	12 (2.9)	4 (2.0)	8 (8.1)	21 (2.3)
Salivation Increased	5 (1.2)	2 (1.0)	3 (3.0)	17 (1.8)

APPENDIX VII-7
PRPORTIONS OF PATIENTS REPORTING ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 1% IN THE ARIPIPRAZOLE GROUP SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Number (%) of Patients			
Body System/	**Placebo**	**Haloperidol**	**Risperidone**	**Aripiprazole**
Primary Term[a]	N = 413	N = 200	N = 99	N = 926
Nervous System (continued)				
Depression	10 (2.4)	3 (1.5)	2 (2.0)	16 (1.7)
Abnormal Dream	4 (1.0)	2 (1.0)	4 (4.0)	13 (1.4)
Hallucination	3 (0.7)	0	0	12 (1.3)
Nervousness	3 (0.7)	2 (1.0)	4 (4.0)	12 (1.3)
Respiratory System				
Rhinitis	14 (3.4)	10 (5.0)	11 (11.1)	40 (4.3)
Pharyngitis	15 (3.6)	9 (4.5)	2 (2.0)	39 (4.2)
URI	12 (2.9)	6 (3.0)	7 (7.1)	31 (3.3)
Coughing	9 (2.2)	5 (2.5)	2 (2.0)	27 (2.9)
Sinusitis	5 (1.2)	5 (2.5)	1 (1.0)	16 (1.7)
Dyspnea	3 (0.7)	3 (1.5)	3 (3.0)	10 (1.1)
Skin/Appendages				
Rash	20 (4.8)	11 (5.5)	8 (8.1)	54 (5.8)
Pruritus	10 (2.4)	1 (0.5)	0	18 (1.9)
Dry Skin	2 (0.5)	1 (0.5)	2 (2.0)	16 (1.7)
Sweating	8 (1.9)	3 (1.5)	0	11 (1.2)
Special Senses				
Blurred Vision	4 (1.0)	12 (6.0)	4 (4.0)	26 (2.8)
Pain Ear	7 (1.7)	1 (0.5)	1 (1.0)	13 (1.4)
Urogenital System				
Dysmenorrhea[c]	6 (5.8)	3 (5.9)	0	14 (6.2)
Vaginitis[c]	5 (4.8)	1 (2.0)	1 (3.6)	7 (3.1)

[a] Modified COSTART term.

[b] Reported terms mapped to accidental injury were reviewed to confirm the appropriateness of the mapping. Reported terms included lacerations, burns, contusions, sprains, fracture, and other minor injuries.

[c] Incidence rate adjusted for gender (women): placebo N = 104, haloperidol N = 51, risperidone N = 28, and aripiprazole N = 227.

APPENDIX VII-8:
LABORATORY ASSESSMENTS IN SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Study	Tests	Schedule of Assessments
93-202	Hematology, Chemistry, U/A, and Prolactin Tests...	Pre-study and weeks 1,2, 3, 4
	Stool Analysis	Pre-study and week 4
	Serum Pregnancy Test	Screening
94-202	Hematology, Chemistry.....	Screening and days 7, 14, 21, 28
	U/A	Screening and day 28
	Serum Pregnancy.....	Screening
	Prolactin Tests	Baseline, days 7,14, 21, 28
	Urine Drug Abuse Screen	Screening and upon readmission to unit
97-201	Hematology, Chemistry, U/A	Screening, baseline, days 14, 28
	Serum Pregnancy	Screening and day 28
	Urine Drug Screen, Serum Alcohol Test	Screening and upon readmission to unit
97-202	Hematology, Chemistry	Screening, baseline, days 14, 28
	Prolactin	Baseline, days 14, 28
	U/A.....	Baseline, days 14, 28
	Serum Pregnancy Test	Screening
	Urine Drug Screens, Serum Alcohol Tests	Screening and upon readmission to unit
138-001	Hematology, Chemistry, Urine	Screening, End of Weeks 3, 6
	Prolactin, Pregnancy Test.....	Screening, Week 6
	Drug Screen, Alcohol Test.....	Screening

APPENDIX VII-9
CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT LABORATORY VALUES

Laboratory Tests	Criteria[a]
Chemistry[b]	
AST (SGOT)	≥ 3 x upper limit of normal
ALT (SGPT)	≥ 3 x upper limit of normal
Alkaline phosphatase	≥ 3 x upper limit of normal
LDH	≥ 3 x upper limit of normal
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
Hematology	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2800/mm^3 or ≥ 16,000/mm^3
Eosinophils	≥ 10%
Neutrophils	Absolute count < 1,000/mm^3
Platelet count	≤ 100,000/mm^3 or ≥ 700,000/mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units

APPENDIX VII-10
INCIDENCE OF PCS CHEMISTRY VALUES
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

		Number of Patients with Potentially Clinically Significant Abnormality[a]/Number Assessed[b] (%)			
Laboratory Test	**On-Study Value**	**Placebo**	**Haloperidol**	**Risperidone**	**Aripiprazole**
AST(SGOT)	≥ 3 x ULN	1/372 (0.3)	0/172 (0.0)	1/88 (1.1)	5/810 (0.6)
ALT(SGPT)	≥ 3 x ULN	2/341 (0.6)	0/159 (0.0)	1/74 (1.4)	5/763 (0.7)
Alkaline Phosphatase	≥ 3 x ULN	0/371 (0.0)	0/183 (0.0)	0/93 (0.0)	0/807 (0.0)
LDH	≥ 3 x ULN	0/371 (0.0)	0/188 (0.0)	0/92 (0.0)	0/822 (0.0)
BUN	≥ 30 mg/dL	1/388 (0.3)	0/189 (0.0)	0/94 (0.0)	0/852 (0.0)
Creatinine	≥ 2.0 mg/dL	0/389 (0.0)	0/188 (0.0)	0/93 (0.0)	0/847 (0.0)
Uric Acid	Abnormal[c]	4/385 (1.0)	0/188 (0.0)	0/94 (0.0)	0/836 (0.0)
Bilirubin (Total)	≥ 2.0 mg/dL	2/384 (0.5)	0/189 (0.0)	1/91 (1.1)	1/857 (0.1)
CPK	≥ 3 x ULN	6/274 (2.2)	3/133 (2.3)	1/79 (1.3)	23/694 (3.3)
Prolactin	> ULN	20/286 (7.0)	80/148 (54.1)	75/84 (89.3)	11/609 (1.8)

[a] Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (Table 5.2.3.2A).

[b] Includes only patients with a baseline value within normal limits.

[c] Uric Acid: Abnormal: ≥ 10.5 mg/dL (men)/≥ 8.5 mg/dL (women).

APPENDIX VII-11
INCIDENCE OF PCS HEMATOLOGY VALUES
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

		Number of Patients with Potentially Clinically Significant Abnormality[a]/Number Assessed[b] (%)							
Laboratory Test	**On-Study Lab**	**Placebo**		**Haloperidol**		**Risperidone**		**Aripiprazole**	
Hematocrit	Abnormal[c]	0/316	(0.0)	1/134	(0.7)	2/83	(2.4)	8/760	(1.1)
Hemoglobin	Abnormal[d]	0/350	(0.0)	0/160	(0.0)	0/79	(0.0)	4/783	(0.5)
WBC	$\leq 2{,}800/mm^3$	1/391	(0.3)	2/188	(1.1)	0/94	(0.0)	5/851	(0.6)
Eosinophils	$\geq 10\%$	10/361	(2.8)	3/176	(1.7)	2/87	(2.3)	9/788	(1.1)
Neutrophils	$< 1{,}000/mm^3$	1/391	(0.3)	1/188	(0.5)	0/95	(0.0)	1/840	(0.1)
Platelet Count	$< 100{,}000/mm^3$	0/389	(0.0)	1/186	(0.5)	1/93	(1.1)	7/849	(0.8)

a Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (Table 5.2.3.2A).

b Includes only patients with a baseline value within normal limits.

c Hematocrit: Abnormal: $\leq 37\%$ (men)/32% (women) and a $\geq 3\%$ decrease from baseline.

d Hemoglobin: Abnormal: ≤ 11.5 g/dL (men)/≤ 9.5 g/dL (women).

APPENDIX VII-12
INCIDENCE OF PCS URINALYSIS VALUES
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Laboratory Test		Number of Patients with Potentially Clinically Significant Abnormality[a]/Number Assessed (%)			
All Patients[b]					
Baseline Level	On-Study Value	Placebo	Haloperidol	Risperidone	Aripiprazole
Protein					
All Patients	≥ 2-unit increase	0/366 (0.0)	0/175 (0.0)	0/94 (0.0)	3/824 (0.4)
= 0	≥ 2-unit increase	0/356 (0.0)	0/169 (0.0)	0/93 (0.0)	3/805 (0.4)
> 0	≥ 2-unit increase	0/6 (0.0)	0/3 (0.0)	0/0 (–)	0/11 (0.0)
Glucose					
All Patients	≥ 2-unit increase	1/366 (0.3)	4/175 (2.3)	1/94 (1.1)	14/824 (1.7)
= 0	≥ 2-unit increase	1/351 (0.3)	3/170 (1.8)	1/88 (1.1)	9/793 (1.1)
> 0	≥ 2-unit increase	0/11 (0.0)	1/2 (50.0)	0/5 (0.0)	5/23 (21.7)

a Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (Table 5.2.3.2A).

b Includes patients with a missing baseline value. The number of patients assessed for each of the baseline strata may not add up to the total number indicated for "all patients."

APPENDIX VII-13
MEDIAN PERCENT CHANGE FROM BASELINE TO ENDPOINT
IN SERUM CHEMISTRY VARIABLES
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES[61]

Lab Measure	Placebo		Aripiprazole	
	N	Median % Change	N	Median % Change
AST (SGOT)	391	0.0	858	0.0
ALT (SGPT)	391	0.0	858	9.1
Alk. Phos	390	0.0	858	-2.2
LDH	391	1.9	857	0.0
BUN	391	0.0	858	0.0
Creatinine	391	0.0	858	0.0
Uric Acid	391	0.0	857	0.0
Tot. Bilirubin	390	0.0	858	0.0
CPK	353	8.5	816	22.1
Prolactin	338	0.0	729	-56.5
Total Protein	391	0.0	857	0.0
Calcium	390	0.0	858	0.0
Sodium	391	0.0	858	0.0
Potassium	390	0.0	858	-2.1
Chloride	391	0.0	857	0.0
Total Cholesterol	34	-4.4	111	-1.4
Glucose (Fasting)	34	-1.0	112	0.0

[61] Changes in total cholesterol and fasting glucose are based on the results of study 138001 only. The other studies did not obtain blood specimens under fasting conditions.

APPENDIX VII-14
MEDIAN-PERCENT CHANGE FROM BASELINE TO ENDPOINT IN HEMATOLOGY VARIABLES

Laboratory Test	Placebo		Aripiprazole	
	N	Median % Change	N	Median % Change
Hematocrit	358	0.9	818	-0.2
Hemoglobin	391	0.7	850	0.0
WBC	391	1.8	850	3.3
Eosinophils	392	-3.4	845	-4.0
Neutrophils	392	-1.5	844	8.1
Platelets	391	1.1	850	3.1

APPEARS THIS WAY
ON ORIGINAL

APPENDIX VII-15
CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS

Vital Sign	Criterion Value[a]	Change from Baseline[a]
Heart rate	120 bpm 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic blood pressure	180 mmHg 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic blood pressure	105 mmHg 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Temperature[b]	≥ 37.8°C	Change of ≥ 1.1°C
Weight[b]	–	Change of ≥ 7% of body weight

APPENDIX VII-16
INCIDENCE OF PCS VITAL SIGN CHANGES IN SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

		Number of Patients with Potentially Clinically Significant Abnormality[a]/ Number Assessed (%)							
Vital Sign Measurement		Placebo		Haloperidol		Risperidone		Aripiprazole	
Systolic Blood Pressure									
Supine	Increase[b]	6/412	(1.5)	4/199	(2.0)	0/99	(0.0)	9/913	(1.0)
	Decrease[c]	36/412	(8.7)	19/199	(9.6)	6/99	(6.1)	54/913	(5.9)
Standing	Increase[b]	4/413	(1.0)	2/199	(1.0)	1/99	(1.0)	9/915	(1.0)
	Decrease[c]	46/413	(11.1)	34/199	(17.1)	15/99	(15.2)	104/915	(11.4)
Diastolic Blood Pressure									
Supine	Increase[d]	15/412	(3.6)	7/199	(3.5)	4/99	(4.0)	29/913	(3.2)
	Decrease[e]	31/412	(7.5)	17/199	(8.5)	9/99	(9.1)	50/913	(5.5)
Standing	Increase[d]	21/413	(5.1)	8/199	(4.0)	7/99	(7.1)	60/915	(6.6)
	Decrease[e]	20/413	(4.8)	14/199	(7.0)	9/99	(9.1)	45/915	(4.9)
Heart Rate	–								
Supine	Increase[f]	6/408	(1.5)	6/199	(3.0)	10/99	(10.1)	23/905	(2.5)
	Decrease[g]	2/408	(0.5)	6/199	(3.0)	1/99	(1.0)	9/905	(1.0)
Standing	Increase[f]	54/413	(13.1)	43/199	(21.6)	38/99	(38.4)	170/911	(18.7)
	Decrease[g]	0/413	(0.0)	0/199	(0.0)	0/99	(0.0)	3/911	(0.3)

APPENDIX VII-17 MEAN CHANGE FROM BASELINE TO ENDPOINT IN VITAL SIGN VARIABLES				
Vital Sign Measure	Aripiprazole		Placebo	
	N	Mean Δ	N	Mean Δ
Standing diastolic BP	909	+0.9	412	-0.3
Supine diastolic BP	904	+0.8	409	-0.6
Standing systolic BP	909	+2.2	412	-1.1
Supine systolic BP	904	+1.7	409	-0.9
Heart rate standing	898	+3.9	409	-0.8
Heart rate supine	891	+2.5	403	-1.2

APPENDIX VII-18 SCHEDULE FOR 12-LEAD ECG TRACINGS SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRNEIA STUDIES		
Study	Duration	Schedule of ECG's
93202	4 weeks	Baseline, weeks 2, 4
94202	4 weeks	Baseline, weeks 2, 4
97201	4 weeks	Baseline, weeks 2, 4
97202	4 weeks	Baseline, weeks 2, 4
138001	6 weeks	Baseline, weeks 3, 6

APPENDIX VII-19
CRITERIA FOR IDENTIFYING POTENTIALLY CLINICALLY SIGNIFICANT ECG MEASUREMENTS

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	≥ 2 per 10 seconds	any increase
Ventricular premature beat	≥ 1 per 10 seconds	any increase
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial fibrillation with rapid ventricular response	≥ 100 bpm	increase of ≥ 15 bpm
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 0.20 second	increase of ≥ 0.05 second
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle branch block	all	not present → present
Right bundle branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 0.12 second	increase of ≥ 0.02 second
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present

APPENDIX VII-19 (CONTINUED)

Variable	Criterion Value[a]	Change Relative to Baseline[a]
ST/T Morphological		
Myocardial ischemia	all	not present → present
Symmetrical T-wave inversions	all	not present → present
Increase in QT_c	$QT_c \geq 450$ millisecond	≥ 10% increase

[a] Criteria developed for a previous BMS filing based upon discussions with the FDA Division of Neuropharmacological Drug Products.

[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d] No current diagnosis of left bundle branch block or right bundle branch block.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX VII-20
PERCENTAGE OF PATIENTS MEETING CRITERIA FOR A POTENTIALLY CLINICALLY SIGNIFICANT ECG MEASUREMENT

	Number of Patients with Potentially Clinically Significant Abnormality[a] (%)			
	Placebo	Haloperidol	Risperidone	Aripiprazole
ECG Parameter	N = 382	N = 185	N = 95	N = 841
Rate				
Tachycardia	5 (1.31)	0 (0.00)	0 (0.00)	2 (0.24)
Bradycardia	4 (1.05)	1 (0.54)	2 (2.11)	3 (0.36)
Rhythm				
Sinus tachycardia	5 (1.31)	0 (0.00)	0 (0.00)	2 (0.24)
Sinus bradycardia	4 (1.05)	1 (0.54)	2 (2.11)	3 (0.36)
Supraventricular premature beat	0 (0.00)	0 (0.00)	1 (1.05)	0 (0.00)
Ventricular premature beat	5 (1.31)	0 (0.00)	1 (1.05)	9 (1.07)
Supraventricular tachycardia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ventricular tachycardia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Atrial fibrillation	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Atrial fibrillation with rapid ventricular response	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Atrial flutter	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Conduction				
1° atrioventricular block	0 (0.00)	1 (0.54)	0 (0.00)	1 (0.12)
2° atrioventricular block	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
3° atrioventricular block	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Left bundle branch block	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Right bundle branch block	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Pre-excitation syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Other intraventricular conduction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Infarction				
Acute infarction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Subacute (recent) infarction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Old infarction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
ST/T Morphological				
Myocardial ischemia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Symmetrical T-wave inversions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

APPENDIX VII-21
MEDIAN CHANGE FROM BASELINE TO THE MINIMUM OR MAXIMUM ON-TREATMENT ECG VALUE
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Placebo		Haloperidol		Risperidone		Aripiprazole	
ECG Parameter	N	Median Change	N	Median Change	N	Median Change	N	Median Change
PR Maximum (msec)	380	2.00	180	3.00	95	5.00	831	2.00
QRS Maximum (msec)	380	1.00	180	0.50	95	2.00	831	2.00
RR								
Maximum (msec)	380	18.00	180	21.00	95	-24.00	831	-11.00
Minimum (msec)	380	-22.50	180	-29.50	95	-90.00	831	-64.00
Heart Rate								
Maximum (bpm)	380	2.00	180	3.00	95	12.00	831	7.00
Minimum (bpm)	380	-1.00	180	-2.00	95	3.00	831	1.00

APPENDIX VII-22
ANALYSES OF THE QTc INTERVAL
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Placebo	Haloperidol	Risperidone	Aripiprazole
Sample Size[a]	379	180	95	828
Baseline QT_{cE} (msec)	390.8	387.0	392.6	389.1
Mean Change at Endpoint (msec)	-3.56	-0.62 *	2.44 **	-4.16
Mean Change at Max QT_{cE} (msec)	0.35	4.07 **	8.10 **	0.12
	Number of Patients/Number Assessed (%)			
> 450 msec[b]	1/382 (0.3)	2/185 (1.1)	0/95 (0.0)	2/841 (0.2)
> 500 msec[b]	0/382 (0.0)	0/185 (0.0)	0/95 (0.0)	0/841 (0.0)
≥ 30 msec increase[c]	21/380 (5.5)	14/180 (7.8)	10/95 (10.5)	36/831 (4.3)
≥ 60 msec increase[c]	0/380 (0.0)	1/180 (0.6)	0/95 (0.0)	0/831 (0.0)

** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$) significantly different from placebo. Comparisons of means were done by ANCOVA, controlling for baseline QT_{cE}. Comparisons of proportions were done by Fisher's exact test.

QT_{cE} = Aripiprazole Fractional Exponent Correction Formula ($QT/RR^{0.35}$).

[a] Includes all patients with both a baseline and an endpoint measurement.

[b] Includes all patients with an on-study measurement.

[c] Includes all patients with both a baseline and on-study measurement.

APPENDIX VII-23
PERCENTAGE OF PATIENTS WITH ≥7% WEIGHT GAIN
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

	Number of Patients with Significant Weight Gain[a]/ Number Assessed (%)			
Study Week	Placebo	Haloperidol	Risperidone	Aripiprazole
Endpoint (OC)[b]	9/173 (5.2)	15/105 (14.3)*	10/63 (15.9)*	56/479 (11.7)*
Endpoint (LOCF)[b]	12/379 (3.2)	16/164 (9.8)**	10/94 (10.6)**	69/852 (8.1)**

** ($P \leq 0.01$), *($0.01 < P \leq 0.05$). Significantly different from placebo (Fisher's exact test).

a ≥ 7% increase from baseline.

b Endpoint for studies 31-93-202, 31-94-202, 31-97-201, 31-97-202 was Week 4 (OC and LOCF) and for study CN138-001 was Week 6 (OC and LOCF).

APPENDIX VII-24
PERCENTAGE OF PATIENTS WITH >ULN PROLACTIN LEVELS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

		Number of Patients with Abnormality/ Number Assessed (%)			
Baseline Level	On-Study Level	Placebo	Haloperidol	Risperidone	Aripiprazole
≤ ULN	> ULN	20/286 (7.0)	80/148 (54.1)**	75/84 (89.3)**	11/609 (1.8)**L
> ULN	> ULN	24/53 (45.3)	32/37 (86.5)**	7/7 (100.0)*	14/123 (11.4)**L

** ($P \leq 0.01$), *($0.01 < P \leq 0.05$), significantly different from placebo (Fisher's exact test).

**L indicates significantly less than placebo.

APPENDIX VII-25
PERCENTAGE OF PATIENTS WITH >ULN PROLACTIN LEVELS
STUDY 98217

Prolactin[a]		Number of Patients with Abnormality/ Number Assessed (%)			
Baseline Level	On-Study Level	Haloperidol		Aripiprazole	
≤ ULN	> ULN	27/44	(61.4)	3/87	(3.4) **
> ULN	> ULN	2/2	(100.0)	0/9	(0.0) *

**(P ≤ 0.01), *(0.01 < P ≤ 0.05), significantly different from haloperidol (Fisher's exact test).

[a] Prolactin was not collected for study 31-98-304-01.

APPENDIX VII-26
PERCENTAGE OF PATIENTS WITH A SUICIDE-RELATED AE
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

	Number (%) of Patients			
	Placebo	Haloperidol	Risperidone	Aripiprazole
Primary Term[a]	N = 413	N = 200	N = 99	N = 926
Any Event	3 (0.7)	1 (0.5)	0 (0)	10 (1.1)
Thought Suicidal	1 (0.2)	1 (0.5)	0 (0)	5 (0.5)
Intentional Injury	1 (0.2)	0 (0)	0 (0)	3 (0.3)
Suicide Attempt[b]	1 (0.2)	0 (0)	0 (0)	2 (0.2)

[a] Modified COSTART term.

[b] None resulted in death during the short-term placebo-controlled studies.

APPENDIX VII-27
PERCENTAGE OF PATIENTS WITH A SUICIDE-RELATED AE
LONG-TERM, HALOPERIDOL-CONTROLLED SCHIZOPHRENIA TRIALS

	Number (%) of Patients	
	Haloperidol	**Aripiprazole**
Primary Term[a]	**N = 431**	**N = 859**
Any Suicide-Related Event	6 (1.4)	12 (1.4)
Thought Suicidal	4 (0.9)	7 (0.8)
Intentional Injury	0 (0)	1 (0.1)
Suicide Attempt[b]	2 (0.5)	4 (0.4)

[a] Modified COSTART term.

[b] Three (0.3%) of the aripiprazole-treated patients (98304-439-60, 98304-509-50, and 98304-558-58) and one (0.2%) of the haloperidol-treated patients (98304-447-55) died as a result of a suicide attempt.

APPENDIX VII-28
PERCENTAGE OF PATIENTS WITH AN EPS-RELATED EVENT
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

	Number (%) of Patients			
EPS Category/	**Placebo**	**Haloperidol**	**Risperidone**	**Aripiprazole**
Primary Term[a]	N = 413	N = 200	N = 99	N = 926
Any Treatment-Emergent EPS-Related AE	80 (19.4)	87 (43.5)	30 (30.3)	195 (21.1)
Dystonic Events	9 (2.2)	13 (6.5)	9 (9.1)	21 (2.3)
Rigidity Neck	6 (1.5)	3 (1.5)	4 (4.0)	15 (1.6)
Dystonia	2 (0.5)	9 (4.5)	5 (5.1)	5 (0.5)
Oculogyric Crisis	1 (0.2)	1 (0.5)	0	1 (0.1)
Parkinsonian Events	44 (10.6)	52 (26.0)	10 (10.1)	105 (11.3)
Extrapyramidal Syndrome	24 (5.8)	39 (19.5)	0	56 (6.0)
Tremor	8 (1.9)	7 (3.5)	2 (2.0)	28 (3.0)
Hypertonia	12 (2.9)	4 (2.0)	8 (8.1)	21 (2.3)
Rigidity Cogwheel	2 (0.5)	4 (2.0)	2 (2.0)	8 (0.9)
Akathisia Events	30 (7.3)	36 (18.0)	15 (15.1)	95 (10.3)
Akathisia	28 (6.8)	36 (18.0)	14 (14.1)	93 (10.0)
Hyperkinesia	2 (0.5)	0	1 (1.0)	2 (0.2)
Dyskinetic Events	6 (1.5)	1 (0.5)	2 (2.0)	6 (0.7)
Dyskinesia	4 (1.0)	0	1 (1.0)	2 (0.2)
Dyskinesia Tardive	1 (0.2)	0	0	2 (0.2)
Syndrome Buccoglossal	0	0	1 (1.0)	0
Residual Events	9 (2.2)	3 (1.5)	0	11 (1.2)
Disorder Movement	5 (1.2)	3 (1.5)	0	5 (0.5)
Twitch	2 (0.5)	0	0	5 (0.5)
Myoclonus	2 (0.5)	0	0	1 (0.1)

[a] Modified COSTART term.

APPENDIX VII-29
PERCENTAGE OF DROPOUTS DUE TO AN EPS-RELATED EVENT SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

EPS Category/ Primary Term[a]	Number (%) of Patients			
	Placebo N = 413	Haloperidol N = 200	Risperidone N = 99	Aripiprazole N = 926
Any Treatment-Emergent EPS-Related AE Leading to Discontinuation of Study Therapy[b]	0	6 (3.0)	1 (1.0)	7 (0.8)
Dystonic Events	0	1 (0.5)	0	1 (0.1)
Dystonia	0	1 (0.5)	0	1 (0.1)
Parkinsonian Events	0	2 (1.0)	1 (1.0)	1 (0.1)
Extrapyramidal Syndrome	0	0	0	1 (0.1)
Hypertonia	0	1 (0.5)	1 (1.0)	0
Rigidity Cogwheel	0	1 (0.5)	0	0
Akathisia Events	0	3 (1.5)	0	6 (0.6)
Akathisia	0	3 (1.5)	0	6 (0.6)

[a] Modified COSTART term.

[b] EPS-related AE for which the "action taken" column on the AE form was marked "discontinue medication".

APPENDIX VII-30
MEAN CHANGE FROM BASELINE IN EPS-RATING SCALES
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

EPS Scale	Placebo	Haloperidol	Risperidone	Aripiprazole
SAS Total Score[a]	**N = 402**	**N = 183**	**N = 94**	**N = 886**
Mean Baseline (SE)	12.39 (0.14)	12.49 (0.22)	11.74 (0.31)	12.38 (0.10)
Change at Endpoint (SE)	-0.08 (0.13)	1.23 (0.20)**	-0.47 (0.29)	-0.06 (0.09)
Change at Highest Score (SE)	0.78 (0.15)	2.95 (0.23)**	0.40 (0.32)	0.96 (0.10)
Barnes Akathisia[b]	**N = 411**	**N = 192**	**N = 95**	**N = 903**
Mean Baseline (SE)	0.60 (0.04)	0.72 (0.07)	0.39 (0.10)	0.55 (0.03)
Change at Endpoint (SE)	-0.05 (0.04)	0.40 (0.07)**	-0.06 (0.09)	0.08 (0.03)*
Change at Highest Score (SE)	0.25 (0.05)	0.92 (0.07)**	0.20 (0.10)	0.40 (0.03)**
AIMS Total Score[c]	**N = 407**	**N = 192**	**N = 94**	**N = 891**
Mean Baseline (SE)	1.97 (0.16)	2.16 (0.24)	1.82 (0.35)	1.66 (0.11)
Change at Endpoint (SE)	-0.02 (0.10)	-0.37 (0.16)	-0.64 (0.22)*	-0.44 (0.07)**
Change at Highest Score (SE)	0.38 (0.10)	0.22 (0.16)	-0.16 (0.23)*	0.06 (0.07)*

** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$) significantly different from placebo by ANCOVA, controlling for baseline and study center. Means and standard errors (SE) are model-based (least squares) estimates.

[a] SAS Total Score ranges from 10 to 50. A negative change score indicates improvement.

[b] Global Clinical Assessment Score ranges from 0 (absent) to 5 (severe akathisia). A negative change score indicates improvement.

[c] AIMS Total Score ranges from 0 to 28. A negative change score indicates imrovement.

APPENDIX VII-31
LISTING OF PATIENTS AUDITED
(Study-Center-Patient Number)

PATIENTS AUDITED FOR ADVERSE EVENT INFORMATION	
138001-8-167	97203-73-4
138001-50-350	97203-66-7
138001-31-501	93202-8-38
138001-15-21	98304-451-51
138001-25-438	98304-440-63
97201-16-1	98304-506-52
00230-1-13	98215-384-37
98217-297-2	98203-353-31
98217-309-1	97301-216-2
99224-620-15	98203-2-13
93201-31-131	97202-90-8
98217-294-12	98304-481-50
98217-277-17	98304-445-54
138003-36-328	138001-57-146
138003-140-453	138001-76-452
138035-1-54	138004-49-33
97202-84-5	97202-90-8
97202-55-3	98217-306-14
94201-1-15	98213-600-1
97203-67-19	
PATIENTS AUDITED FOR REASON FOR DROPOUT	
93202-9-116	138001-12-427
94202-1-244	138001-13-180
97202-76-8	98217-306-4
97201-39-15	98217-309-1
97201-30-19	98304-416-55

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

/s/

Greg Dubitsky
6/12/02 09:16:59 AM
MEDICAL OFFICER

Robert D. Harris
6/12/02 04:37:08 PM
MEDICAL OFFICER

Thomas Laughren
7/21/02 01:37:11 PM
MEDICAL OFFICER
I agree that, from a clinical standpoint, this NDA is approvable; see memo to file for more detailed comments.--TPL

APPEARS THIS WAY
ON ORIGINAL

Safety Update Review: N/A

APPEARS THIS WAY
ON ORIGINAL