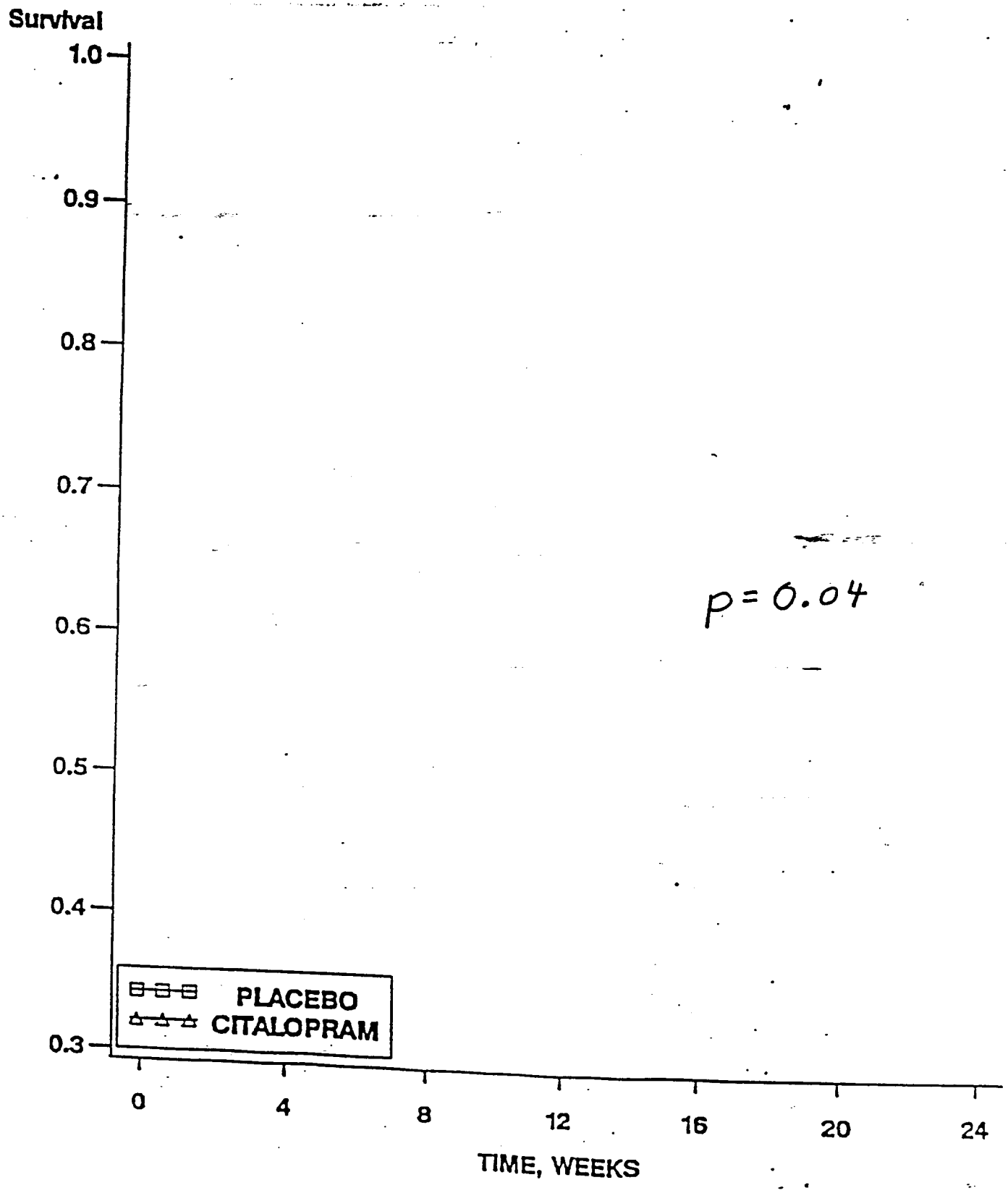
APPENDIX 7.2.1.6

KAPLAN MEIER SURVIVAL ANALYSIS: STUDY 89304



APPENDIX 7.2.1.7

STUDY 89305: PRINCIPAL INVESTIGATORS	
Investigator(s) (Center #)	**Location**
A. H. Mahmood, M.D. Al-Bachari, M.D. (1)	Upton, U.K.
Gilbert Andrews, M.D. (2)	Surrey, U.K.
Joseph M. A. Ansari, M.D. (3)	Merseyside, U.K.
John A. D'Souza, M.D. (6)	Blackpool, U.K.
Jasbir Singh, M.D. (7)	Calow Chesterfield, U.K.
R. H. Mahmood, M.D. (9)	Wirral, U.K.
Halley Mathew, M.D. (10)	Dewsbury W. Yorks, U.K.
Yvonne I. Michael, M.D. (11)	Dettering, U.K.
Dennis H. Morgan, M.D. (13)	King's Lynn, U.K.
Achmau Perez, M.D. (15)	Duston Northampton, U.K.
K. Sundararajan, M.D. (18)	Halifax, U.K.
Basic Paul Maragakis, M.D. (20)	Wigan, U.K.
Nas Choudry, M.D. (21)	Poole, U.K.
Michael Ford, M.D. (22)	Dorchester, U.K.
Kelly, M.D. (23)	Rotherham, U.K.
Mutela, M.D. (24)	London, U.K.
K. Balasubramaniam, M.D. (25)	Bedford, U.K.
T. Venkateswarlu, M.D. (26)	St. Leonards-on-Sea, U.K.
B.S. Weerakoon, M.D. (27)	Ormskirk, U.K.
A. G. Patel, M.D. (28)	Herts, U.K.

APPENDIX 7.2.1.7

STUDY 89305: DEMOGRAPHIC CHARACTERISTICS					
Treatment Groups	N	Age (years)		Sex [N(%)]	
		Median	Range	Male	Female
CIT 20mg	48	45		19(40%)	29(60%)
CIT 40mg	57	40		21(37%)	36(63%)
CIT/PLAC	42	47		11(26%)	31(74%)

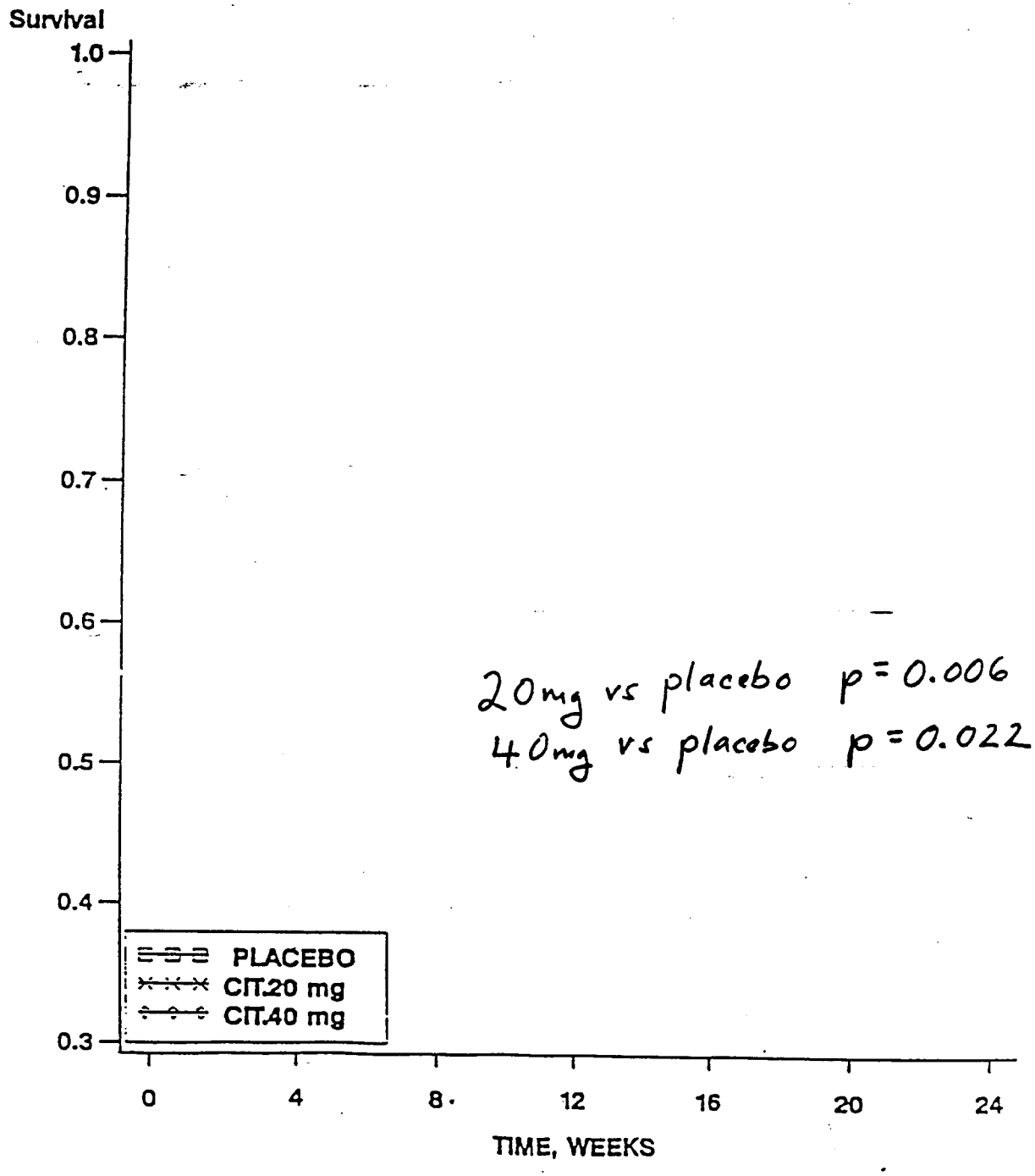
STUDY 89305: COMPLETERS by VISIT							
Treatment Groups	ITT	Completers [N(%)]					
		Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24
CIT 20mg	48	45 (94%)	39 (81%)	37 (77%)	33 (69%)	30 (63%)	26 (54%)
CIT 40mg	57	55 (96%)	46 (81%)	44 (77%)	43 (75%)	37 (65%)	36 (63%)
CIT/PLAC	42	40 (95%)	31 (74%)	29 (69%)	26 (62%)	22 (52%)	19 (45%)

STUDY 89305: CUMULATIVE NUMBER(%) of PATIENTS WHO RELAPSED*							
	ITT	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24
CIT 20mg	48	0 (0%)	1 (2%)	3 (6%)	3 (6%)	4 (8%)	4 (8%)
CIT 40mg	57	2 (4%)	3 (5%)	5 (9%)	6 (11%)	7 (12%)	7 (12%)
PLAC	42	1 (2%)	7 (17%)	9 (21%)	11 (26%)	13 (31%)	13 (31%)

* Denominators = ITT.

APPENDIX 7.2.1.7

KAPLAN MEIER SURVIVAL ANALYSIS: STUDY 89305



APPENDIX 7.4

Summary of Efficacy Results from Short-Term Studies (Significance of Drug/Placebo Comparisons for the LS Mean Change from Baseline to Final Study Week)[1]

Study	Dose (mg/d)	HAM-D total[2]		HAM-D item #1		MADRS total		CGI-severity	
		LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
85A	20-80	*	*	*	*	N/A	N/A	*	*
91206	10	ns	ns	*	*	ns	tr	ns	ns
	20	ns	ns	tr	ns	ns	ns	ns	ns
	40	*	tr	*	*	*	tr	tr	ns
	60	*	ns	*	*	*	tr	ns	ns
86141	10-30	ns	*	ns	*	ns	tr	ns	ns
89303	20	ns	ns	ns	ns	ns	ns	tr	tr
	40	ns	ns	*	ns	ns	ns	*	*
89306	20	N/A	N/A	N/A	N/A	ns	*	ns	ns
	40	N/A	N/A	N/A	N/A	ns	ns	ns	ns

[1]Statistical Significance Codes (except 91206): ns= not significant (p>0.10); tr= trend (0.05<p≤0.10); *= significant (p≤0.05)

For study 91206 (based on Dunnett's adjustment): ns= not significant (p>0.05); tr= trend (0.014<p≤0.05); *= significant (p≤0.014)

[2]The protocol-specified version of the HAM-D was used.

Appendix 8.1.1.1

By Patient Listing of Deaths Recorded During Citalopram Treatment in the Development Program
Cutoff Date = 10/1/96

STUDY	PAT. ID	PAT. INITIAL	AGE	SEX	DRUG	MG/ DAY	DAYS TX	BODY SYSTEM	PREFERRED TERM	REPORTED EVENT
7808	103		62	F	Citalopram	0	63	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
8105	1		43	F	Citalopram	60	51	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
8105	9		61	F	Citalopram	50	43	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
8206	53		59	M	Citalopram	60	45	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
8213	109		74	F	Citalopram	30	905	GENERAL NEOPLASM	RECTAL CARCINOMA	RECTAL CARCINOMA
8213	231		42	F	Citalopram	40	242	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
8213	252		49	F	Citalopram	20	21	HEART RATE AND RHYTHM DISORDERS	CARDIAC ARREST	CARDIAC ARREST
8213	464		56	M	Citalopram	60	18	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
8213	530		86	M	Citalopram			VASCULAR (EXTRACARDIAC) DISORDERS	CEREBRAL HAEMORRHAGE	CEREBRAL HAEMORRHAGE
8213	531		83	F	Citalopram			MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION
8213	624		86	M	Citalopram	30	120	RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	BRONCHOPNEUMONIA
8213	627		75	M	Citalopram	20	578	NEOPLASM	GASTRIC CARCINOMA	GASTRIC CARCINOMA
8213	628		60	F	Citalopram	30	386	RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	PNEUMONIA
8213	632		83	M	Citalopram	30		RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	BRONCHOPNEUMONIA
8213	638		72	F	Citalopram	30	717	PLATELET, BLEEDING & CLOTTING DISORDERS	EMBOLISM PULMONARY	EMBOLISM PULMONARY
8213	657		76	F	Citalopram	20	1	NEOPLASM	PULMONARY CARCINOMA	PULMONARY CARCINOMA

Appendix 8.1.1.1

STUDY	PAT. ID	PAT. INITIAL	AGE	SEX	DRUG	MG/ DAY	DAYS TX	BODY SYSTEM	PREFERRED TERM	REPORTED EVENT
8213	687		60	M	Citalopram	10		VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER	CEREBROVASCULAR DISORDER
8213	980		54	F	Citalopram	60	313	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
8213	1010		69	F	Citalopram	30	181	PLATELET, BLEEDING & CLOTTING DISORDERS	EMBOLISM PULMONARY	EMBOLISM PULMONARY
8213	1024		79	M	Citalopram	20	91	CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE	CARDIAC FAILURE
8302	4		66	F	Citalopram	40	32	VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER	STROKE
8311	133		67	F	Citalopram	20	347	RESPIRATORY SYSTEM DISORDERS	EMBOLISM PULMONARY	EMBOLISM PULMONARY
8311	421		79	M	Citalopram	20	84	RESPIRATORY SYSTEM DISORDERS	EMBOLISM PULMONARY	EMBOLISM PULMONARY
8311	514		78	M	Citalopram	20	31	RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	BRONCHOPNEUMONIA
86141	113		86	M	Citalopram	20	17	VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER	CEREBRAL INSULT
88105	326		47	M	Citalopram	10	26	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE ATTEMPT: GUN
88701	104		69	M	Citalopram	30	47	RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	BRONCHOPNEUMONIA
88701	131		81	M	Citalopram	20	21	VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER	CEREBROVASCULAR DISORDER
88701	137		81	F	Citalopram	40	365	RESPIRATORY SYSTEM DISORDERS	BRONCHITIS	BRONCHITIS
88701	147		79	M	Citalopram	30	93	RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	PNEUMONIA
88701	161		78	M	Citalopram	20	2	HEART RATE & RHYTHM DISORDERS	CARDIAC ARREST	CARDIAC ARREST
89304	1304		51	M	Citalopram	20	26	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
89304	2004		60	F	Citalopram	40	139	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
89404	22		30	F	Citalopram			PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
89411	433		53	F	Citalopram	20	23	METABOLIC & NUTRITIONAL DISORDERS	URAEMIA	URAEMIC SYNDROME
89411	478		47	M	Citalopram	40	31	OTHERS (NOT WHO)	TRAUMATIC INJURY	TRAUMATIC INJURY
89411	577		70	F	Citalopram	30	107	NEOPLASMS	BREAST NEOPLASM MALIGNANT FEMALE	BREAST NEOPLASM MALIGNANT
89411	837		46	M	Citalopram	40	35	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE

Appendix 8.1.1.1

STUDY	PAT. ID	PAT. INITIAL	AGE	SEX	DRUG	MG/ DAY	DAYS TX	BODY SYSTEM	PREFERRED TERM	REPORTED EVENT
89411	855		56	F	Citalopram	40	216	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
89411	1127		65	M	Citalopram	60	28	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
89421	111		59	M	Citalopram	60	28	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
89422	9		52	M	Citalopram	40	65	MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION
89422	161		44.3	F	Citalopram	30	27	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
89423	6		42	F	Citalopram	60	72	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
90404	101		78	F	Citalopram	10	31	RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	PNEUMONIA
90411	382		32	M	Citalopram	40		PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
90411	554		60	M	Citalopram	20	29	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
91203	308		72	M	Citalopram	40	45	BODY AS A WHOLE - GENERAL DISORDERS	CONDITION AGGRAVATED	CONDITION AGGRAVATED
91203	339		83	F	Citalopram	40	97	BODY AS A WHOLE - GENERAL DISORDERS	DEATH	DEATH
91302	174		38	F	Citalopram	40	25	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
91304	40		43	F	Citalopram	40	293	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
91901	614		63	M	Citalopram	20	3	VASCULAR (EXTRACARDIAC) DISORDERS	ARTERIOSCLEROSIS	ARTERIOSCLEROSIS
91901	718		76	M	Citalopram	10	42	NEOPLASMS	RENAL CARCINOMA	RENAL CARCINOMA
92302	1101		82	F	Citalopram	40	88	RED BLOOD CELL DISORDERS	ANAEMIA	ANAEMIA
92302	5180 (1224)				Citalopram			VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER	CEREBROVASCULAR DISORDER
92302	5196 (1244)				Citalopram			NEOPLASM	PANCREAS NEOPLASM MALIGNANT	PANCREAS NEOPLASM MALIGNANT
92419	385		82	M	Citalopram	20		CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE	CARDIAC FAILURE
92420	1095		72	F	Citalopram	20	10	MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS	CARDIAC FAILURE	CARDIAC FAILURE
92420	B013		25	M	Citalopram	40	8	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
92420	B021		25	F	Citalopram	40	29	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE ATTEMPT

Appendix 8.1.1.1

STUDY	PAT. ID	PAT. INITIAL	AGE	SEX	DRUG	MG/ DAY	DAYS TX	BODY SYSTEM	PREFERRED TERM	REPORTED EVENT
92420	B102		76	M	Citalopram	20	9	CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE	CARDIAC FAILURE
92420	B104		69	F	Citalopram	10	18	CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE	CARDIAC FAILURE
92421	91		78	F	Citalopram	10	33	NEOPLASMS	NEOPLASM MALIGNANT	NEOPLASM MALIGNANT
92421	251		84	F	Citalopram	20	2	GASTRO-INTESTINAL SYSTEM DISORDERS	APPENDICITIS	APPENDICITIS
92421	1015		80	F	Citalopram	10	5	PLATELET, BLEEDING & CLOTTING DISORDERS	THROMBOSIS CEREBRAL	THROMBOSIS CEREBRAL
92421	1793		82	M	Citalopram	20	56	MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION
92422	43		79	F	Citalopram	20	67	MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS	CARDIAC FAILURE	CARDIAC FAILURE
92422	75		73	F	Citalopram	20	118	RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	PNEUMONIA
92422	126		87	F	Citalopram	20	50	GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER	GASTRIC ULCER
92422	452		82	M	Citalopram	10	194	VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER	CEREBROVASCULAR DISORDER
92422	465		90	F	Citalopram	10	25	VASCULAR (EXTRACARDIAC) DISORDERS	HAEMORRHAGE INTRACRANIAL	SUBDURAL HAEMATOMA
92422	507			M	Citalopram	40	80	RESISTANCE MECHANISM DISORDERS	INFECTION	INFECTION
92422	677		83	F	Citalopram	10	65	CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE	CARDIAC FAILURE
92422	687		91	M	Citalopram	20	123	LIVER & BILIARY SYSTEM DISORDERS	CHOLECYSTITIS	CHOLECYSTITIS
92430	113		66	F	Citalopram			PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
93401	65		74	M	Citalopram	20	35	BODY AS A WHOLE - GENERAL DISORDERS	SUDDEN DEATH	SUDDEN DEATH
93401	315		71	M	Citalopram	20	8	CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE	CARDIAC FAILURE

Appendix 8.1.1.1

STUDY	PAT. ID	PAT. INITIAL	AGE	SEX	DRUG	MG/ DAY	DAYS TX	BODY SYSTEM	PREFERRED TERM	REPORTED EVENT
93401	351		89	F	Citalopram	40	117	CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE	CARDIAC FAILURE
93401	755		87	F	Citalopram	40	176	BODY AS A WHOLE - GENERAL DISORDERS	SUDDEN DEATH	SUDDEN DEATH
93401	774		67	M	Citalopram	40	86	NEOPLASM	PULMONARY CARCINOMA	PULMONARY CARCINOMA
93401	790		85	F	Citalopram	40	48	HEART RATE AND RHYTHM DISORDERS	ARRHYTHMIA VENTRICULAR	ARRHYTHMIA VENTRICULAR
93410	166		76	M	Blinded		11	RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	PNEUMONIA
93410	209		78	F	Blinded		17	VASCULAR EXTRACARDIA	CEREBRAL VASCULAR DISORDER	CEREBRAL APOPLEXY
93410	229		97	F	Blinded		19	BODY AS A WHOLE - GENERAL DISORDERS	DEATH	DEATH
93410	253		75	F	Blinded		17	NEOPLASMS	NEOPLASM MALIGNANT	NEOPLASM MALIGNANT
93410	359		83	F	Blinded		8	NEOPLASMS	BILE DUCT CARCINOMA	BILE DUCT CARCINOMA
93410	369		96	F	Blinded		31	CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE	CARDIAC FAILURE
93410	556		70	F	Blinded		6	PLATELET, BLEEDING AND CLOTTING DISORDERS	EMBOLISM PULMONARY	EMBOLISM PULMONARY
93421	132		69	M	Citalopram	20	65	NEOPLASMS	RENAL CARCINOMA	RENAL CARCINOMA
93421	165		78	M	Citalopram	0	10	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
93421	166		82	F	Citalopram	20	8	MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS	CARDIAC FAILURE	CARDIAC FAILURE
93429	970		96	F	Citalopram	20	83	BODY AS A WHOLE - GENERAL DISORDERS	DEATH	DEATH
94406	S271		57	M	Citalopram	40	52	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
95208	1073		40	M	Citalopram	40	61	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
96902	5		63	M	Citalopram			RESPIRATORY SYSTEM DISORDERS	RESPIRATORY DISORDER	RESPIRATORY DISORDER

NOTE: BLANK ENTRIES=DATA NOT PROVIDED.

Appendix 8.1.1.1

By Patient Listing of Deaths Recorded During Placebo Treatment in the Development Program
Cutoff Date = 10/1/96

STUDY	PAT. ID	PAT. INITIAL	AGE	SEX	DRUG	MG/ DAY	DAYS TX	BODY SYSTEM	PREFERRED TERM	REPORTED EVENT
85A	2856		40	M	Placebo	0	9	PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
86141	313		79	F	Placebo	0		BODY AS A WHOLE - GENERAL DISORDERS	SUDDEN DEATH	SUDDEN DEATH
91202	1122		23	M	Placebo	0		PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
91202	4337		38	F	Placebo	0		BODY AS A WHOLE - GENERAL DISORDERS	DEATH	DEATH
91203	965		81	M	Placebo	0		VASCULAR (EXTRACARDIAC) DISORDERS	CEREBRAL HAEMORRHAGE	CEREBRAL HAEMORRHAGE
91901	606		50	M	Placebo	0		MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS	CARDIAC FAILURE	CARDIAC FAILURE
91901	740		76	F	Placebo	0	33	BODY AS A WHOLE - GENERAL DISORDERS	SUDDEN DEATH	SUDDEN DEATH

NOTE: BLANK ENTRIES=DATA NOT PROVIDED.

NOTE: Three patients (#s 313, 1122, 4337), died during placebo lead-in, prior to randomization.

Appendix 8.1.1.1

By Patient Listing of Deaths Recorded During Treatment with Other Antidepressants in the Development Program
Cutoff Date = 10/1/96

STUDY	PAT. ID	PAT. INITIAL	AGE	SEX	DRUG	MG/ DAY	DAYS TX	BODY SYSTEM	PREFERRED TERM	REPORTED EVENT
8009	25		58	M	Mianserin	0		CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	HEMIPLEGIA	HEMIPLEGIA
8009	32		44	M	Mianserin	60	26	MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS	CARDIAC FAILURE	CARDIAC FAILURE
88105	392		64	F	Impiramine	0		PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
91302	909		47	M	Fluoxetine			PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	SUICIDE
92302[A]	1516[A]		89	F	Amitriptyline[A]		7	METABOLIC AND NUTRITIONAL DISORDERS	URAEMIA	RENAL FAILURE, CHRONIC
92302	5347		71	M	Amitriptyline	50	29	VISION DISORDERS	DIPLOPIA	DIPLOPIA
93401	66		90	F	Mianserin	30	94	VASCULAR (EXTRACARDIAC) DISORDERS	CEREBRAL HAEMORRHAGE	CEREBRAL HAEMORRHAGE
93401	243		73	F	Mianserin	30	45	NEOPLASMS	COLON CARCINOMA	COLON CARCINOMA
93401	246		68	M	Mianserin	30	19	MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS	CORONARY ARTERY DISORDER	CORONARY SCLEROSIS
93401	599		85	F	Mianserin	30	15	VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER	CEREBRAL ISCHEMIA
93401	734		92	M	Mianserin	30	49	AUTONOMIC NERVOUS SYSTEM DISORDERS	SYNCOPE	SYNCOPE

NOTE: BLANK ENTRIES=DATA NOT PROVIDED.
[A] Patient 1516 in Study 92302 was assigned to amitriptyline treatment but died during the placebo lead-in period.

NOTE: The patient on fluoxetine (#909), actually died during washout, prior to the randomization phase.

Appendix 8.1.5.3.1

Treatment-Emergent Adverse Events Occurring in > 2% within any of the Citalopram Dose Groups in Study 91206 (Total N=650)					
	Placebo (N=129)	10 mg (N=131)	20 mg (N=130)	40 mg (N=131)	60 mg (N=129)
Body as a Whole					
Fatigue	5%	3%	4%	8%	16%
Back pain	5%	5%	4%	5%	5%
Fever	1%	5%	5%	4%	2%
Chest pain	1%	1%	4%	2%	2%
Hot flushes	1%	2%	2%	1%	2%
Asthenia	0%	1%	1%	0%	4%
Flu-like symptoms	2%	1%	1%	2%	1%
Malaise	0%	2%	2%	0%	0%
Pain	1%	2%	0%	2%	2%
Rigors	2%	0%	2%	1%	1%
Trauma-non-pathological	1%	2%	3%	1%	2%
Gastrointestinal System					
Nausea	11%	19%	28%	23%	22%
Mouth Dry	6%	15%	18%	13%	18%
Diarrhea	11%	13%	11%	16%	16%
Dyspepsia	9%	8%	8%	8%	9%
Constipation	5%	4%	9%	4%	8%
Abdominal pain	3%	7%	9%	2%	2%
Flatulence	3%	5%	4%	2%	3%
Vomiting	3%	1%	5%	2%	5%
Dysphagia	0%	0%	0%	2%	2%
Tooth disorder	1%	1%	0%	0%	2%
Cardiovascular System					
Bradycardia	0%	2%	2%	2%	0%
Palpitations	2%	2%	4%	2%	2%
Psychiatric Disorders					

Insomnia	11%	13%	15%	21%	24%
Somnolence	4%	9%	13%	22%	19%
Anorexia	2%	6%	8%	5%	9%
Nervousness	5%	5%	5%	3%	5%
Anxiety	4%	2%	6%	5%	2%
Libido decreased	1%	2%	3%	6%	5%
Yawning	0%	2%	2%	5%	7%
Agitation	2%	0%	2%	2%	5%
Dreaming abnormal	5%	1%	2%	2%	1%
Concentration impaired	1%	1%	2%	3%	1%
Confusion	1%	2%	2%	2%	2%
Paroniria	1%	1%	3%	1%	0%
Appetite increased	0%	2%	0%	1%	1%
Depression	0%	1%	0%	1%	2%
Central and Peripheral Nervous System					
Headache	33%	35%	36%	40%	23%
Dizziness	5%	5%	11%	10%	9%
Tremor	0%	2%	5%	6%	5%
Paresthesia	2%	4%	2%	1%	3%
Hypertonia	0%	0%	2%	2%	2%
Hypoesthesia	4%	2%	6%	5%	2%
Cramps legs	0%	1%	1%	2%	0%
Speech disorder	0%	2%	0%	2%	0%
Muscle contractions involuntary	0%	0%	1%	2%	1%
Hyperkinesia	0%	0%	0%	2%	0%
Respiratory System					
Upper respir. infection	10%	11%	8%	11%	9%
Rhinitis	9%	9%	6%	8%	12%
Pharyngitis	6%	8%	5%	8%	5%
Sinusitis	1%	7%	3%	8%	2%
Coughing	2%	4%	3%	2%	3%
Bronchitis	1%	2%	0%	0%	1%

Dyspnea	0%	0%	1%	2%	1%
Bronchospasm	0%	2%	0%	1%	0%
White cell and RES Disorders					
Lymphadenopathy	2%	0%	0%	2%	0%
Platelet, Bleeding, and Clotting Disorders					
Epistaxis	1%	0%	1%	2%	1%
Purpura	0%	2%	1%	0%	0%
Metabolic and Nutritional Disorders					
Weight decrease	0%	1%	2%	0%	1%
Skin and Appendages Disorders					
Sweating	2%	2%	8%	11%	12%
Rash	3%	1%	2%	3%	0%
Pruritis	1%	1%	2%	2%	2%
Dry skin	0%	0%	0%	0%	2%
Vision disorders					
Conjunctivitis	1%	0%	1%	2%	1%
Vision abnormal	0%	2%	0%	2%	3%
Xerophthalmia	0%	2%	1%	1%	0%
Special senses, other					
Tinnitus	2%	0%	0%	2%	3%
Taste perversion	1%	0%	2%	2%	2%
Urinary system					
Micturition frequency	2%	1%	2%	2%	4%
Micturition disorder	1%	0%	0%	2%	1%
Urine abnormal	1%	1%	2%	0%	0%
Reproductive disorders, male					
Impotence	0%	1%	0%	7%	5%
Ejaculation disorder	0%	0%	3%	2%	2%
Ejaculation failure	0%	2%	0%	2%	2%
Reproductive disorders, female					
Dysmenorrhea	2%	3%	4%	3%	5%
Menorrhagia	1%	0%	2%	2%	0%

Pregnancy unintended	1%	0%	2%	1%	0%
Musculo-Skeletal System					
Myalgia	4%	4%	5%	3%	3%
Arthralgia	3%	1%	5%	2%	4%
Dystonia	0%	0%	0%	2%	0%
Muscle weakness	0%	0%	2%	0%	0%
Resistance mechanism disorders					
Infection	2%	3%	2%	0%	1%

Appendix 8.1.5.3.2

Categorical Incidence of Treatment-Emergent Adverse Events Reported in Citalopram Patients from all Group 1 Studies (N=4168)[1,2]

Cardiovascular *Frequent:* tachycardia, postural hypotension. *Infrequent:* hypotension, edema, hypertension, angina pectoris, extrasystoles, cardiac failure, cerebrovascular disorder, myocardial infarction, flushing, arrhythmia, peripheral ischemia, myocardial ischemia. *Rare:* phlebitis, coronary artery disorder, cardiac arrest, atrial fibrillation, bundle branch block.

Central and Peripheral Nervous System Disorders *Infrequent:* vertigo, extrapyramidal disorder, convulsions, hypokinesia, neuralgia, dystonia, abnormal gait, ataxia. *Rare :* abnormal coordination, hyperesthesia, aphasia, dementia, ptosis, stupor, generalized spasm.

Endocrine Disorders *Rare:* hypothyroidism, goiter, gynecomastia.

Gastrointestinal Disorders *Frequent:* saliva increased. *Infrequent:* gastritis, gastroenteritis, eructation, stomatitis, hemorrhoids, teeth grinding, gingivitis, esophagitis, dental abscess. *Rare:* colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, appendicitis, hiccups.

General *Infrequent:* allergic reaction, alcohol intolerance, syncope, leg pain. *Rare:* abnormal crying, carpal tunnel syndrome.

Hemic and Lymphatic Disorders *Infrequent:* anemia, leukocytosis, leucopenia. *Rare:* pulmonary embolism, hematoma, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, gingival bleeding.

Metabolic and Nutritional Disorders *Frequent:* increased weight. *Infrequent:* increased hepatic enzymes, thirst, dry eyes, increased alkaline

phosphatase, abnormal glucose tolerance. *Rare:* bilirubinemia, hypokalemia, obesity, hypoglycemia, dehydration.

Musculoskeletal System Disorders *Infrequent:* arthritis, skeletal pain, fracture. *Rare:* bursitis.

Psychiatric Disorders *Frequent:* amnesia, apathy, suicide attempt. *Infrequent:* manic reaction, increased libido, aggressive reaction, drug dependence, depersonalization, euphoria, hallucination, psychotic depression, neurosis, delusion, paranoid reaction, emotional lability, drug abuse, panic reaction, psychosis. *Rare:* catatonic reaction, hysteria, melancholia.

Reproductive Disorders/Female[3] *Frequent:* vaginitis, amenorrhea, menstrual irregularity, premenstrual tension. *Infrequent:* galactorrhea, breast neoplasm, breast pain, uterine disorder, premenstrual syndrome, salpingitis, breast enlargement, vaginal hemorrhage, pelvic inflammation.

Reproductive Disorders/Male[4] *Infrequent:* prostatic disorder, perineal pain.

Respiratory System Disorders *Infrequent:* pneumonia. *Rare*: asthma, laryngitis, sinus congestion, pneumonitis, sputum increased, hyperventilation.

Skin and Appendages Disorders *Infrequent:* photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, psoriasis. *Rare:* hypertrichosis, injection site reaction, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani, verruca.

Special Senses *Frequent*: accommodation abnormal. *Infrequent:* earache, otitis media, eye pain. *Rare:* mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss, otitis externa, decreased hearing.

Urinary System Disorders - *Frequent:* polyuria. *Infrequent:* urinary tract infection, urinary incontinence, urinary retention, cystitis, dysuria. *Rare:* hematuria, oliguria, pyelonephritis, renal calculus, renal pain.

[1]All events are included except those already listed in Appendix 8.1.5.3.1, those occurring in only one patient, and those reported in terms so general as to be uninformative.
[2] Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.
[3]Based on female subjects; n=2784; [4]Based on male subjects; n=1384

Appendix 8.1.6.1

Laboratory Assessments in the Group 1 Short-Term, Placebo-Controlled Studies		
Study	**Assessments**	**Frequency**
85A	Chemistry (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, uric acid, alkaline phosphatase, GGT, LDH, AST, ALT, total bilirubin, triglycerides, cholesterol, total protein, albumin) Hematology (hematocrit, hemoglobin, WBC count with differential) Urinalysis (specific gravity, protein, glucose, occult blood, ketones, bilirubin, microscopic WBC and RBC, casts)	Baseline, weeks 1, 2, 3, 4
91206	Chemistry (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, uric acid, alkaline phosphatase, AST, ALT, total bilirubin, cholesterol, total protein, albumin) Hematology (hematocrit, hemoglobin, WBC count with differential, platelets) Urinalysis (color, appearance, specific gravity, pH, nitrite, bilirubin, urobilinogen, WBC and RBC counts, leucocyte esterase,)	Screening, weeks 2, 6
86A	Chemistry (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, uric acid, alkaline phosphatase, ALT, AST, GGT, LDH, total bilirubin, cholesterol, triglycerides, total protein, albumin) Hematology (hematocrit, hemoglobin, WBC count with differential, platelets, MCV, MCH, MCHC) Urinalysis (specific gravity, glucose, protein)	Baseline, weeks 1, 2, 3, 4
87A	Chemistry (sodium, potassium, chloride, phosphorus, bicarbonate, BUN, creatinine, glucose, calcium, uric acid, alkaline phosphatase, ALT, AST, GGT, LDH, total bilirubin, cholesterol, triglycerides, total protein, albumin) Hematology (hematocrit, hemoglobin, WBC count with differential, platelets) Urinalysis (specific gravity, glucose, protein, ketones, bilirubin, occult blood, WBCs, RBCs, casts)	Baseline, weeks 1, 2, 3, 4, 6
86141	Chemistry (sodium, potassium, creatinine, glucose, alkaline phosphatase, ALT, AST, GGT, total bilirubin, albumin) Hematology (hematocrit, hemoglobin, WBC count with differential, platelets, ESR, MCV)	Baseline, weeks 2, 6

89303	Chemistry (sodium, potassium, BUN, creatinine, alkaline phosphatase, ALT, AST, bilirubin, total protein, albumin) Hematology (hematocrit, hemoglobin, RBC count, WBC count, platelets)	Baseline, weeks 3, 6
89306	Chemistry (sodium, potassium, chloride, phosphorus, bicarbonate, BUN, creatinine, glucose, calcium, uric acid, alkaline phosphatase, ALT, AST, GGT, LDH, total bilirubin, cholesterol, total protein, albumin) Hematology (hematocrit, hemoglobin, RBC count, WBC count with differential, platelets, ESR, MCV)	Baseline, week 6
9I202	Chemistry (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, uric acid, CPK, alkaline phosphatase, ALT, AST, GGT, LDH, total bilirubin, cholesterol, triglycerides, total protein, albumin) Hematology (hematocrit, hemoglobin, RBC count, WBC count with differential, platelets, MCV)	Baseline, weeks 6, 8

Appendix 8.1.6.3.1.1: Mean Change from Baseline to Last On-Drug Visit in Serum Chemistry Values in Group 1 Placebo-Controlled Studies
(Cutoff Date: October 1, 1996)

	Citalopram			Placebo		
Parameter	N	$Mean_{BL}$	Mean Δ_{BL}	N	$Mean_{BL}$	Mean Δ_{BL}
Renal						
Creatinine (mg/dl)	1069	0.9	-0.00	457	1.0	-0.00
BUN (mg/dl)	986	13.0	-0.24	413	13.5	-0.00
Potassium (mmol/l)	949	4.3	0.03	394	4.4	0.07
Sodium (mmol/l)	992	141	0.5	416	141	0.4
Liver						
AST (U/L)	1007	24	0.0	425	25	0.2
ALT(U/L)	941	23	0.4	386	25	1.5
Alk phosphatase ((U/L)	1075	104	1.0	461	104	2.0
LDH (U/l)	129	124	-5.6	110	110	-5.8
Bilirubin (total) (mg/dl)	1073	0.6	-0.02	462	0.6	0.01*

GGT (U/l)	452	24	2.9	244	22	2.5
Albumin (g/dl)	1077	4.5	0.06	464	4.5	0.05
Globulin (g/dl)	509	2.5	0.03	161	2.5	0.02
Protein (total) (g/dl)	971	7.2	0.10	408	7.2	0.07
Other						
Calcium (mg/dl)	904	9.6	0.13	367	9.6	0.06*
Chloride (mmol/l)	842	106	0.3	342	106	0.2
Cholesterol (mg/dl)	790	211	0.5	309	212	1.5
Triglycerides (mg/dl)	351	155	1.8	189	158	3.0
Glucose (mg/dl)	806	90	1.0	314	90	-0.7
Uric acid (mg/dl)	791	5.0	0.16	308	5.0	0.01*

*Statistically significant mean changes from baseline as compared with placebo ($p<0.05$ on t-test)

Appendix 8.1.6.3.1.2: Mean Change from Baseline to Last On-Drug Visit in Hematology Values in Group 1 Placebo-Controlled Studies
(Cutoff Date: October 1, 1996)

	Citalopram			Placebo		
Parameter	N	$Mean_{BL}$	Mean Δ_{BL}	N	$Mean_{BL}$	Mean Δ_{BL}
Hemoglobin (g/dl)	1071	14.3	0.18	459	14.4	0.20
Hematocrit (PCV) (%)	1007	43	0.7	424	43	0.7
RBC count ($10^6/mm^3$)	960	4.7	0.07	356	4.7	0.04
MCV (fl)	956	91	0.1	354	91	0.1
MCH (pg)	870	30	-0.1	305	30	-0.0
MCHC (g/dl)	848	34	-0.1	294	33	-0.1
WBC count ($10^3/mm^3$)	1070	7.3	0.33	459	7.1	0.19
Eosinophils ($10^3/mm^3$)	833	0.2	-0.00	336	0.2	0.00

Neutrophils ($10^3/mm^3$)	761	4.5	0.20	257	4.3	0.10
Platelets ($10^3/mm^3$)	953	272	5.3	356	263	-0.6*

*Statistically significant mean changes from baseline as compared with placebo ($p<0.5$ on t-test)

Appendix 8.1.6.3.1.3: Mean Change from Baseline to Last On-Drug Visit in Urinalysis in Group 1 Placebo-Controlled Studies (Cutoff Date: October 1, 1996)

	Citalopram			Placebo		
Parameter	N	$Mean_{BL}$	Mean Δ_{BL}	N	$Mean_{BL}$	Mean Δ_{BL}
Specific gravity	537	1.019	-0.001	216	1.020	0.000

Appendix 8.1.6.3.2.1: Criteria for Identifying Patients with Potentially Clinically Significant Change in Clinical Chemistry Analytes

Analyte	Unit	Criteria
Renal		
Creatinine	mg/dL	> 2
BUN	mg/dL	> 30
Potassium	mmol/L	< 3.0 or > 5.5
Sodium	mmol/L	< 130 or > 150
Liver		
AST	U/L	> 3 x ULN
ALT	U/L	> 3 x ULN
Alkaline phosphatase	U/L	≥ 3 x ULN
LDH	U/L	> 3 x ULN
Bilirubin (total)	mg/dL	> 2
GGT	U/L	≥ 3 x ULN
Albumin	g/dL	< 2.5
Globulin	g/dL	< 0.5 x LLN or > 2 x ULN
Protein (total)	g/dL	< 0.9 x LLN or > 1.1 x ULN
Other		
Calcium	mg/dL	< 7 or > 12

Chloride	mmol/L	< 0.9 x LLN or >1.1 x ULN
Cholesterol	mg/dL	> 300
Triglycerides	mg/dl	> 300
Glucose	mg/dL	< 50 or > 250
Uric acid, male	mg/dL	> 10.0
Uric acid, female	mg/dL	> 8.0

Appendix 8.1.6.3.2.2: Criteria for Identifying Patients with Potentially Clinically Significant Change in Hematology Analytes

Analyte	Unit	Criteria
Hematocrit	PCV (%)	< 0.9 x LLN
Hemoglobin	g/dl	< 0.9 x LLN
RBC count	$10^6/mm^3$	< 0.9 x LLN; > 1.1 x ULN
MCV	fl	< 0.8 x LLN; > 1.2 x ULN
MCH	pg	< 0.8 x LLN; >1.2 x ULN
MCHC	g/dl	< 0.8 x LLN; >1.2 x ULN
WBC count	$10^3/mm^3$	< 2.5; > 15.0
Eosinophils	$10^3/mm^3$	> 0.7
Neutrophils	$10^3/mm^3$	< 1.0
Platelets	$10^3/mm^3$	< 75; > 700

Appendix 8.1.6.3.2.3: Criteria for Identifying Patients with Potentially Clinically Significant Change in Urinary Analytes

Analyte	Criteria
Protein	Not negative
Glucose	Not negative
Blood	Not negative
Specific gravity	> 1.1

Appendix 8.1.6.3.2.4: Incidence of Potentially Clinically Significant Changes in Serum Chemistry Values in Group 1 Placebo-Controlled, Short-Term Studies
(Cutoff Date: October 1, 1996)

	Citalopram			Placebo		
Parameter & PCS criteria	**Total N**	**Abnormal #**	**%**	**Total N**	**Abnormal #**	**%**
Renal						
Creatinine -H	1069	2	0.2	457	0	0.0
BUN -H	986	2	0.2	413	1	0.2
Potassium -L	949	0	0.0	394	0	0.0
Potassium -H	949	10	1.1	394	9	2.3
Sodium -L	992	3	0.3	416	0	0.0
Sodium -H	992	1	0.1	416	2	0.5
Liver						
AST -H	1007	4	0.4	425	1	0.2
ALT -H	941	3	0.3	386	1	0.3
Alk phosphatase -H	1075	0	0.0	461	0	0.0
LDH -H	129	0	0.0	110	0	0.0
Bilirubin (total) -H	1073	2	0.2	462	3	0.6
GGT -H	452	7	1.5	244	4	1.6
Albumin -L	1077	0	0.0	464	0	0.0
Globulin -L	509	0	0.0	161	0	0.0
Globulin -H	509	0	0.0	161	0	0.0
Protein (total) -L	971	4	0.4	408	2	0.5
Protein (total) -H	971	0	0.0	408	1	0.2
Other						
Calcium -L	904	1	0.1	367	1	0.3
Calcium -H	904	0	0.0	367	0	0.0
Chloride -L	842	0	0.0	342	0	0.0
Chloride -H	842	0	0.0	842	0	0.0

Cholesterol -H	790	33	4.2	309	13	4.2
Triglycerides -H	351	37	10.5	189	24	12.7
Glucose -L	806	9	1.1	314	1	0.3
Glucose -H	806	2	0.2	314	0	0.0
Uric acid (F) -H	481	5	1.0	159	0	0.0
Uric acid (M) -H	310	1	0.3	149	1	0.7

Appendix 8.1.6.3.2.5: Incidence of Potentially Clinically Significant Changes in Hematology Values in Group 1 Placebo-Controlled, Short-Term Studies
(Cutoff Date: October 1, 1996)

	Citalopram			Placebo		
Parameter & PCS criteria	**Total N**	**Abnormal #**	**%**	**Total N**	**Abnormal #**	**%**
Hemoglobin -L	1071	14	1.3	459	10	2.2
Hematocrit -L	1007	18	1.8	424	9	2.1
RBC count -H	960	3	0.3	356	0	0.0
RBC count -L	960	22	2.3	356	5	1.4
MCV -L	956	1	0.1	354	0	0.0
MCV -H	956	0	0.0	354	0	0.0
MCH -L	870	1	0.1	305	0	0.0
MCH -H	870	0	0.0	305	0	0.0
MCHC -L	848	1	0.1	294	0	0.0
MCHC -H	848	0	0.0	294	0	0.0
WBC count -L	1070	4	0.4	459	1	0.2
WBC count -H	1070	9	0.8	459	6	1.3
Eosinophils -H	833	14	1.7	336	3	0.9
Neutrophils -L	761	2	0.3	257	0	0.0
Platelets -L	953	1	0.1	356	0	0.0
Platelets -H	953	0	0.0	356	0	0.0

Appendix 8.1.6.3.2.6: Incidence of Potentially Clinically Significant Changes in Urinalysis Results in Group 1 Placebo-Controlled, Short-Term Studies
(Cutoff Date: October 1, 1996)

	Citalopram			Placebo		
Parameter & PCS criteria	**Total N**	**Abnormal #**	**%**	**Total N**	**Abnormal #**	**%**
Protein	540	199	36.9	215	66	30.7
Glucose	539	18	3.3	216	5	2.3
Blood	433	76	17.6	115	12	10.4

Appendix 8.1.6.3.3: Citalopram Patient Withdrawals Due to Clinical Chemistry Abnormalities

Study	Patient	Dose (mg /day)	Study day[1]	ALT (U/L)	AST (U/L)	GGT (U/L)	Bilirubin (mg/dL)	Alk. Phos (U/L)	Glc (mg/dl)	K+ (mmol /l)	Reason for Withdrawal
85A	2017	60	7								Infectious hepatitis
92301	449	20	51								Bilirubinemia
	161	20	11								GGT ↑
	427	20	54								SGPT ↑
8213	1132	40	15								GGT ↑
	1311	20	274								GGT ↑
	428	20	310								AlkPhos ↑
	1235	20	201								Laxative abuse
89304	1605	20	56			-	-				SGOT ↑
91202	912	60	177			-	-				SGOT ↑
86141	310	20	14								IDDM
91206	621	40	20								↑ Glc
92302	1244	20	40								Pancreatic CA

[1]Days of treatment received at time of event onset

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Appendix 8.1.6.3.4: Citalopram Withdrawals Due to Hematology Abnormalities

Study	Patient	Dose (mg/day)	Study day	Hemoglobin (g/dL)	Hematocrit (%)	Reason for Withdrawal
91206	603	60				Anemia

Appendix 8.1.7.1: Vital Sign Assessments in the Group 1 Short-Term, Placebo-Controlled Studies

Study	Assessments	Frequency
85A	Supine and standing blood pressure and pulse Weight	Baseline, weeks 1, 2, 3, 4 Baseline, week 4
91206	Sitting blood pressure and pulse Weight	Baseline, weeks 1-6
86A	Supine and standing blood pressure and pulse Weight	Baseline, weeks 1, 2, 3, 4 Baseline, week 4
87A	Supine and standing blood pressure and pulse	Baseline, weeks 1, 2, 3, 4, 6
86141	Supine and standing blood pressure and pulse	Baseline, weeks 2, 4, 6
91202	Supine and standing blood pressure and pulse	Baseline, week 8

Appendix 8.1.7.3.1: Mean Change from Baseline to Last On-Dosing Vital Sign Assessment in Group 1 Short-term Placebo-Controlled Studies; Cutoff date: October 1, 1996

Parameter	Citalopram			Placebo		
	N	Mean Base-line	Mean Change	N	Mean Base-line	Mean Change
Systolic BP, sitting (mmHg)	529	117.7	-1.6	135	114.8	0.8 *
Diastolic BP, sitting (mmHg)	529	76.5	-1.0	135	75.2	-0.6
Pulse, sitting (bpm)	528	75.3	-2.2	134	72.6	1.7 *
Systolic BP, standing (mmHg)	450	128.8	-2.8	239	127.8	-1.9
Diastolic BP, standing (mmHg)	450	82.3	-1.9	239	82.5	-1.6
Pulse, standing (bpm)	446	79.3	-2.4	238	79.0	1.6 *
Systolic BP, supine (mmHg)	462	130.9	-3.8	243	128.6	-1.8
Diastolic BP, supine (mmHg)	462	79.8	-1.6	243	80.5	-1.9
Pulse, supine (bpm)	460	74.2	-2.6	243	74.3	0.5 *
Weight (kg)	957	73.7	-0.4	359	71.7	-0.1*

*Statistically significant mean changes from baseline as compared to placebo ($p<0.05$ on t-test)

Appendix 8.1.7.3.2.1: Criteria for Identifying Vital Sign Changes of Potential Clinical Significance	
Variable	**Criteria**
Systolic Blood Pressure	Increase of ≥ 20 mmHg and BP ≥ 180 mmHg OR Decrease of ≥ 20 mmHg and BP ≤ 90 mmHg
Diastolic Blood Pressure	Increase of ≥ 15 mmHg and BP ≥ 105 mmHg OR Decrease of ≥ 15 mmHg and BP ≤ 50 mmHg
Pulse	Increase of ≥ 15 bpm and rate ≥ 120 bpm OR Decrease of ≥ 15 bpm and rate ≤ 50 bpm
Weight	Change of ≥ 7% body weight

Appendix 8.1.7.3.2.2 Proportion of Patients with Vital Sign Changes of Potential Clinical Significance for Group 1 Short-Term Placebo-Controlled Studies; Cutoff: October 1, 1996

	Citalopram			Placebo		
Parameter	Total	Abnormal	%	Total	Abnormal	%
↑ SBP (standing)	450	5	1.1	239	2	0.8
↓ SBP (standing)	450	7	1.6	239	2	0.8
↑ DBP (standing)	450	2	0.4	239	3	1.3
↓ DBP (standing)	450	0	0.0	239	0	0.0
↑ Pulse (standing)	446	1	0.2	238	1	0.4
↓ Pulse (standing)	446	1	0.2	238	1	0.4
↑ SBP (sitting)	529	0	0.0	135	0	0.0
↓ SBP (sitting)	529	5	0.9	135	2	1.5
↑ DBP (sitting)	529	1	0.2	135	0	0.0
↓ DBP (sitting)	529	11	2.1	135	1	0.7
↑ Pulse (sitting)	528	2	0.4	134	0	0.0
↓ Pulse (sitting)	528	2	0.4	134	1	0.7
↑ SBP (supine)	462	6	1.3	243	3	1.2
↓ SBP (supine)	462	3	0.6	243	0	0.0
↑ DBP (supine)	462	4	0.9	243	0	0.0
↓ DBP (supine)	462	0	0.0	243	0	0.0
↑ Pulse (supine)	460	0	0.0	243	0	0.0
↓ Pulse (supine)	460	2	0.4	243	1	0.4
↑ Weight	957	7	0.7	359	2	0.6
↓ Weight	957	13	1.4	359	8	2.2

Appendix 8.1.8.1: Schedule for ECG Recording in Five Placebo-Controlled Group 1 Studies	
Study	**Frequency**
85A	Baseline, weeks 1, 2, 3, 4
91206	Screening, weeks 2, 6
86141	Baseline, weeks 2, 6
89304	Weeks 0, 8 of Period A; Weeks 8, 24 of Period B
91203	Screening, weeks 6, 12

Appendix 8.1.8.3.1: Mean Change from Baseline to Last On-Drug Assessment for ECG Parameters in Five Group 1 Placebo-Controlled Studies (Cutoff date: October 1, 1996)

	Citalopram			**Placebo**		
Parameter	N	Mean Base-line	Mean Change	N	Mean Base-line	Mean Change
PQ-interval (sec)	780	0.16	-0.001	236	0.16	-0.001
QRS-interval (sec)	804	0.08	0.001	240	0.08	0.000
QT_c (sec)	797	0.41	-0.002	241	0.41	-0.000
Heart rate	802	69	1.7	241	68	0.0 *
T-wave amplitude	794	4.6	0.33	237	5.3	0.14

*$p < 0.05$ on t-test, mean change between citalopram and placebo.

Appendix 8.1.8.3.2.1: Criteria for Determining Potentially Clinically Significant Changes in ECG Results	
Variable	**Criteria**
PQ interval	> 0.24 sec
QRS interval	> 0.12 sec
QT_c	> 0.50 sec
Sinus bradycardia	< 50 bpm
Sinus tachycardia	> 100 bpm
T-wave flattening	Amplitude < 2 mm

Appendix 8.1.8.3.2.2: Proportions of Patients with ECG Changes of Potential Clinical Significance for Five Group 1 Placebo-Controlled Studies; Cutoff date: October 1, 1996

	Citalopram			**Placebo**		
Parameter	N	Abnormal #	Abnormal %	N	Abnormal #	Abnormal %
PQ-interval	780	0	0.0	236	0	0.0
QRS-interval	804	16	2.0	240	2	0.8
QT_c	797	9	1.1	241	1	0.4
Sinus bradycardia	802	38	4.7	241	12	5.0
Sinus tachycardia	802	7	0.9	241	1	0.4
T-wave flattening	794	34	4.3	237	4	1.7

Appendix 8.1.12.1

Summary of Patient Narrative Information for Group 1 and 3 Patients who Ingested Overdose (All Recovered)					
Pt. #	**Study #**	**Age/ Sex**	**Citalopram (mg)**	**Other Drugs**	**Symptoms/Blood Levels**
0021	7801	35/M	unknown	none	Tiredness, dizziness, tremor, nausea. ECGs, vital signs, serum chemistries normal. 4 and 60 hours post-OD: 3-4x the patient's normal steady state and 6x higher than average levels.
183	8213	46/M	unknown	none	Tired, dizzy, nausea, tremor. No ECG changes.
1309	95208	31/F	unknown	Oxazepam, noctran	Coma.
588	89411	35/F	80	Clorazepate, 50 mg; zolpidem, 40 mg	No symptom information.
101	93401	90/F	120	Oxazepam, diazepam, levo-mepromazine	No symptom information.
S062	94406	53/F	180	none	Nausea, headache, dizziness.
184	88701	68/M	200-240	Probably EtOH	ECG: sinus tachycardia), and no other abnormalities.
1911	89304	33/F	240	2 TCAs, benzodiazepine	No symptom information.
261	8213	34/M	300	none	Only reported symptom was slight sedation.

733	88105	50/F	Approx. 300	Benzodiazepine, EtOH	Unconscious on admission with no ECG, VS abnormalities. Blood citalopram demethylcitalopram , didemethylcitalopram= . Levels suggest patient may not have taken OD.
60	90416	41/M	360	Temazepam, 150 mg	Drowsiness.
127	91202	19/F	400	none	Nausea, sedation.
PG	92415	29/M	460	none	No information.
608	8213	51/F	600	Insulin, 40 IU	No symptoms, abnormalities noted.
3702	89304	64/F	600	Oxazepam, prazepam	Bradycardia , no other reported abnormalities.
678	88105	42/M	700	none	Somnolence, VS and ECG normal.
168	89201	17/F	1000	none	Sweating, normal ECG and labs
136	89401	54/M	1120	EtOH	Sweating, tremor, hyperventilation, hypokalemia, hypophosphatemia , delirium tremens.
377	89306	43/F	1200	EtOH	Floppy limbs, drowsy. Normal reflexes & vital signs. Blood levels 3 days later: citalopram demethylcitalopram , didemethylcitalopram
25	8213	40/F	1400	EtOH	Reported asymptomatic.
913	89304	51/F	1520	Temazepam, 180 mg	Comatose on admission, sinus bradycardia, repolarization and conduction abnormalities, ventricular extrasystoles. Two days later paresthesia, "precordalgia", seizure
606	8213	61/F	1800	none	Unconscious, cyanotic, muscle cramps, , no ECG abnormalities. Serum citalopram demethylcitalopram

1135	8213	29/F	2000	Lorazepam, 375 mg; levomepromazine, 2400 mg; cyamemazine, 1200 mg; triazolam, 10 mg	Comatose on admission, no other information.

Appendix 8.1.12.2

SRS Patients Who Ingested Fatal Overdoses of Citalopram				
DSU #	**Age/ Sex**	**Citalopram (mg)**	**Other Drugs**	**Post-Mortem Blood Levels**
960430	33/M	unknown	EtOH	Cit
960188	48/F	unknown	Diazepam, zopiclone, trimeprazine	Cit desmethylcit
960184	53/F	840	Diazepam	Cit ; desmethylcit
960183	30/F	1900	EtOH	Cit desmethylcit
960186	56/M	1960	none	Cit desmethylcit
960187	23/M	1960	Diazepam, EtOH	Cit desmethylcit=trace

Appendix 8.2.1.3: Summary of Deaths in the Development Program Due to Arrhythmia or Possible Arrhythmia						
Study /Pt.#	Age /Sex	Dose (mg)	Time (days)	Event(s)	Medical Conditions	Other Meds
93401 #790	85/F	40	46	Torsades	Dementia, atrial fibrillation, recurrent infection, cachexia, anemia	Digoxin, cisapride, antibiotics
8213 #161	78/M	20	123	Loss of consciousness, vent. fibrillation, possible MI	Dementia, h/o MI with continuing atrial arrhythmia, prostate CA, CVA, bronchopneumonia	Warfarin, furosemide, digoxin, amitriptyline
8213 #252	49/F	20	21	Cardiac arrest	"Circulatory insufficiency"	Dihydroergotamine
89422 #9	52/M	30	65	Sudden death in sleep, MI	No info.	None.
91203 #339	83/F	40	90	Found dead in home	Alzheimer's	No info.