Appendix 2 Supplementary tables A-M [posted as supplied by author]

List of Tables

Table A – Pairwise comparison tables – Primary and secondary efficacy variables (8 weeks)

Primary Efficacy Variables [8 Weeks]

		Omnibus	Paroxetine v. Placebo	Imipramine v. Placebo	Paroxetine v. Imipramine
		Analysis of Variance			
HAM-D Change	**OC**	**0.255**	**0.106**	**0.673**	**0.261**
	LOCF	**0.204**	**0.153**	**0.895**	**0.109**
		Logistical Regression			
HAM-D Response ≥50% drop or ≤8	**OC**	**0.131**	**0.044**	**0.337**	**0.332**
	LOCF	**0.269**	**0.117**	**0.651**	**0.253**

Secondary Efficacy Variables [8 Weeks]

		Omnibus	Paroxetine v. Placebo	Imipramine v. Placebo	Paroxetine v. Imipramine
		Analysis of Variance			
K-SADS-L Change	**OC**	**0.459**	**0.209**	**0.679**	**0.447**
	LOCF	**0.131**	**0.072**	**0.902**	**0.084**
CGI Mean Score	**OC**	**0.086**	**0.034**	**0.269**	**0.289**
	LOCF	**0.155**	**0.084**	**0.836**	**0.124**
Autonomous Function Check List Change	**OC**	**0.325**	**0.166**	**0.243**	**0.903**
	LOCF	**0.367**	**0.145**	**0.498**	**0.490**
Self Perception Profile Change	**OC**	**0.875**	**0.904**	**0.702**	**0.619**
	LOCF	**0.788**	**0.711**	**0.489**	**0.761**
Sickness Impact Profile Change	**OC**	**0.244**	**0.752**	**0.070**	**0.191**
	LOCF	**0.233**	**0.504**	**0.055**	**0.302**

Analysis of Variance - with Treatment and Site Effects in the model
Logistical Regression - with Treatment and Site Effects in the model
OC – Observed Cases
LOCF – Last Observation Carried Forward
Note - All p values uncorrected for multiple variable sampling

Table B – Additional AEs found during review of 93 CRFs (acute phase plus taper)

SOC Type	Paroxetine (n=31)	Imipramine (n=40)	Placebo (n=22)
Cardiovascular	0	5	0
Gastrointestinal	4	4	2
Psychiatric	12	1	4
Respiratory	0	1	1
Other	7	6	3
Total	**23**	**17**	**10**

Table C – Breakdown of new adverse events found during CRF review by System Organ Class (SOC) (MedDRA)

SOC	Adverse Event	Paroxetine N=31	Imipramine N=40	Placebo n=22
		No. found in CRF review	**No. found in CRF review**	**No. found in CRF review**
Psychiatric disorders	Suicidal ideation	2	0	1
	Feelings of hopelessness	1	0	0
	Self harm/suicidal gesture	1	0	0
	Depression worsening	2	0	1
	Psychosis	1	0	0
	Increased anger/aggression	1	0	0
	Insomnia	1	0	0
	Agitation	1	0	0
	Somnolence	0	0	0
	Nervousness	0	1	0
	Decreased concentration	0	0	1
	Mutism/soft speech	2	0	0
	Increased anxiety	0	0	1
	Total	**12**	**1**	**4**
Gastrointestinal disorders	Nausea	1	1	2
	Gastrointestinal complaints	1	0	0
	Increased sickness	1	0	0
	Diarrhoea	1	1	0
	Vomiting	0	1	0
	Heartburn	0	1	0
	Total	**4**	**4**	**2**
Metabolism and nutrition disorders	Loss of appetite	1	0	0
	Weight loss	2	0	0
	Dehydration	0	1	0
	Total	**3**	**1**	**0**
Musculoskeletal and connective tissue disorders	Neck pain	0	0	1
	Joint pain	0	0	1
	Total	**0**	**0**	**2**
General disorders and administration site conditions	Fatigue	4	1	0
	Body shakes	0	1	0
	Fever	0	0	1
	Total	**4**	**4**	**1**
Nervous systems disorders	Headache	0	2	0
	Total	**0**	**2**	**0**
Respiratory, thoracic and mediastinal disorders	Chest congestion	0	1	0
	Cough	0	0	1
	Total	**0**	**1**	**1**
Cardiac disorders	Tachycardia	0	0	0
	Dizziness	0	3	0
	Low systolic BP	0	1	0
	High BP	0	1	0
	Total	**0**	**5**	**0**
Skin and subcutaneous tissue disorders	Sweating	0	1	0
	Total	**0**	**1**	**0**
Total Psychiatric disorders		**12**	**1**	**4**
TOTAL ALL OTHER AES		**11**	**16**	**6**
GRAND TOTAL		**23**	**17**	**10**

NB. All AEs found for the paroxetine and imipramine patients were reported during the acute phase. For the placebo group, 2 additional AEs ('depression worsening' & 'increased irritability') were found during the continuation phase.

Table D – Summary of all adverse events within each SOC, including those classed as 'Severe' by investigator

SOC	Paroxetine N=93		Imipramine N=95		Placebo N=87	
	No. AEs reported (CSR check)	No. reported as SEVERE	No. AEs reported (CSR check)	No. reported as SEVERE	No. AEs reported (CSR check)	No. reported as SEVERE
Cardiac and vascular disorders	44	1 (2.3%)	130	3 (2.3%)	32	0
Gastrointestinal disorders	112	25 (22.3%)	147	20 (13.6%)	79	4 (5.1%)
Psychiatric disorders	103	32 (31.1%)	63	4 (6.3%)	24	6 (25%)
Nervous system disorders	101	7 (6.9%)	114	14 (12.3%)	77	7 (9.1%)
Respiratory, thoracic and mediastinal disorders	42	2 (4.8%)	22	1 (4.5%)	39	4 (10.3%)
General disorders	15	2 (13.3%)	10	1 (10.0%)	17	1 (5.9%)
Skin and subcutaneous tissue disorders	10	0	17	1 (5.9%)	10	1 (10%)
Renal and urinary disorders	5	0	9	1 (11.1%)	4	0
Immune system disorders	2	0	2	0	3	0
Endocrine disorders	1	0	1	1 (100%)	1	0
Blood and lymphatic disorders	1	0	4	0	3	0
Musculoskeletal and connective tissue disorders	8	0	7	0	16	0
Reproductive system and breast disorder	4	0	4	1 (25%)	4	1 (25%)
Infections	6	1 (16.7%)	5	1 (20%)	4	1 (25%)
Eye disorders	5	0	4	0	1	0
Metabolism and nutritional disorders	17	0	6	0	10	1 (10%)
Ear and labyrinth Disorders	1	0	0	-	0	-
Injuries, poisoning & procedural complications	3	0	3	1 (33.3%)	6	0
Pregnancy, puerperium and perinatal conditions	0	-	2	1 (50%)	0	-
Surgical and medical procedures	1	0	2	0	0	-
TOTAL NUMBER OF AEs	**481**	**70 (14.6%)**	**552**	**50 (9.1%)**	**330**	**26 (7.9%)**

Table E – Full breakdown of all adverse events within each SOC, including those classed as 'Severe' by investigator – events from CSR check only

SOC	MedDRA preferred term	Paroxetine N=93		Imipramine N=95		Placebo N=87	
		No. AEs reported (CSR check)	No. reported as Severe	No. AEs reported (CSR check)	No. reported as Severe	No. AEs reported (CSR check)	No. reported as Severe
Cardiac and vascular disorders	Arrhythmia	0	-	1	0	1	0
	Atrial ectopic	0	-	0	-	1	0
	AV block	1	0	2	0	2	0
	Bradycardia	0	-	1	0	1	0
	Bundle branch block	0	-	1	0	1	0
	Chest pain	2	1	5	1	2	0
	Dizziness	35	0	57	1	18	0
	ECG/ T-ECG abnormal	0	-	7	0	2	0
	Hot flush	0	-	6	0	2	0
	Postural hypotension/ hypotension	3	0	17	0	1	0
	QT interval prolonged	0	-	3	0	0	-
	Tachycardia	3	0	28	1	1	0
	Hypertension	0	-	2	0	0	-
	TOTAL	**44**	**1**	**130**	**3**	**32**	**0**
Gastrointestinal disorders	Abdominal pain	0	-	0	-	2	0
	Constipation	7	0	10	2	4	0
	Cramps	14	1	11	0	14	0
	Diarrhea	12	6	8	3	9	0
	Dry Mouth	20	0	48	2	12	1
	Dyspepsia/ heartburn	8	0	12	0	4	0
	Food poisoning	1	0	0	-	1	1
	Gastroenteritis/ GI complaints	0	-	1	1	0	-
	Nausea/ sickness	37	10	43	5	27	2
	Reflux	1	0	0	-	0	-
	Retching	0	-	1	0	0	-
	Sores	0	-	0	-	1	0
	Stomatitis	0	-	2	2	0	-
	Ulcer	1	1	0	0	0	0
	Vomiting	11	7	11	5	5	0
	TOTAL	**112**	**25**	**147**	**20**	**79**	**4**
Psychiatric disorders	Abnormal dreams	3	0	5	0	2	0
	Aggravated depression	5	3	3	0	2	2
	Aggression/ increased anger	7	3	3	2	0	-
	Agitation	1	-	1	0	0	-
	Akathisia	18	1	12	1	8	0
	Anorgasmia	1	1	0	-	0	-
	Anxiety	2	1	0	-	1	1
	Concentration low	2	0	1	0	0	-

	Depersonalisation	0	-	1	0	1	0
	Disinhibition	4	3	1	0	2	1
	Drug withdrawal syndrome	2	1	0	-	0	-
	Hallucinations	1	1	1	1	0	-
	Hopelessness (feelings of)	0	-	0	-	0	-
	Impulsive behaviour	1	-	0	-	0	-
	Insomnia	16	2	14	0	4	1
	Nervousness	0		0	-	0	-
	Paranoia	1	0	0	-	0	-
	Psychosis	1	1	0	-	0	-
	Somnolence	24	6	14	0	3	0
	Substance abuse	1	1	1	0	0	-
	Suicidal ideation/gesture	5	4	3	0	1	1
	Suicide attempt	8	4	3	0	0	-
	TOTAL	**103**	**32**	**63**	**4**	**24**	**6**
Nervous system disorders	Bad taste	0	-	3	0	0	-
	Convulsion	0	-	1	1	0	-
	Dystonia	5	0	7	0	3	0
	Headache	59	3	59	9	56	4
	Laryngitis	1	0	0	-	0	-
	Memory loss	0	-	1	0	0	-
	Migraine	1	0	1	1	0	-
	Myoclonus	4	1	1	0	0	-
	Paresthesia	1	0	1	0	0	-
	Sore throat	10	1	12	1	11	2
	Tics	1	0	1	0	0	-
	Tinnitus	0	-	2	0	0	-
	Toothache	6	1	0	-	3	1
	Tremor	11	1	20	1	2	0
	Vision blurred	2	0	5	1	2	0
	TOTAL	**101**	**7**	**114**	**14**	**77**	**7**
Respiratory, thoracic and mediastinal disorders	Chest cold/ congestion	11	1	6	0	14	1
	Coughing	6	0	4	0	6	0
	Dyspnea	3	1	5	1	2	0
	Epistaxis	1	0	1	0	0	-
	Nasopharyngitis	3	0	0	-	1	0
	Respiratory disorder	0		0	-	2	0
	Rhinitis	10	0	3	0	5	1
	Sinusitis	8	0	3	0	8	2
	Sneezing	0	-	0	-	1	0
	TOTAL	**42**	**2**	**22**	**1**	**39**	**4**
General disorders and administration site conditions	Body Shakes	0	-	0	-	0	-
	Fatigue	15	2	8	1	11	1
	Fever	0	-	2	0	4	0
	Pain	0	-	0	-	2	0
	TOTAL	**15**	**2**	**10**	**1**	**17**	**1**
Skin and subcutaneous tissue disorders	Acne	3	0	2	0	1	0
	Dermatitis	1	0	2	0	1	0
	Itchy	0	-	1	0	1	1
	Rash	4	0	5	1	4	0

	Scabies	0	-	0	-	1	0
	Sweating	2	0	7	0	1	0
	Syncope	0	-	0	-	1	0
	TOTAL	**10**	**0**	**17**	**1**	**10**	**1**
Renal and urinary disorders	Albuminuria	0	-	0	-	4	0
	Cystitis	1	0	0	-	0	-
	Nocturia	0	-	1	0	0	-
	Polyuria	0	-	1	0	0	-
	Pyuria	0	-	1	0	0	-
	Urinary abnormality	3	0	0	-	0	-
	Urinary retention	0	-	6	1	0	-
	UTI	1	0	0	-	0	-
	TOTAL	**5**	**0**	**9**	**1**	**4**	**0**
Immune system disorders	Allergy	1	0	1	0	3	0
	Urticaria	1	0	1	0	0	-
	TOTAL	**2**	**0**	**2**	**0**	**3**	**0**
Endocrine disorders	Amenorrhea	1	0	0	-	0	-
	Hyperglycemia	0	-	1	1	1	0
	TOTAL	**1**	**0**	**1**	**1**	**1**	**0**
Blood and lymphatic disorders	Anaemia	1	0	1	0	0	-
	Eosinophilia	0	-	1	0	1	0
	Leukopenia	0	-	2	0	0	-
	Lymphadenopathy	0	-	0	-	1	0
	Thrombocythemia	0	-	0	-	1	0
	TOTAL	**1**	**0**	**4**	**0**	**3**	**0**
Musculoskeletal and connective tissue disorders	Arthralgia	1	0	1	0	4	0
	Back pain	5	0	2	0	10	0
	Chills	0	-	3	0	0	-
	Myalgia	2	0	1	0	2	0
	TOTAL	**8**	**0**	**7**	**0**	**16**	**0**
Reproductive system and breast disorder	Breast enlargement	1	0	0	-	0	-
	Dysmenorrhea	3	0	4	1	4	1
	TOTAL	**4**	**0**	**4**	**1**	**4**	**1**
Infections	Herpes zoster	0	-	0	-	1	0
	Infection	4	0	3	1	3	1
	Otitis media	2	1	2	0	0	-
	TOTAL	**6**	**1**	**5**	**1**	**4**	**1**
Eye disorders	Conjunctivitis	2	0	0	-	1	0
	Itchy eyes	2	0	1	0	0	-
	Mydriasis	0	-	1	0	0	-
	Photosensitivity	1	0	1	0	0	-
	Photopsia	0	-	1	0	0	-
	TOTAL	**5**	**0**	**4**	**0**	**1**	**0**
Metabolism and nutritional disorders	Decreased appetite	9	0	2	0	4	0
	Dehydration	0	-	0	-	0	-
	Increased appetite	4	0	1	0	1	0
	Thirst	0	-	2	0	3	0

	Weight gain	2	0	0	-	0	-
	Weight loss	2	0	1	0	2	1
	TOTAL	**17**	**0**	**6**	**0**	**10**	**1**
Ear and labyrinth disorders	Ear pain	1	0	0	-	0	-
	TOTAL	**1**	**0**	**0**	**-**	**0**	**-**
Injuries, poisoning and procedural complications	Head injury	0	-	1	0	0	-
	Overdose	0	-	1	1	0	-
	Trauma	3	0	1	0	6	0
	TOTAL	**3**	**0**	**3**	**1**	**6**	**0**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	-	2	1	0	-
	TOTAL	**0**	**-**	**2**	**1**	**0**	**-**
Surgical and medical procedures	Tooth extraction	1	0	2	0	0	-
	TOTAL	**1**	**0**	**2**	**0**	**0**	**-**
		Total AEs	**TOTAL SAEs**	**Total AEs**	**TOTAL SAEs**	**Total AEs**	**TOTAL SAEs**
TOTAL NUMBER OF AEs		**481**	**70 (14.6%)**	**552**	**50 (9.1%)**	**330**	**26 (7.9%)**

Table F – Summary of adverse events during taper phase only

SOC	Paroxetine N=19		Imipramine N=32		Placebo N=9	
	No. AEs reported (CSR check)	No. reported as Severe	No. AEs reported (CSR check)	No. reported as Severe	No. AEs reported (CSR check)	No. reported as Severe
Cardiac and vascular Disorders	4	0	9	0	0	0
Gastrointestinal Disorders	9	4	18	4	4	0
Psychiatric Disorders	15	8	2	0	1	1
Nervous system Disorders	7	1	9	2	0	0
Respiratory, thoracic and mediastinal disorders	3	0	1	0	0	0
General disorders and administration site conditions	1	0	1	0	0	0
Renal and urinary Disorders	3	0	1	0	2	0
Immune system disorders	0	0	1	0	0	0
Endocrine disorders	0	0	1	1	0	0
Blood and lymphatic disorders	1	0	2	0	1	0
Musculoskeletal and connective tissue disorders	0	0	2	0	1	0
Reproductive system and breast disorder	1	0	0	0	0	0
Infections	0	0	1	0	0	0
Metabolism and nutritional disorders	3	0	0	0	1	0
Injuries, poisoning and procedural complications	0	0	1	1	0	0
Pregnancy, puerperium and perinatal conditions	0	0	1	1	0	0
	Total AEs	TOTAL SAEs	Total AEs	TOTAL SAEs	Total AEs	TOTAL SAEs
TOTAL NUMBER OF AEs	47	13	50	9	10	1

Table G – Breakdown of adverse events during taper phase only

SOC	MedDRA preferred term	Paroxetine N=19		Imipramine N=32		Placebo N=9	
		No. AEs reported (CSR check)	No. reported as Severe	No. AEs reported (CSR check)	No. reported as Severe	No. AEs reported (CSR check)	No. reported as Severe
Cardiac and vascular disorders	Arrythmia	0	0	1	0	0	0
	AV block	1	0	0	0	0	0
	Bradycardia	0	0	1	0	0	0
	Chest pain	0	0	1	0	0	0
	Dizziness	3	0	2	0	0	0
	ECG/ T-ECG abnormal	0	0	1	0	0	0
	QT interval prolonged	0	0	1	0	0	0
	Tachycardia	0	0	2	0	0	0
	TOTAL	**4**	**0**	**9**	**0**	**0**	**0**
Gastrointestinal disorders	Constipation	1	0	2	0	0	0
	Dry mouth	0	0	1	0	0	0
	Diarrhea	0	0	2	0	0	0
	Dysepsia	0	0	3	0	0	0
	Cramps	1	0	0	0	1	0
	Gastroenteritis	0	0	1	1	0	0
	Nausea/ sickness	4	2	6	1	1	0
	Sores	0	0	0	0	1	
	Ulcer	1	1	0	0	0	0
	Vomiting	2	1	3	2	1	0
	TOTAL	**9**	**4**	**18**	**4**	**4**	**0**
Psychiatric disorders	Aggravated depression	0	0	0	0	1	1
	Aggression	2	2	0	0	0	0
	Akathisia	2	1	1	0	0	0
	Concentration low	1	0	0	0	0	0
	Drug withdrawal syndrome	2	1	0	0	0	0
	Insomnia	1	0	0	0	0	0
	Paranoia	1	0	0	0	0	0
	Somnolence	1	0	0	0	0	0
	Substance abuse	1	1	0	0	0	0
	Suicidal ideation/gesture	2	2	1	0	0	0
	Suicide attempt	2	1	0	0	0	0
	TOTAL	**15**	**8**	**2**	**0**	**1**	**1**
Nervous system disorders	Convulsion	0	0	1	1	0	0
	Headache	4	1	7	1	0	0
	Sore throat	1	0	1	0	0	0
	Tremor	1	0	0	0	0	0
	Vision blurred	1	0	0	0	0	0
	TOTAL	**7**	**1**	**9**	**2**	**0**	**0**
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	0	0	0	0	0
	Rhinitis	2	0	0	0	0	0
	Sinusitis	0	0	1	0	0	0
	TOTAL	**3**	**0**	**1**	**0**	**0**	**0**

General disorders and site administration conditions	Fatigue	1	0	1	0	0	0
	TOTAL	**1**	**0**	**1**	**0**	**0**	**0**
Renal and urinary disorders	Albuminuria	0	0	0	0	2	0
	Pyuria	0	0	1	0	0	0
	Urinary abnormality	2	0	0	0	0	0
	UTI	1	0	0	0	0	0
	TOTAL	**3**	**0**	**1**	**0**	**2**	**0**
Immune system disorders	Urticaria	0	0	1	0	0	0
	TOTAL	**0**	**0**	**1**	**0**	**0**	**0**
Endocrine disorders	Hyperglycemia	0	0	1	1	0	0
	TOTAL	**0**	**0**	**1**	**1**	**0**	**0**
Blood and lymph disorders	Anaemia	1	0	1	0	0	0
	Eosinophilia	0	0	1	0	0	0
	Thrombocythemia	0	0	0	0	1	0
	TOTAL	**1**	**0**	**2**	**0**	**1**	**0**
Musculoskeletal and connective tissue disorders	Arthralgia	0	0	1	0	0	0
	Back pain	0	0	0	0	1	0
	Myalgia	0	0	1	0	0	0
	TOTAL	**0**	**0**	**2**	**0**	**1**	**0**
Reproductive system and breast disorder	Dysmenorrhea	1	0	0	0	0	0
	TOTAL	**1**	**0**	**0**	**0**	**0**	**0**
Infections	Otitis media	0	0	1	0	0	0
	TOTAL	**0**	**0**	**1**	**0**	**0**	**0**
Metabolism and nutritional disorders	Decreased appetite	0	0	0	0	1	0
	Increased appetite	1	0	0	0	0	0
	Weight gain	2	0	0	0	0	0
	TOTAL	**3**	**0**	**0**	**0**	**1**	**0**
Injuries, poisoning and procedural complications	Overdose	0	0	1	1	0	0
	TOTAL	**0**	**0**	**1**	**1**	**0**	**0**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	0	1	1	0	0
	TOTAL	**0**	**0**	**1**	**1**	**0**	**0**
		Total AEs	**TOTAL SAEs**	**Total AEs**	**TOTAL SAEs**	**Total AEs**	**TOTAL SAEs**
TOTAL NUMBER OF AEs		**47**	**13**	**50**	**9**	**10**	**1**

Table H – Changes to 'reasons for discontinuation' during acute (plus taper) phase

a) <u>Paroxetine group</u>

TAPER PHASE: In total 67 patients completed the 8 week acute phase. Of these, 16 were discontinued at the 8 week visit. The proposed changes to the reasons for discontinuation are given for each below:

Patient ID	GSK reason for discontinuation	Proposed reason for discontinuation	Notes
329.001.00068	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.001.00206	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00081	Lack of Efficacy	OTHER (misc)	HAM-D scores indicate patient a 'Responder'
329.003.00089	Lack of Efficacy	AE (suicidal)	SAE narrative: "the patient became agitated and said she would kill herself following threats of punishment from her mother to control her behavior. The patient was deemed at risk to herself and was brought to the crisis service. She was hospitalized... and the decision was made she would not enter the continuation phase.
329.003.00248	Lack of Efficacy	Lack of Efficacy	Abnormal blood around same time as down-titration- but investigator deemed 'mild' & 'unrelated'. Experienced 'severe' withdrawal symptoms.
329.003.00250	AE (overdose)	AE (suicidal)	End of week 58 dose reduced, while patient was 'waiting to start phase II meds'. During this interim period, patient was hospitalised for attempted suicide and subsequently withdrawn.
329.005.00258	Other (going for general surgery)	Lost to FU	Patient eligible for continuation but scheduled for general surgery.
329.005.00300	Lack of Efficacy	Lost to FU	Patient never turned up for final visit during down titration (see page 222 of CRF)
329.005.00336	Other (no study meds)	PV (investigator)	No meds
329.008.00188	PV (non compliance)	PV (non compliance)	Migraine & Anxiety 9dys 48 & 52), 'over-compliance 128%' day 55.
329.009.00193	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.009.00196	Withdrawn Consent	Withdrawn Consent	No acute phase conclusion page in CRF. Info from Appendix G

329.009.00201	AE (paranoia & aggression)	AE (paranoia & aggression)	
329.009.00324	AE (rash)	AE (rash)	
329.009.00329	Lack of Efficacy	AE (depression worsening)	Worsening of depression reported as AE just prior to initiating down titration
329.012.00025	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)

CRF REVIEW: Out of 31 reviewed CRFs, 9 changes to reasons for withdrawal were proposed:

	Patient ID	**GSK reason for withdrawal (as per Appendix G)**	**RIAT reason for withdrawal**
Reason for withdrawal changes	329.001.00065	AE (aggression)	AE (suicidal)
	329.002.00058	AE (overdose)	AE (suicidal gesture/attempt) – OD (Tylenol x 80 pills) 3 days after discontinuing meds
	329.003.00313	AE (hospitalisation)	AE (suicidal)
	329.004.00015 *	Other (conflict with school and study)	Withdrawn consent
	329.004.00212	PV (non compliance)	AE (sedation)
	329.005.00333	Lack of Efficacy	AE (suicidal)
	329.009.00133	Lost to Follow Up	Lack of Efficacy
	329.011.00288	Lack of Efficacy	AE (agitation, possibly suicidal)
	329.012.00228	PV	Withdrawn consent

In addition a further 8 participants of those reviewed, who were originally described as having withdrawn for 'AE including intercurrent illness' according to Appendix G, were further defined. These were as follows:

	Patient ID	**GSK reason for withdrawal (as per Appendix G)**	**RIAT reason for withdrawal**
Adverse Events further defined	329.001.00063	AE inc intercurrent illness	AE (mania)
	329.002.00058	AE inc intercurrent illness	AE (suicidal)
	329.002.00245	AE inc intercurrent illness	AE (intentional overdose)
	329.003.00250 *	AE inc intercurrent illness	AE (suicidal)
	329.005.00011 *	AE inc intercurrent illness	AE (suicidal)
	329.005.00152	AE inc intercurrent illness	AE (GI – nausea/vomit/diarrhoea)
	329.009.00240	AE inc intercurrent illness	AE (worsening depression)
	329.012.00226	AE inc intercurrent illness	AE (cardiac)

* withdrawn during CONTINUATION phase

b) Imipramine group

TAPER PHASE: In total 56 patients completed the 8 week acute phase. Of these, 17 were discontinued at the 8 week visit. Proposed changes to the 'reasons for discontinuation' (if any) for these patients are given below:

Patient ID	GSK reason for discontinuation	Proposed reason for discontinuation	Notes
329.002.00098	Lack of Efficacy	Adverse Event (dry mouth)	Patient reported ongoing 'dry mouth' and 'tremor'. Note on pages 222 and 226 showing a dose reduction/ down titration due to these AEs.
329.002.00244	Lack of Efficacy	PV (investigator)	Week 8 meds unavailable. (p250)
329.003.00090	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00249	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00314	PV non compliance	PV non compliance	
329.003.00317	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00009	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00117	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.005.00255	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00295	Adverse Event (homicidal)	Adverse Event (homicidal)	Wanted to kill parents
329.005.00332	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00335	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.008.00187	Lack of Efficacy	AE (tachycardia)	Pt experiencing 'persistent side effects' at time of withdrawal (p222), including pulse rate >110 for 2 consecutive weeks.
329.009.00134	AE (tachycardia/ inc QT/ QTc)	AE (tachycardia/ inc QT/ QTc)	
329.009.00137	Other (ADHD)	PV (investigator)	'Team felt due to continuing ADHD symptoms pt needed treatment with stimulant'. Patient had 'severe' symptoms of ADHD at baseline (p69).
329.009.00199	PV non compliance	PV non compliance	77% and 71% compliance
329.009.00262	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)

CRF REVIEW: Out of 40 reviewed CRFs, 3 changes to reasons for withdrawal were proposed:

	Patient ID	GSK Reason for withdrawal (as per Appendix G)	RIAT reason for withdrawal
'Reason for withdrawal' changes	329.002.00243	AE (accident/trauma)	AE (postural hypotension)
	329.004.00211	AE (dehydration)	AE (nausea/vomiting)
	329.012.00223	Lack of Efficacy	AE (suicidal gesture)

A further 10 participants from the cohort of reviewed CRFs, who were described as having withdrawn for 'AE including intercurrent illness' according to Appendix G, were further defined. These were as follows:

	Patient ID	GSK reason for withdrawal (as per Appendix G)	RIAT reason for withdrawal
Adverse events further defined	329.001.00061	AE inc intercurrent illness	AE (widened QTc)
	329.001.00066	AE inc intercurrent illness	AE (tachycardia)
	329.001.00067	AE inc intercurrent illness	AE (postural hypotension)
	329.001.00070	AE inc intercurrent illness	AE (tachycardia)
	329.003.00073	AE inc intercurrent illness	AE (vomiting)
	329.004.00014	AE inc intercurrent illness	AE (nausea)
	329.005.00003	AE inc intercurrent illness	AE (tachycardia)
	329.004.00215	AE inc intercurrent illness	AE (hallucinations/ nightmares)
	329.005.00113	AE inc intercurrent illness	AE (suicidal)
	329.009.00236	AE inc intercurrent illness	AE (dizziness/sedation)

c) Placebo group

TAPER PHASE: In total 66 patients completed the 8 week acute phase. Of these, 32 were discontinued at the 8 week visit. A number of changes to the 'reason for discontinuation' are proposed:

Patient ID	GSK reason for discontinuation	Proposed reason for discontinuation	Notes
329.001.00069	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.001.00071	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.001.00207	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.002.00049	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.002.00059	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.002.00246	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00078	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.003.00080	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00085	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00094	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00252	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.003.00315	Withdrawn consent	Withdrawn consent	
329.003.00316	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)

329.004.00018	Withdrawn consent	Withdrawn consent	
329.005.00001	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00120	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.005.00253	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00293	Other (no study meds)	PV (investigator)	
329.005.00331	Other (no study meds)	PV (investigator)	
329.006.00259	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.007.00266	Other 'moved out of state'	Withdrawn consent	
329.007.00267	PV (positive drug test)	PV (positive drug test)	
329.009.00136	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.009.00198	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.009.00238	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.009.00276	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.009.00306	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.009.00312	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.010.00263	Withdrawn consent	Withdrawn consent	
329.010.00282	Other (no study meds)	PV (investigator)	
329.011.00285	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.011.00287	Withdrawn consent	Withdrawn consent	

CRF REVIEW: Out of 22 CRFs checked, 6 changes to reasons for withdrawal were proposed. A further 1 participant who was described as having withdrawn for 'AE including intercurrent illness' according to Appendix G was defined. These were as follows:

	Patient ID	**GSK reason for withdrawal (as per Appendix G)**	**RIAT reason for withdrawal**
'Reason for withdrawal' changes	329.006.00037	PV non compliance (pt refused FU safety evaluation)	PV by investigator (screening error)
	329.007.00141	AE (angina)	PV by investigator (screening error)
	329.009.00129	Lack of Efficacy	AE (suicidal)
	329.009.00237	PV non compliance	PV by investigator (screening error)
	329.009.00327	Lack of Efficacy	AE (anxiety/depression worse)
	329.012.00217	AE (ambivalence about meds)	PV by investigator (screening error)
Adverse Events further defined	329.009.00330	AE inc intercurrent illness	AE (nausea/vomiting)

Table I - Baseline screening errors (found during safety review)

Five 'Protocol violations by investigator' were found in the placebo group, one in the imipramine group, and none in the paroxetine:

Patient ID number	Drug Group	Inclusion criteria error
329.012.00221	Imipramine	Patient reported as having 'severe' suicidal ideation at the initial screening/baseline visits on both Kiddie-SADS (5-severe) and HAM-D (3 – suicidal ideas/gestures).
329.002.00241	Placebo	Patient reported as having 'severe' suicidal ideation at the initial screening visit. Two suicidal acts were reported within the current depressive episode with one of these occurring within the last 2 weeks. The patient also found to have an abnormality (arrhythmia) during baseline EKG, however this was cleared following a referral to a cardiologist.
329.006.00037	Placebo	Patient had a severity score HIGHER than 60 on the Clinical Global Assessment Scale (C-GAS). Reported as a PV in CRF query logs.
329.007.00141	Placebo	Patient was withdrawn for ANGINA however angina was reported as a presenting condition at screening. CRF states comments on reason for withdrawal *'physician discretion due to comparator arm, vis-à-vis AE of chest pain.'*
329.009.00237	Placebo	ELIGIBILITY CHECKLIST *'Is patient currently in episode of Major Depression for at least 8 weeks?'* 'NO' is checked – therefore not meeting criteria for MDD. In addition patient found to have SINUS BRADYCARDIA at screening.
329.012.217	Placebo	Has been re-coded as 'PV by investigator'. Patient was 'extremely' suicidal at screening with no suicidal acts (see Kiddie-SADS & HAM-D). Patient showed 'worsening depression' during the study, was admitted to hospital during week 4 and given Zoloft. GSK reason for withdrawal was AE 'ambivalence towards meds'. Alternatively could argue was withdrawn for 'AE worsening depression'.

Table J – Suicidality at screening (Kiddie-SADS)

From the sample of reviewed CRFs, 27% of patients were reported as having severe (or extreme) suicidal ideation at screening, compared with 13% in the paroxetine group and 3% in imipramine (see table 5).

a) Kiddie-SADS items 108 to 117 'Suicidal Ideation' at screening visit (-1 week)

		Paroxetine N=31	Imipramine N=40	Placebo N=22
Suicidal Ideation	**Current episode**	2.9	2.7	3.1
	Last 2 weeks	2.2	2.3	2.6
Number of Suicidal Acts	**Current episode**	0.0	0.1	0.3
	Last 2 weeks	0.0	0.0	0.0
Seriousness of Suicidal acts	**Current episode**	0.7	0.6	0.7
	Last 2 weeks	0.5	0.5	0.5
Medical lethality of suicidal acts	**Current episode**	0.6	0.5	0.6
	Last 2 weeks	0.5	0.4	0.4
Number of non suicidal self harm	**Current episode**	1.7	1.3	0.9
	Last 2 weeks	1.3	1.1	0.7

NB. Rating scale from 0 (n/a) to 7 (very extreme)

b) Kiddie-SADS item 108 'Suicidal Ideation' - 'Current Episode' at screening (-1 week)

	Paroxetine N=31	Imipramine N=40	Placebo N=22
0 - N/A	0	0	0
1 - None	6 (19%)	7 (18%)	4 (18%)
2 - Min	7 (23%)	12 (30%)	4 (18%)
3 - Mild	7 (23%)	10 (25%)	6 (27%)
4 - Moderate	7 (23%)	10 (25%)	2 (9%)
5 + - Severe/EXTREME/ V EXTREME	4 (13%)	1 (3%)	6 (27%)

c) Kiddie-SADS item 109 'Suicidal ideation' – 'Last Two Weeks' at Screening (-1 week)

	Paroxetine N=31	Imipramine N=40	Placebo N=22
0 - N/A	0	0	0
1 - None	14 (45%)	13 (33%)	6 (27%)
2 - Min	7 (23%)	9 (23%)	5 (23%)
3 - Mild	3 (10%	12 (30%)	4 (18%)
4 - Moderate	5 (16%)	5 (13%)	5 (23%)
5 + - Severe/EXTREME/ V EXTREME	2 (6%)	1 (3%)	2 (9%)

Table K – Types of medication taken 1 month prior to enrolment

ATC Level 2 drug type grouping	Drug	Paroxetine (n=24)	Imipramine (n=31)	Placebo (n=26)
Analgesics	Acetylsalicylic acid (aspirin)	1	1	0
	cinnamedrine hydrochloride (Midol)	1	0	0
	paracetamol	10	9	4
	Paracetamol plus (Tylenol/Benadryl cold/flu)	2	1	1
	Codeine phosphate	0	1	0
	Diphenhydramine citrate (Exedrin PM)	0	1	0
	Mepyramine maleate (Pamprin)	0	0	1
	Analgesic unknown	0	1	1
	Unknown Chinese medicine	0	1	0
	Total	**14**	**15**	**7**
Antibiotics	amoxicillin	1	2	4
	tetracycline	1	0	0
	erythromycin	0	1	2
	azithromycin	0	0	1
	Total	**2**	**3**	**7**
Psychoanaleptics	Fluoxetine (Prozac)	1	0	0
	Sertraline	1	0	0
	Amitriptyline	0	0	1
	Total	**2**	**0**	**1**
Psycholeptics	diazepam	0	0	1
	Total	**0**	**0**	**1**
Opthalmologicals	Polymyxin b sulphate (eye drops)	1	0	0
	Sulfacetamide sodium	0	1	0
	Total	**1**	**1**	**0**
Systemic antihistamine	loratadine	1	0	0
	Total	**1**	**0**	**0**
Antipruritics	Diphendydramine hydrochloride	1	0	2
	Total	**1**	**0**	**2**
GI Antispas/ anticholin	Phenobarbital, hyocyamine, atropine (Donnatal)	1	0	0
	Total	**1**	**0**	**0**

Vaccines	Hepatitis B vaccine	1	0	0
	Total	**1**	**0**	**0**
Nasal prep	Clemastine fumarate (Tavist-D)	1	0	0
	Total	**1**	**0**	**0**
Antianaemic prep	Vit B 12	0	1	0
	Total	**0**	**1**	**0**
Sex hormones/stimulants	Ethinylestradiol (Desogen28; Loestrin or Ovcon)	0	3	1
	Oral contraceptive unknown	0	1	0
	Injectable contraceptive (NOS)	0	0	1
	Total	**0**	**4**	**2**
Antimycotics	Ketoconazole (Nizoral)	0	1	0
	Total	**0**	**1**	**0**
Anti inflammatory	ibuprofen	0	3	1
	Naproxen sodium	0	0	1
	oxaprozin	0	0	1
	Total	**0**	**3**	**3**
Cough & cold prep	Dextromethorphan hydrobromide (Nyquil)	0	1	0
	Guaifenesin (Robitussin)	0	1	0
	Total	**0**	**2**	**0**
Antidiarrhea	Loperamide hydrochloride	0	1	0
	Total	**0**	**1**	**0**
Antiasthmatics	salbutamol	0	0	1
	Total	**0**	**0**	**1**
Chemotherapeutics	Trimethoprim (Bactrim)	0	0	1
	Total	**0**	**0**	**1**
Antiepileptics	clonazepam	0	0	1
	Total	**0**	**0**	**1**

Table L – Adverse events occurring in patients taking other medication prior to enrolment vs. those taking no other medication

a) Paroxetine group

SOC	MedDRA preferred term	Patients taking 'other Medications' during month pre-enrolment	Patients taking 'No Medication' during month pre-enrolment
Gastrointestinal Disorders	Abdominal pain	0	0
	Constipation	0	7
	Cramps	3	11
	Diarrhea	1	11
	Dry Mouth	5	15
	Dyspepsia	1	7
	Food poisoning	1	0
	Gastroenteritis	0	0
	Nausea	8	29
	Reflux	1	0
	Retching	0	0
	Sores	0	0
	Stomatitis	0	0
	Ulcer	0	1
	Vomiting	2	9
	TOTAL	**22**	**90**
Nervous system disorders	Bad taste	0	0
	Convulsion	0	0
	Dystonia	4	1
	Headache	25	34
	Laryngitis	0	1
	Memory loss	0	0
	Migraine	0	1
	Myoclonus	3	1
	Paresthesia	0	1
	Sore throat	7	3
	Tics	0	1
	Tinnitus	0	0
	Toothache	4	2
	Tremor	4	7
	Vision blurred	0	2
	TOTAL	**47**	**54**
General disorders	Fatigue	6	9
	Fever	0	0
	Pain	0	0
	TOTAL	**6**	**9**
Psychiatric disorders	Abnormal dreams	0	3
	Aggravated depression	0	5
	Aggression	1	6
	Agitation	0	1
	Akathisia	10	8

	Anorgasmia	1	0
	Anxiety	0	2
	Concentration low	1	1
	Depersonalisation	0	0
	Disinhibition	1	3
	Drug withdrawal syndrome	0	2
	Hallucination	0	1
	Impulsive behaviour	0	1
	Insomnia	4	12
	Paranoia	1	0
	Psychosis	0	1
	Somnolence	9	15
	Substance abuse	0	1
	Suicidal ideation/gesture	0	5
	Suicide attempt	2	6
	TOTAL	**30**	**73**
Respiratory, thoracic and mediastinal disorders	Coughing	4	2
	Chest cold	2	9
	Epistaxis	0	1
	Dyspnea	0	3
	Nasopharyngitis	2	1
	Respiratory disorder	0	0
	Rhinitis	4	6
	Sinusitis	3	5
	Sneezing	0	0
	TOTAL	**15**	**27**
Cardiac disorders	Atrial ectopic	0	0
	AV block	0	1
	Bradycardia	0	0
	Bundle branch block	0	0
	Dizziness	14	21
	Chest pain	0	2
	ECG/ T-ECG abnormal	0	0
	Hot flush	0	0
	Hypertension	0	0
	Postural hypotension	1	2
	QT interval prolonged	0	0
	Tachycardia	1	2
	TOTAL	**16**	**28**
Skin and subcutaneous tissue disorders	Acne	1	2
	Dermatitis	0	1
	Itchy	0	0
	Rash	1	3
	Scabies	0	0
	Sweating	1	1
	Syncope	0	0
	TOTAL	**3**	**7**

Renal and urinary disorders	Albuminuria	0	0
	Cystitis	0	1
	Nocturia	0	0
	Polyuria	0	0
	Pyuria	0	0
	Urinary abnormality	1	2
	Urinary retention	0	0
	UTI	0	1
	TOTAL	**1**	**4**
Immune system disorders	Allergy	0	1
	Urticaria	0	1
	TOTAL	**0**	**2**
Endocrine disorders	Amenorrhea	1	0
	Hyperglycemia	0	0
	TOTAL	**1**	**0**
Blood and lymphatic system disorders	Anaemia	0	1
	Eosinophilia	0	0
	Leukopenia	0	0
	Lymphadenopathy	0	0
	Thrombocythemia	0	0
	TOTAL	**0**	**1**
Musculoskeletal and connective tissue disorders	Arthralgia	1	0
	Back pain	5	0
	Chills	0	0
	Myalgia	0	2
	TOTAL	**6**	**2**
Reproductive system and breast disorder	Breast enlargement	0	1
	Dysmenorrhea	2	1
	TOTAL	**2**	**2**
Infections	Herpes zoster	0	0
	Infection	2	2
	Otitis media	0	2
	TOTAL	**2**	**4**
Eye disorders	Conjunctivitis	2	0
	Itchy eyes	1	1
	Mydriasis	0	0
	Photosensitivity	0	1
	Photopsia	0	0
	TOTAL	**3**	**2**
Metabolism and nutritional disorders	Decreased appetite	3	6
	Increased appetite	0	4
	Thirst	0	0
	Weight gain	1	1
	Weight loss	0	2
	TOTAL	**4**	**13**

Ear and labyrinth disorders	Ear pain	0	1
	TOTAL	**0**	**1**
Injuries, poisoning and procedural complications	Head injury	0	0
	Overdose	0	0
	Trauma	0	3
	TOTAL	**0**	**3**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	0
	TOTAL	**0**	**0**
Surgical and medical procedures	Tooth extraction	0	1
	TOTAL	**0**	**1**
Total number of AEs		**158**	**323**

b) Imipramine group

SOC	**MedDRA preferred term**	**Patients taking 'other Medications' during month pre-enrolment**	**Patients taking 'No Medication' during month pre-enrolment**
Gastrointestinal Disorders	Abdominal pain	0	0
	Constipation	2	8
	Cramps	1	10
	Diarrhea	6	2
	Dry Mouth	15	33
	Dyspepsia	4	8
	Food poisoning	0	0
	Gastroenteritis	0	1
	Nausea	14	29
	Reflux	0	0
	Retching	0	1
	Sores	0	0
	Stomatitis	0	2
	Vomiting	6	5
	TOTAL	**48**	**99**
Nervous system disorders	Bad taste	1	2
	Convulsion	1	0
	Dystonia	2	5
	Headache	32	27
	Laryngitis	0	0
	Memory loss	0	1
	Migraine	1	0
	Myoclonus	0	1
	Paresthesia	0	1
	Sore throat	7	5
	Tics	0	1

	Tinnitus	0	2
	Toothache	0	0
	Tremor	14	6
	Vision blurred	1	4
	TOTAL	**59**	**55**
General disorders	Fatigue	5	3
	Fever	0	2
	Pain	0	0
	TOTAL	**5**	**5**
Psychiatric disorders	Abnormal dreams	1	4
	Aggravated depression	2	1
	Aggression	1	2
	Agitation	0	1
	Akathisia	6	6
	Anorgasmia	0	0
	Anxiety	0	0
	Concentration low	1	0
	Depersonalisation	0	1
	Disinhibition	0	1
	Drug withdrawal syndrome	0	0
	Hallucinations	1	0
	Insomnia	3	11
	Paranoia	0	0
	Psychosis	0	0
	Somnolence	3	11
	Substance abuse	0	1
	Suicidal ideation/gesture	0	3
	Suicide attempt	1	2
	TOTAL	**19**	**44**
Respiratory, thoracic and mediastinal disorders	Coughing	2	2
	Chest cold	0	6
	Epistaxis	0	1
	Dyspnea	4	1
	Nasopharyngitis	0	0
	Respiratory disorder	0	0
	Rhinitis	1	2
	Sinusitis	2	1
	Sneezing	0	0
	TOTAL	**9**	**13**
Cardiac disorders	Atrial ectopic	0	0
	AV block	1	1
	Bradycardia	0	1
	Bundle branch block	0	1
	Dizziness	19	38
	Chest pain	4	1
	ECG/ T-ECG abnormal	3	4
	Hot flush	3	3
	Hypertension	0	2
	Arrythmia	0	1
	Postural hypotension	7	10
	QT interval prolonged	2	1

	Tachycardia	12	16
	TOTAL	**51**	**79**
Skin and subcutaneous tissue disorders	Acne	2	0
	Dermatitis	2	0
	Itchy	0	1
	Rash	2	3
	Scabies	0	0
	Sweating	5	2
	Syncope	0	0
	TOTAL	**11**	**6**
Renal and urinary disorders	Albuminuria	0	0
	Cystitis	0	0
	Nocturia	1	0
	Polyuria	0	1
	Pyuria	0	1
	Urinary abnormality	0	0
	Urinary retention	1	5
	UTI	0	0
	TOTAL	**2**	**7**
Immune system disorders	Allergy	0	1
	Urticaria	1	0
	TOTAL	**1**	**1**
Endocrine disorders	Amenorrhea	0	0
	Hyperglycemia	1	0
	TOTAL	**1**	**0**
Blood and lymphatic system disorders	Anaemia	0	1
	Eosinophilia	1	0
	Leukopenia	2	0
	Lymphadenopathy	0	0
	Thrombocythemia	0	0
	TOTAL	**3**	**1**
Musculoskeletal and connective tissue disorders	Arthralgia	1	0
	Back pain	0	2
	Chills	0	3
	Myalgia	1	0
	TOTAL	**2**	**5**
Reproductive system and breast disorders	Breast enlargement	0	0
	Dysmenorrhea	2	2
	TOTAL	**2**	**2**
Infections	Herpes zoster	0	0
	Infection	2	1
	Otitis media	1	1
	TOTAL	**3**	**2**
Eye disorders	Conjunctivitis	0	0
	Itchy eyes	0	1
	Mydriasis	1	0

	Photosensitivity	1	0
	Photopsia	0	1
	TOTAL	**2**	**2**
Metabolism and nutritional disorders	Decreased appetite	1	1
	Increased appetite	0	1
	Thirst	0	2
	Weight gain	0	0
	Weight loss	1	0
	TOTAL	**2**	**4**
Ear and labyrinth disorders	Ear pain	0	0
	TOTAL	**0**	**0**
Injuries, poisoning and procedural complications	Head injury	0	1
	Overdose	0	1
	Trauma	0	1
	TOTAL	**0**	**3**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	2
	TOTAL		**2**
Surgical and medical procedures	Tooth extraction	0	2
	TOTAL	**0**	**2**
Total number of AEs		**220**	**332**

c) Placebo group

SOC	**MedDRA preferred term**	**Patients taking 'other Medications' during month pre-enrolment**	**Patients taking 'No Medication' during month pre-enrolment**
Gastrointestinal Disorders	Abdominal pain	2	0
	Constipation	1	3
	Cramps	3	11
	Diarrhea	6	3
	Dry Mouth	4	8
	Dyspepsia	0	4
	Food poisoning	0	1
	Gastroenteritis	0	0
	Nausea	14	13
	Reflux	0	0
	Retching	0	0
	Sores	0	1
	Stomatitis	0	0
	Vomiting	2	3
	TOTAL	**32**	**47**

Nervous system disorders	Bad taste	0	0
	Convulsion	0	0
	Dystonia	2	1
	Headache	29	27
	Laryngitis	0	0
	Memory loss	0	0
	Myoclonus	0	0
	Paresthesia	0	0
	Sore throat	3	8
	Tics	0	0
	Tinnitus	0	0
	Toothache	1	2
	Tremor	1	1
	Vision blurred	2	0
	TOTAL	**38**	**39**
General disorders	Fatigue	3	8
	Fever	1	3
	Pain	1	1
	TOTAL	**5**	**12**
Psychiatric disorders	Abnormal dreams	0	2
	Aggravated depression	1	1
	Aggression	0	0
	Agitation	0	0
	Akathisia	2	6
	Anorgasmia	0	0
	Anxiety	1	0
	Concentration low	0	0
	Depersonalisation	1	0
	Disinhibition	0	2
	Drug withdrawal syndrome	0	0
	Hallucination	0	0
	Insomnia	2	2
	Paranoia	0	0
	Psychosis	0	0
	Somnolence	1	2
	Substance abuse	0	0
	Suicidal ideation/gesture	1	0
	Suicide attempt	0	0
	TOTAL	**9**	**15**
Respiratory, thoracic and mediastinal disorders	Coughing	1	5
	Chest cold	8	6
	Epistaxis	0	0
	Dyspnea	0	2
	Nasopharyngitis	0	1
	Respiratory disorder	1	1
	Rhinitis	2	3
	Sinusitis	5	3
	Sneezing	0	1
	TOTAL	**17**	**22**

Cardiac disorders	Atrial ectopic	1	0
	AV block	1	1
	Bradycardia	1	0
	Bundle branch block	0	1
	Dizziness	5	13
	Chest pain	1	1
	ECG/ T-ECG abnormal	2	0
	Hot flush	1	1
	Arrhythmia	0	1
	Postural hypotension	1	0
	QT interval prolonged	0	0
	Tachycardia	0	1
	TOTAL	**13**	**19**
Skin and subcutaneous tissue disorders	Acne	1	0
	Dermatitis	0	1
	Itchy	1	0
	Rash	3	1
	Scabies	0	1
	Sweating	1	0
	Syncope	0	1
	TOTAL	**6**	**4**
Renal and urinary disorders	Albuminuria	0	4
	Cystitis	0	0
	Nocturia	0	0
	Polyuria	0	0
	Pyuria	0	0
	Urinary abnormality	0	0
	Urinary retention	0	0
	UTI	0	0
	TOTAL	**0**	**4**
Immune system disorders	Allergy	3	0
	Urticaria	0	0
	TOTAL	**3**	**0**
Endocrine disorders	Amenorrhea	0	0
	Hyperglycemia	0	1
	TOTAL	**0**	**1**
Blood and lymphatic disorders	Anaemia	0	0
	Eosinophilia	0	1
	Leukopenia	0	0
	Lymphadenopathy	1	0
	Thrombocythemia	0	1
	TOTAL	**1**	**2**
Musculoskeletal and connective tissue disorders	Arthralgia	2	2
	Back pain	3	7
	Chills	0	0
	Myalgia	1	1
	TOTAL	**6**	**10**

Reproductive system and breast disorder	Breast enlargement	0	0
	Dysmenorrhea	2	2
	TOTAL	**2**	**2**
Infections	Herpes zoster	0	1
	Infection	1	2
	Otitis media	0	0
	TOTAL	**1**	**3**
Eye disorders	Conjunctivitis	0	1
	Itchy eyes	0	0
	Mydriasis	0	0
	Photosensitivity	0	0
	Photopsia	0	0
	TOTAL	**0**	**1**
Metabolism and nutritional disorders	Decreased appetite	1	3
	Increased appetite	0	1
	Thirst	1	1
	Weight gain	0	0
	Weight loss	1	1
	TOTAL	**4**	**6**
Ear and labyrinth disorders	Ear pain	0	0
	TOTAL	**0**	**0**
Injuries, poisoning and procedural complications	Head injury	0	0
	Overdose	0	0
	Trauma	0	6
	TOTAL	**0**	**6**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	0
	TOTAL	**0**	**0**
Surgical and medical procedures	Tooth extraction	0	0
	TOTAL	**0**	**0**
Total number of AEs		**137**	**193**

Table M – Attrition of patients by week

Treatment group	Efficacy [randomised]	Status	Week							
			1	2	3	4	5	6	7	8
Imipramine	94 [95]	total	94	90	81	77	74	64	58	56
		data	91	88	77	69	68	63	57	56
Paroxetine	90 [93]	total	90	84	80	78	76	73	71	67
		data	88	81	77	76	72	72	68	67
Placebo	87 [87]	total	87	85	79	77	74	68	66	66
		data	84	82	75	73	70	66	63	66

Four of the randomised patients had no post-treatment visits [1 Imipramine, 3 Paroxetine].
“total” is the number of patients in the study for each week.
“data” is the number with data for each week.