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TABLE OF ALL STUDIES	
PHASE 1 STUDIES	
PHARMACOKINETIC STUDIES IN HEALTHY SUBJECTS	
204636/0001-UK*	DB, randomized, three-arm incomplete crossover comparison of three single doses, placebo controlled trial; normal males (n=9 quetiapine, n=3 placebo), quetiapine doses (25,50 and 100 mg).
204636/0002-UK*	DB, randomized, placebo controlled, three-arm incomplete crossover comparison of three increasing single doses of quetiapine; normal males (n=5 for 2 mg; n=6 for 5 mg; n=6 for 10 mg).
204636/0003-UK*	DB, randomized, parallel, placebo controlled trial; normal males (n=5 quetiapine, n=2 placebo); quetiapine dose (25 mg), 9 days.
H-15-11 & H-11-12-Japan*	Single-blind, randomized, placebo-controlled, comparison of single dose of quetiapine; normal males (n=6 for 1 mg and 10 mg quetiapine; n=6 for 5 mg and 20 mg quetiapine, n=4 placebo).
H-15-13-Japan*	Single-blind, randomized, multiple dose, placebo-controlled trial; normal males (n=6 quetiapine, n=2 placebo); quetiapine dose (10 mg), 4 days.
PHARMACOKINETIC STUDIES IN SCHIZOPHRENIC SUBJECTS	
5077IL/0016-US	Open-label, multiple dose trial; schizophrenic subjects (n=41); quetiapine doses (25-375 mg bid), 16 days.
5077IL/0008-US	Open-label, multiple dose trial; schizophrenic men (n=13); quetiapine doses (25-150 mg tid), 12 days.
5077IL/0004-US	DB, parallel, placebo-controlled, multiple dose; inpatient schizophrenic males (n=8 quetiapine; n=4 placebo); quetiapine doses (25-250 mg tid), 21 days.
SPECIAL STUDIES	
5077IL/0064-US	Open label, single site, randomized, 2 period, multidose safety and pharmacokinetic study of quetiapine coadministered with thioridazine, haloperidol or risperidone; psychotic disorders (n=36); quetiapine (25-300 mg BID).

5077IL/0035-US	Open-label, comparison of immediate-release(IR)to two sustained-release(SR) formulations; schizophrenic males; quetiapine IR (25-250 mg bid for 9 days; n=16), quetiapine SR (Two preparations both were 400 mg n=16 combined); open-label extension.
5077IL/0044-US	Open-label, 3 center, randomized, crossover, multiple dose, relative bioavailability trial; psychotic disorder; quetiapine doses (25-200 mg bid), six days, n=33.
5077IL/0026-UK	DB, randomized, single dose, comparative crossover, bioavailability trial for two tablet formulations; normal males (n=35); quetiapine dose (25 mg).
5077IL/0025-UK	Open-label, randomized, single dose three-way crossover, bioequivalence trial for 2 tablet formulations; normal males (n=24); quetiapine dose (25 mg).
5077IL/0007-US	Open-label, randomized crossover, single dose, relative bioavailability trial; normal males (n=24); quetiapine dose (25 mg).
5077IL/0018-US	Open-label, single dose, comparative PK trial; hepatically impaired (n=8),normal subjects (n=8); quetiapine dose (25 mg).
5077IL/0019-US	Open-label, single dose, comparative PK trial; renally impaired subjects (n=8), normal subjects (n=8); quetiapine dose (25 mg).
5077IL/0017-US	Open-label, multi center, multiple dose, PK trial; elderly subjects with psychotic disorders (n=12); quetiapine dose (25-250 tid), 27 days with open-label extension.
5077US/0002-US	Open-label, PK trial; schizophrenic subjects (n=8); quetiapine dose (25-150 mg tid for 10 days), C-Quetiapine dose (150 mg, single radioactive dose after 10 day dosing of quetiapine).
5077IL/0044 US	Open label, multicenter, crossover bioavailability study; men with psychotic disorders (n=33); quetiapine single dose (200 mg as to be marketed and investigational formulation).
5077IL/0020-US	Open-label, PK interaction study of antipyrine and quetiapine; male subjects with psychotic disorder (n=13); quetiapine doses (25-250 tid) antipyrine (1000 mg single dose before and after administration of quetiapine), 9 days.
5077IL/0047-US	Open-label, PK interaction study with quetiapine & cimetidine; male subjects with psychotic disorder (n=13); quetiapine doses (25-150 tid, 17 days), cimetidine (400 mg tid for 4 days); with open-label extension.

5077IL/0045-US	Open-label, multiple dose, PK interaction with quetiapine and phenytoin; male subjects with psychotic disorder (n=17); quetiapine doses (25-250 mg tid x 10 days), phenytoin doses (100 mg days 13-22); open-label extension.
5077IL/0027-US	Single-blind quetiapine and open-label lorazepam, PK interaction study; male subjects with psychotic disorder (n=10); quetiapine doses (25-250 tid x 13 days), lorazepam dose (2 mg before and after administration of quetiapine).
5077IL/0046-US	Open-label, multiple dose, PK interaction study of lithium and quetiapine; male subjects with psychotic disorder (n=10); quetiapine doses (25 mg-250 mg), lithium doses (300-1200 mg tid), eleven days with open-label extension.
5077IL/0061 US	Multicenter 3 period safety trial to evaluate withdrawal and switching from other antispychotic drugs to quetiapine; psychotic disorders (n=33); haloperidol 5-30 mg/d, risperidone 4-10 mg/d, or thioridazine 200-600 mg/d X 3 d followed by quetiapine titrated to 600 mg/d followed by randomization to continued quetiapine or placebo.
5077IL/0029-EUR	Open-label, nonrandomized multiple dose, PET Scan, PK trial; schizophrenic males (n=11); quetiapine doses (25-150 tid x 7 days, 150 tid x 21 days), C-racloprides (4 doses), C-N-methyl spiperone (4 doses); open-label extension.
5077IL/0033-EUR	Open-label, 2 center, multiple dose, randomized, PET Scan, PK trial; schizophrenic male subjects (n=4); quetiapine doses (50-250 mg tid for 4 weeks, then decreased weekly by 100 mg x 1 week, 50 mg tid x 2 weeks).
5077IL/0024-US (Part A)	Single-blind, placebo-controlled, PK interaction trial of multiple doses quetiapine and single dose alcohol; male subjects with psychotic disorder (n=10); quetiapine doses (25-250 mg tid x 18 days), alcohol dose (0.8 g/kg), eighteen days.
5077IL/0024-US (Part B)	Single-blind, placebo-controlled, PK interaction trial of multiple doses quetiapine and single dose alcohol; male subjects with psychotic disorder (n=1), quetiapine(25-250 mg x 18 days), alcohol (0.8 g/kg); eighteen days with open-label extension.
PHASE 2-3 STUDIES	
PLACEBO CONTROLLED STUDIES	
5077IL/0006-US	DB, parallel group, placebo-controlled, double-blind, 13-center; inpatient schizophrenic subjects (n=109); quetiapine doses (75-750 mg/day), six weeks.

204636/0008-US/ EUR	DB, parallel group, placebo-controlled, randomized, 46-center, comparison of low and high doses of quetiapine; inpatient schizophrenic subjects (n=286); quetiapine doses (low: up to 250 mg/day; high: up to 750 mg/day), six weeks.
5077IL/0013-US/ CAN	DB, parallel group, placebo-controlled, randomized, 26-center, fixed dose comparison trial to haloperidol; inpatient schizophrenic subjects (n=361); quetiapine dose (75/150/300/600/750 mg/day), haloperidol dose (12 mg/day), six weeks with open label extension.
ACTIVE CONTROLLED STUDIES	
5055IL/0015-US/ CAN	DB, 37-center, randomized, fixed-dose, relapse prevention trial of quetiapine and haloperidol; schizophrenic outpatients; quetiapine doses (75/300/600 mg/day; n≈85/group), haloperidol (12 mg/day; n=41); one year with open label extension.
204636/007-EUR/ SOUTH AFRICA	DB, multi center comparison trial of quetiapine and chlorpromazine; schizophrenic inpatients; quetiapine doses (75-750 mg/day; n=101), chlorpromazine (75-750 mg; n=100); six weeks.
5077IL/0012-EUR/ ISRAEL/ CANADA	DB, multi center, randomized, comparison of dose regimen, control was subtherapeutic dose (50 mg quetiapine); schizophrenic subjects (n=618); quetiapine doses (225 mg bid 150 mg tid, and 25 mg bid), six weeks with open label extension.
5077IL/0014-EUR/ SOUTH AFRICA/ AUSTRALIA	DB, multi center, randomized comparison trial of quetiapine and haloperidol; schizophrenic subjects; quetiapine doses (50-800 mg/day; n=221), haloperidol doses (0.5-16 mg/day; n=221), 6 weeks with open label extension.
UNCONTROLLED STUDY	
5077IL/0005-US/ EUROPE/ SOUTH AFRICA	Open-label, multi center, multiple oral dose; inpatient subjects with psychotic disorder (n=35); quetiapine doses (25-750 mg/day); UK: six weeks, US: four weeks.
OTHER TRIALS	
5077IL/0056 US	Open label, multicenter, comparison of quetiapine versus usual care with respect to health outcomes; schizophrenia and schizoaffective disorder (n= 540 planned); ONGOING.
5077IL/0048-US	Open-label, 12 center, safety trial; elderly patients with psychotic disorder, including Parkinson's disease (n=78); quetiapine doses (25-800 mg/day), 52 weeks.

5077IL/0031-US/ CAN	DB, randomized, 23 site, comparison trial of quetiapine, chlorpromazine, and haloperidol; treatment-resistant schizophrenic subjects (n=122; 264 planned, ongoing); quetiapine doses (600 mg: 4-6 weeks), haloperidol dose (40 mg qd: 4 weeks), chlorpromazine dose (1200 mg 4-6 weeks). Open label extension.
H-15-21-Japan*	Open-label, nonrandomized, early Phase II trial; schizophrenic subjects (n=54); quetiapine doses (60-750 mg/day), 8 weeks.
H-15-22-Japan*	Open-label, nonrandomized, late Phase II trial; schizophrenic subjects (n=165); quetiapine doses (75-750 mg/day), 8 weeks with open label extension.
H-15-23 Japan*	Open label exetension of H-15-22-Japan (see above).

*** Data is not included in primary integrated data base.**

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TABLE 5.1.1.1 Summary of all trials (adapted from sponsor's safety update submission)				
	Emuneration by treatment group			
Pools by trial design	Quetiapine	Active control Haloperidol	Chlorpromaznie	Placebo
PHASE I (CLINICAL PHARMACOLOGY)				
Single dose	111			
Multiple dose	232			
SUBTOTAL	343			
PHASES II - III (ANTIPSYCHOTIC STUDIES)				
Placebo controlled				
Inpt/fixed dose	258	52		51
Inpt/dose titration	252			155
Active controlled				
Outpt/fixed dose	260			
Outpt/flexible dose	1			
Inpt/fixed dose	618			
Inpt/flexible dose	322	227	100	
Uncontrolled*				
Outpt/flexible dose	1378 (915)+			
Inpatient/flexible dose	118			
SUBTOTAL	3207 (915)+	320	100	206
SINGLE DOSE TOTAL	111			
MULTIPLE DOSE TOTAL	2524	320	100	206
GRAND TOTAL**	2635	320	100	206

+Number represents all quetiepine treated subjects for the cell; number in parentheses represents subjects also counted under previous headings (95 of whom were previous Phase I exposures). Subtracting the number in parentheses from the first number provides the number of unique exposures for the cell.

*Of the 409 new exposures to quetiapine in uncontrolled trials, 173 had received placebo or active comparator in controlled trials.

**All subjects who received drug had follow-up safety measurements.

Inpt = Inpatient; Outpt = Outpatient

Appendix Table 5.1.2.1 Demography for subjects exposed to quetiapine in Phase I clinical trials (adapted from the sponsor's electronic safety update submission)

Number of subjects exposed	343
Age, y	
n	343
Mean (SD)	38 (12)
Range	
Age distribution, n (%)	
< 40 years	214 (62)
40 - 64 years	119 (35)
65 years	10 (3)
Sex, n (%)	
Men	318 (93)
Women	25 (7)
Weight, kg	
n	343
Mean (SD)	79 (13)
Range	
Race, n (%)	
White	218 (64)
Black	84 (25)
Hispanic	25 (7)
Asian/Oriental[a]	9 (3)
Other[b]	7 (2)

[a]Includes East Indian.
[b]Other includes special subgroups and mixed or undefined races.

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APPENDIX TABLE 5.1.2.2 Demographic profile for Phase II and III trials (adapted from sponsor's electronic submission)

Parameter	Quetiapine (n = 2387)	Placebo (n = 206)	Active Control (n = 420)
Age (years)			
n	2386	206	420
Mean	40 (15)	37 (9)	36 (11)
Range			
Age distribution (%)			
< 40 years	1407 (59)	125 (61)	271 (65)
40 - 64 years	789 (33)	81 (39)	144 (34)
≥ 65 years	190 (8)	0 (0)	5 (1)
Sex			
Male	1666 (70)	159 (77)	290 (69)
Female	721 (30)	47 (23)	130 (31)
Race			
White	1875 (79)	143 (69)	355 (85)
Black	266 (11)	47 (23)	34 (8)
Hispanic	74 (3)	5 (2)	6 (1)
Asian/Oriental[#]	35 (2)	4 (2)	4 (1)
Other[*]	53 (2)	7 (3)	21 (5)
Weight (kg)			
n	2285	197	412
Mean	76 (17)	78 (16)	72 (17)
Range			

*Includes 1710 subjects exposed to quetiapine in controlled trials and 452 new exposures to quetiapine in uncontrolled trials (804 subjects were exposed in controlled trials and entered uncontrolled trials).
[#]Includes East Indian.
[*]Other includes special subgroups and race undefined, not specified or not collected.

APPENDIX TABLE 5.1.3.1 Number and percent of all subjects receiving quetiapine according to mean daily dose and duration in Phase I trials (n = 343) (adapted from sponsor's electronic safety update submission)

Duration (days)	≤75 mg	>75 mg ≤150 mg	>150 mg ≤300 mg	>300 mg ≤450 mg	>450 mg ≤600 mg	>600 mg ≤800 mg	Total (%)
1	34	0	0	0	0	0	34 (10)
2-7	84	7	11	2	0	0	104 (30)
8-14	1	3	49	18	29	0	100 (29)
15-21	0	0	21	46	9	7	83 (24)
22-28	0	0	1	5	1	1	8 (2)
29-35	0	8	0	0	0	1	9 (3)
36-42	1	0	0	0	4	0	5 (2)
Total	120	18	82	71	43	9	343 (100)
%	35	5	24	21	13	3	100

APPENDIX TABLE 5.1.3.2 Number (%) of all subjects receiving quetiapine according to mean daily dose and duration in Phase II and III trials (n = 2317*) (adapted from sponsor's electronic safety update submission)

Duration (days)	≤75 mg	>75 mg ≤150 mg	>150 mg ≤300 mg	>300 mg ≤450 mg	>450 mg ≤600 mg	>600 mg ≤800 mg	> 800 mg	Total (%)
1	18	0	0	1	1	0	0	20 (1)
2-7	76	37	69	7	2	0	0	191 (8)
8-14	34	16	67	50	18	2	0	187 (8)
15-21	24	24	44	40	23	5	0	160 (7)
22-28	13	12	49	58	26	4	0	162 (7)
29-35	10	5	18	29	12	8	0	82 (4)
36-42	11	9	82	114	101	25	0	342 (15)
43-112	36	46	103	131	82	20	0	418 (18)
113-183	25	31	50	37	36	14	0	193 (8)
184-365	28	47	63	57	59	27	0	281 (12)
366-548	3	11	64	26	26	16	1	147 (6)
549-730	2	5	35	26	14	7	0	89 (4)
> 730	1	1	8	17	11	6	1	45 (2)
Total	281	244	652	593	411	134	2	2317* (100)
%	12	11	28	26	18	6	0.09	100

*Does not include 70 subjects who did not have first dose dates for open label therapy

Appendix table 5.1.3.3 Patient years of exposure in the primary integrated database (adapted from sponsor's table 4.7 of safety update)

	Number ofpatients	Patient-years exposure*
Quetiapine	2387	865.3
Haloperidol	320	42.5
Chlorpromazine	100	9.2
Placebo	206	14.6

*Patient-years is defined as the sum of every subject's days on treatment (duration) divided by 365 days.

Appendix table 7.2.1.1 INVESTIGATOR AND CENTER LIST, Study 0006 (adapted from sponsor's electronic submission)

Center number	Investigator	Address
008	RL Borison MD PhD Principal Investigator B Diamond PhD	Psychiatry Service, 116A-U Augusta VA Medical Center One Freedom Way Augusta, GA 30910
001	JP McEvoy MD	John Umstead Hospital 12th Street Butner, NC 27509
002	JS Carman MD	Brawner Psychiatric Institute 3180 Atlanta Street SE Smyrna, GA 30080
003	W Ryan MD N Smith MD	University Hospital Jefferson Towers, North Wing University of Alabama at Birmingham School of Medicine 619 S. 19th Street Birmingham, AL 35233
004	LD Alphs MD	Lafayette Clinic 951 East Lafayette Avenue Detroit, MI 48207 and Detroit VA Medical Center Southfield and Outer Drive Allen Park, MI 48101
005	R Hirshfeld MD	Department of Psychiatry and Behavioral Sciences University of Texas Medical Branch 1014 Texas Avenue Galveston, TX 77550
006	S Mukherjee MD	Creedmoor Psychiatric Center Research Division, Building 74 80-45 Winchester Boulevard Queens Village, NY 11427
007	C Tamminga MD	Maryland Psychiatric Research Center Inpatient Unit, PO Box 21247 Spring Grove Hospital Grounds Baltimore, MD 21228
009	G Gewirtz MD (deceased)	New York State Psychiatric Institute 722 West 168th Street New York, NY 10032
010	M Hamner MD	VA Medical Center Inpatient Psychiatry: 5BN 109 Bee Street, Charleston SC 29045

011	G Oxenkrug MD PhD	Psychiatric Services, 116A VA Medical Center 830 Chalkstone Avenue Providence, RI 02908
012	H Nasrallah MD	Department of Psychiatry The Ohio State University College of Medicine 473 W. 12th Avenue Columbus, OH 43210

Appendix table 7.2.1.2 **Trial 0006 - Demographic characteristics** (adapted from sponsor's electronic submission)									
Treatment groups	n	Age (years)		Sex (n [%])		Race (n [%])			
		Mean	Range	Male	Female	Caucasian	Black	Hispanic	Other
Quetiapine	54	36		48 (89)	6 (11)	32 (59)	21 (39)	1 (2)	0
Placebo	55	37		50 (91)	5 (9)	34 (62)	18 (33)	1 (2)	2 (4)

Appendix table 7.2.1.3 St udy 0006 - Patient completion rates (adapted from sponsor's electronic submission)									
Treatment groups	Number randomized	Intent-to-treat sample*	Number (%) of patients completing						
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6#
Quetiapine	54	53	53 (100)	46 (87)	41 (77)	35 (66)	32 (60)	28 (53)
Placebo	55	53	53 (100)	47 (89)	39 (74)	30 (57)	27 (51)	23 (43)

*Patients who received assigned medication and had one or more efficacy assessments.
#Patient 004/00406 withdrew from the trial at Day 40. Efficacy data obtained at this time were included with Day 42 data for the placebo group (n = 23 at Day 42). However, this patient was not considered to have completed the trial.

Appendix table 7.2.1.4 Trial 0006 - Mean quetiapine dose by trial week for all patients (adapted from sponsor's electronic submission)			
	Quetiapine dose (mg)		
	n	Mean	SD
Week 1	53	151	95
Week 2	46	334	153
Week 3	41	402	173
Week 4	35	418	160
Week 5	32	431	160
Week 6	28	420	180

SD = Standard deviation.

TABLE Trial 5077IL/0006 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Last observation carried forward analysis

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Quetiapine	53	55.79	53	-3.18	53	-5.55	53	-7.00	53	-8.44	53	-8.66	53	-8.08
Placebo	53	54.09	53	-0.73	53	-0.47	53	-2.03	53	-1.78	53	-1.25	53	-2.13
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo*			0.2023		0.0508		0.0888		0.0224		0.0186		0.0694	

TABLE Trial 5077IL/0006 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Observed case analysis

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine	53	55.79	53	-3.51	46	-7.35	41	-11.80	35	-13.11	32	-14.64	28	-13.64
Placebo	53	54.09	53	-0.83	47	-2.61	39	-9.43	30	-11.91	27	-13.17	23	-13.85
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo*			0.1648		0.0656		0.3572		0.6045		0.6296		0.9510	

*Baseline compairson p value =0.019 (ANOVA)

TABLE Trial 5077IL/0006 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Last observation carried forward analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine	53	4.96	53	0.03	53	-0.07	53	-0.30	53	-0.28	53	-0.30	53	-0.22
Placebo	53	4.64	53	0.15	53	0.29	53	0.24	53	0.28	53	0.28	53	0.23
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo*			0.4776		0.0770		0.0192		0.0122		0.0191		0.0693	

TABLE Trial 5077IL/0006 - Mean change from baseline in CGI - Severity of Illness score(adapted from sponsor's electronic submission)

Observed case analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine	53	4.96	53	-0.01	46	-0.32	41	-0.72	35	-0.74	32	-0.86	28	-0.65
Placebo	53	4.64	53	0.13	47	0.04	39	-0.24	30	-0.58	27	-0.67	23	-0.72
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo*			0.4003		0.0592		0.0269		0.4367		0.4981		0.8410	

*Baseline comparison p value = 0.03 (ANOVA)

TABLE Trial 5077IL/0006 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine	53	4.32	53	-0.34	53	-0.65	53	-0.73	53	-0.96	53	-0.99	53	-0.89
Placebo	53	4.03	53	-0.13	53	-0.21	53	-0.30	53	-0.22	53	-0.19	53	-0.33
2-sded pvalues for pairwise comparisons														
Quetiapine vs pacebo			0.2236		0.0470		0.0704		0.0038		0.0030		0.0557	

TABLE Trial 5077IL/0006 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Observed case analysis														
	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine	53	4.32	53	-0.37	46	-0.76	41	-1.12	35	-1.33	32	-1.34	28	-1.10
Placebo	53	4.03	53	-0.15	47	-0.33	39	-0.88	30	-0.90	27	-0.98	23	-1.15
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo			0.2115		0.0547		0.2968		0.1183		0.2328		0.8892	

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

TABLE Trial 5077IL/0006 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Last observation carried forward analysis														
	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine	51	14.06	49	-0.05	51	-0.13	51	-0.57	51	-0.87	51	-1.05	51	-1.04
Placebo	51	13.96	50	0.57	51	0.92	51	0.85	51	0.70	51	0.62	51	0.56
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo			0.2449		0.1153		0.0437		0.0240		0.0299		0.0519	

TABLE Trial 5077IL/0006 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Observed case analysis														
	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine	51	14.06	49	-0.04	45	-0.15	38	-0.85	27	-0.75	31	-1.11	28	-0.88
Placebo	51	13.96	50	0.62	44	0.49	34	-0.65	24	-1.40	26	-1.35	23	-1.40
2-sided p-values for pairwise comparisons														
Quetiapine vs placebo			0.2084		0.3766		0.8116		0.5172		0.8189		0.6783	

Appendix 7.2.2.1

INVESTIGATOR AND CENTER LIST: Study 0008 (adapted from sponsor's electronic submission) N.B. U.S. and foreign sites had different protocols and study nos.

Center number	Investigator	Address
STUDY 5077US/0001		
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APPENDIX TABLE 7.2.2.2 Trial 0008 - Demographic characteristics (adapted from sponsor's electronic submission)

Treatment groups	n	Age (years)		Sex (n [%])		Race (n [%])				
		Mean	Range	Male	Female	Caucasian	Black	Hispanic	Asian	Other
Quetiqpine High dose	96	36		66 (69)	30 (31)	66 (69)	19 (20)	7 (7)	1 (1)	3 (3)
QuetiapineLow dose	94	37		73 (78)	21 (22)	63 (67)	20 (21)	6 (6)	3 (3)	2 (2)
Placebo	96	38		64 (67)	32 (33)	73 (76)	16 (17)	2 (2)	2 (2)	3 (3)

APPENDIX TABLE 7.2.2.2 Study 0008 - Patient completion rates (adapted from sponsor's electronic submission)

Treatment groups	Number randomized	Intent-to-treat sample*	Number (%) of patients completing					
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Quetiapine High dose	96	95	95 (100)	80 (84)	70 (74)	61 (64)	52 (55)	49 (51)
Quetiapine Low dose	94	93	93 (100)	85 (91)	69 (74)	56 (60)	46 (49)	39 (41)
Placebo	96	94	94 (100)	81 (86)	60 (64)	50 (53)	45 (48)	41 (43)

* Patients who received assigned medicaiton and had one or more efficacy assessments.

APPENDIX TABLE 7.2.2.3 Trial 0008 - Mean quetiapine dose daily dose (mg) by trial week for all patients (adapted from sponsor's electronic submission)

	Quetiapine Low dose			Quetiapine High dose		
	n	Mean	SD	n	Mean	SD
Week 1	93	154	71	95	184	136
Week 2	85	242	38	80	410	191
Week 3	69	245	24	70	502	166
Week 4	56	246	27	61	538	149
Week 5	46	246	23	52	534	134
Week 6	40	248	19	49	489	126

TABLE Trial 0008 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Last observation carried forward analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine														
High dose	94	41.04	94	-2.41	94	-4.55	94	-6.32	94	-7.58	94	-7.84	94	-8.74
Low dose	92	38.89	92	-1.00	92	-2.00	92	-3.27	92	-4.28	92	-4.00	92	-4.16
Placebo	94	38.35	93	-0.46	94	0.11	94	-0.68	94	-0.45	94	-0.21	94	-0.96
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.1675		0.0108		0.0059		0.0007		0.0003		0.0006	
Low dose vs placebo			0.7019		0.2450		0.2030		0.0658		0.0718		0.1515	
High dose vs low dose			0.3175		0.1628		0.1357		0.1139		0.0699		0.0413	

TABLE Trial 0008 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Observed case analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine														
High dose	94	41.04	94	-2.23	80	-6.97	70	-12.90	61	-12.10	52	-13.56	49	-15.12
Low dose	92	38.89	92	-0.22	85	-3.13	69	-9.00	55	-9.50	46	-10.15	39	-11.39
Placebo	94	38.35	93	-0.02	81	-2.14	60	-9.58	50	-7.93	44	-7.60	41	-9.65
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.1243		0.0136		0.0807		0.0450		0.0102		0.0297	
Low dose vs placebo			0.8889		0.5965		0.7510		0.4472		0.2659		0.5001	
High dose vs low dose			0.1598		0.0429		0.0301		0.1899		0.1361		0.1454	

TABLE Trial 0008 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Last observation carried forward analysis

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine														
High dose	95	5.07	95	-0.08	95	-0.26	95	-0.40	95	-0.47	95	-0.55	95	-0.61
Low dose	92	5.05	92	-0.05	92	-0.16	92	-0.19	92	-0.23	92	-0.32	92	-0.30
Placebo	94	4.94	94	0.01	94	0.00	94	-0.04	94	-0.03	94	-0.01	94	-0.08
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.4074		0.0766		0.0184		0.0071		0.0012		0.0030	
Low dose vs placebo			0.5791		0.2630		0.3445		0.2230		0.0625		0.2282	
High dose vs low dose			0.7880		0.5194		0.1584		0.1403		0.1690		0.0768	

TABLE Trial 0008 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Observed case analysis

	Treatment week													
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine														
High dose	95	5.07	95	-0.05	80	-0.54	70	-0.97	61	-0.87	52	-0.93	49	-1.05
Low dose	92	5.05	92	0.00	84	-0.39	69	-0.62	56	-0.51	46	-0.66	39	-0.65
Placebo	94	4.94	94	0.04	81	-0.29	60	-0.73	50	-0.63	45	-0.49	41	-0.60
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.3989		0.1007		0.1315		0.2071		0.0290		0.0408	
Low dose vs placebo			0.6927		0.5212		0.4925		0.5252		0.3934		0.8518	
High dose vs low dose			0.6552		0.2976		0.0234		0.0525		0.2027		0.0786	

TABLE Trial 0008 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine High dose	94	3.61	94	-0.35	94	-0.52	94	-0.72	94	-0.81	94	-0.86	94	-0.90
Quetiapine Low dose	92	3.63	92	-0.32	92	-0.48	92	-0.58	92	-0.65	92	-0.60	92	-0.61
Placebo	94	3.52	94	-0.29	94	-0.36	94	-0.39	94	-0.37	94	-0.35	94	-0.37

2-sided p-values for pairwise comparisons

Quetiapine High dose vs placebo	0.6205	0.2582	0.0486	0.0103	0.0035	0.0030
Quetiapine Low dose vs placebo	0.7614	0.3912	0.2539	0.0996	0.1549	0.1728
High dose vs low dose	0.8502	0.7891	0.4090	0.3611	0.1335	0.1080

TABLE Trial 0008 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Observed case analysis

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine														
Quetiapine High dose	94	3.61	94	-0.29	80	-0.62	70	-1.02	61	-1.06	52	-1.13	49	-1.22
Quetiapine Low dose	92	3.63	92	-0.24	85	-0.48	69	-0.80	55	-0.87	46	-0.84	39	-0.96
Placebo	94	3.52	94	-0.23	81	-0.41	60	-0.87	50	-0.78	44	-0.66	41	-0.70

2-sided p-values for pairwise comparisons

Quetiapine						
Quetiapine High dose vs placebo	0.5904	0.2036	0.4073	0.1603	0.0384	0.0302
Quetiapine Low dose vs placebo	0.9118	0.6656	0.7211	0.6277	0.4335	0.3067
High dose vs low dose	0.6694	0.3831	0.2170	0.3459	0.2027	0.2847

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

TABLE Trial 0008 - Mean change from baseline in SANS summary score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine High dose	55	15.76	54	-0.23	55	-0.67	55	-1.00	55	-1.41	55	-1.53	55	-1.65
Quetiapine Low dose	51	15.82	50	0.07	51	0.20	51	0.14	51	-0.11	51	0.27	51	0.27
Placebo	56	14.50	55	-0.17	56	-0.31	56	0.03	56	0.05	56	-0.09	56	-0.14
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.8957		0.5210		0.0737		0.0198		0.0220		0.0210	
Low dose vs placebo			0.6543		0.3750		0.8605		0.7982		0.5766		0.5381	
High dose vs low dose			0.5618		0.1283		0.0528		0.0407		0.0051		0.0041	

TABLE: Trial 0008 - Mean change from baseline in SANS summary score* (adapted from sponsor's electronic submission)

Observed case analysis

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine High dose	55	15.76	54	-0.20	47	-1.01	44	-1.62	39	-2.37	35	-2.77	33	-3.52
Quetiapine Low dose	51	15.82	50	0.20	46	-0.09	36	-0.82	27	-1.42	30	-0.62	18	-0.94
Placebo	56	14.50	55	-0.18	47	-0.42	35	-0.52	31	-0.36	37	-0.50	26	-0.93
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.9741		0.3383		0.1011		0.0114		0.0079		0.0082	
Low dose vs placebo			0.4926		0.5934		0.6723		0.2100		0.8981		0.9981	
High dose vs low dose			0.4679		0.1309		0.2192		0.2390		0.0220		0.0180	

*SANS completed at US centers only.

TABLE Trial 0008 - Mean change from baseline in PANSS negative scale score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine High dose	38	27.47	38	-1.21	38	-2.25	38	-2.97	38	-3.68	38	-3.93	38	-4.39
Quetiapine Low dose	38	25.50	38	-0.01	38	-0.91	38	-1.53	38	-2.32	38	-2.39	38	-2.86
Placebo	37	24.43	37	0.02	37	0.36	37	-0.96	37	-1.33	37	-1.54	37	-1.88
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.2313		0.0369		0.1322		0.0966		0.1013		0.1047	
Low dose vs placebo			0.9797		0.2998		0.6632		0.4736		0.5538		0.5186	
High dose vs low dose			0.2358		0.2738		0.2742		0.3299		0.2826		0.3149	

TABLE Trial 0008 - Mean change from baseline in PANSS negative scale score* (adapted from sponsor's electronic submission)

Observed case analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine High dose	38	27.47	38	-4.02	29	-4.88	26	-5.63	22	-5.49	17	-4.06	16	-4.38
Quetiapine Low dose	38	25.50	38	-2.77	38	-2.89	31	-5.02	28	-5.20	25	-2.12	22	-2.57
Placebo	37	24.43	37	-2.15	32	-1.72	22	-5.13	19	-4.78	17	-1.94	15	-2.48
2-sided p-values for pairwise comparisons														
Quetiapine														
High dose vs placebo			0.0641		0.0272		0.6484		0.6300		0.1550		0.2671	
Low dose vs placebo			0.5350		0.3648		0.9153		0.7575		0.8930		0.9561	
High dose vs low dose			0.2035		0.1343		0.5354		0.8256		0.1556		0.2478	

*PANSS(N) completed at European centers only.

Appendix 7.2.2.1 INVESTIGATOR AND CENTER LIST (adapted from sponsor's electronic study report)

Trial number: 5077IL/0013

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APPENDIX TABLE 7.2.3.1 Trial 0013 - Demographic characteristics (adapted from sponsor's electronic submission)

Treatment Groups	n	Age (years)		Sex (n [%])		Race (n [%])				
		Mean	Range	Male	Female	White	Black	Hispanic	Asian	Other
Quetiapine 75 mg	53	37		39 (74)	14 (26)	36 (68)	14 (26)	2 (4)	1 (2)	0
150 mg	48	38		39 (81)	9 (19)	36 (75)	9 (19)	1 (2)	1 (2)	1 (2)
300 mg	52	38		37 (71)	15 (29)	36 (69)	13 (25)	3 (6)	0	0
600 mg	51	39		38 (75)	13 (25)	36 (71)	9 (18)	4 (8)	1 (2)	1 (2)
750 mg	54	35		38 (70)	16 (30)	38 (70)	11 (20)	3 (6)	1 (2)	1 (2)
Placebo	51	36		41 (80)	10 (20)	35 (69)	10 (20)	2 (4)	2 (4)	2 (4)
Haloperidol 12 mg	52	37		42 (81)	10 (19)	37 (71)	14 (27)	1 (2)	0	0

APPENDIX TABLE 7.2.3.2 Trial 0013 - Patients completion rates (adapted from sponsor's electronic submission)

Treatment groups	Number randomized	Intent-to-treat sample*	Number (%) of patients completing					
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Quetiapine 75 mg	53	52	52 (100)	47 (90)	25 (48)	22 (42)	17 (33)	16 (31)
150 mg	48	48	48 (100)	46 (96)	37 (77)	25 (52)	23 (48)	21 (44)
300 mg	52	51	51 (100)	49 (96)	41 (80)	32 (63)	29 (57)	24 (47)
600 mg	51	51	51 (100)	42 (82)	35 (69)	30 (59)	29 (57)	27 (53)
750 mg	54	54	54 (100)	48 (89)	36 (67)	31 (57)	30 (56)	29 (54)
Placebo	51	51	51 (100)	46 (90)	30 (59)	26 (51)	22 (43)	17 (33)
Haloperidol 12 mg	52	50	50 (100)	45 (90)	36 (72)	24 (48)	20 (40)	18 (36)

*Patients who had at least one efficacy assessment on trial medication.

TABLE Trial 0013 - Mean change from baseline in BPRS total score (adapted from sopnsor's electronic submission)

Last observation carried forward analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Quetiapine 75 mg	52	45.71	52	-3.62	52	-3.56	52	-2.13	52	-1.91	52	-2.38	52	-2.24
150 mg	48	47.15	48	-3.83	48	-6.58	48	-6.77	48	-7.99	48	-8.66	48	-8.67
300 mg	51	45.29	51	-4.11	51	-7.07	51	-8.67	51	-9.64	51	-9.04	51	-8.59
600 mg	51	43.45	51	-3.94	51	-5.79	51	-6.72	51	-7.31	51	-6.92	51	-7.68
750 mg	53	45.72	53	-3.27	53	-4.65	53	-7.22	53	-7.55	53	-6.08	53	-6.33
Haloperidol 12 mg	50	44.00	50	-4.60	50	-8.60	50	-8.52	50	-7.53	50	-8.32	50	-7.58
Placebo	51	45.31	51	-2.23	51	0.02	51	1.05	51	1.17	51	1.76	51	1.71
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.9301		0.4162		0.6119		0.6620		0.4103		0.5041	
150 mg vs placebo			0.8909		0.0294		0.0143		0.0038		0.0010		0.0021	
300 mg vs placebo			0.8039		0.0143		0.0010		0.0003		0.0005		0.0019	
600 mg vs placebo			0.8562		0.0632		0.0132		0.0074		0.0076		0.0057	
750 mg vs placebo			0.9783		0.1800		0.0065		0.0050		0.0180		0.0224	
Haloperidol 12 mg vs placebo			0.2360		0.0004		0.0003		0.0014		0.0003		0.0016	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9994		0.9534		1.0000		0.8952		0.9991		0.9967	

*Best quetiapine dose overall.

TABLE Trial 0013 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Observed case analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n		n	mean	n	mean
Quetiapine 75 mg	52	45.71	52	-3.62	46	-5.01	25	-10.16	22	-10.58	17	-14.87	16	-14.24
150 mg	48	47.15	48	-3.83	46	-7.09	37	-9.22	25	-14.79	23	-16.46	21	-16.75
300 mg	51	45.29	51	-4.11	49	-7.37	40	-11.26	32	-16.90	29	-16.01	24	-17.64
600 mg	51	43.45	51	-3.94	42	-7.32	35	-9.92	30	-14.94	29	-13.84	27	-16.53
750 mg	53	45.72	53	-3.27	48	-4.63	36	-11.15	31	-13.72	30	-11.14	29	-12.72
Haloperidol 12 mg	50	44.00	50	-4.60	45	-9.43	35	-11.75	24	-15.56	19	-17.74	18	-17.11
Placebo	51	45.31	51	-2.23	46	-0.91	30	-2.03	26	-3.86	21	-3.75	17	-7.06

2-sided p-values for pairwise comparisons

Quetiapine 75 mg vs placebo	0.9301	0.3441	0.0448	0.1765	0.0250	0.3804
150 mg vs placebo	0.8909	0.0608	0.0531	0.0048	0.0034	0.1056
300 mg vs placebo	0.8039	0.0412	0.0058	0.0002	0.0028	0.0556
600 mg vs placebo	0.8562	0.0558	0.0306	0.0025	0.0194	0.0913
750 mg vs placebo	0.9783	0.4270	0.0083	0.0081	0.1284	0.4788
Haloperidol 12 mg vs placebo	0.2360	0.0010	0.0014	0.0009	0.0007	0.0364
Quetiapine 300 mg* vs haloperidol 12 mg	0.9994	0.8752	0.9999	0.9907	0.9827	1.0000

*Best quetiapine dose overall.

TABLE Trial 0013 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Last observation carried forward analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine 75 mg	52	4.90	52	-0.20	52	-0.28	52	-0.18	52	-0.05	52	-0.13	52	-0.15
150 mg	48	5.00	48	-0.11	48	-0.18	48	-0.31	48	-0.32	48	-0.45	48	-0.49
300 mg	51	5.08	51	-0.28	51	-0.48	51	-0.64	51	-0.69	51	-0.73	51	-0.69
600 mg	51	4.88	51	-0.03	51	-0.33	51	-0.45	51	-0.52	51	-0.46	51	-0.46
750 mg	54	5.00	54	-0.17	54	-0.29	54	-0.49	54	-0.60	54	-0.54	54	-0.46
Haloperidol 12 mg	50	5.02	50	-0.36	50	-0.62	50	-0.64	50	-0.62	50	-0.71	50	-0.69
Placebo	51	4.92	51	-0.07	51	0.10	51	0.23	51	0.22	51	0.25	51	0.25
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.8494		0.1271		0.1348		0.5034		0.2321		0.2215	
150 mg vs placebo			0.9991		0.3803		0.0304		0.0331		0.0045		0.0039	
300 mg vs placebo			0.4219		0.0056		0.0001		<0.0001		<0.0001		0.0001	
600 mg vs placebo			0.9987		0.0625		0.0030		0.0013		0.0030		0.0049	
750 mg vs placebo			0.9205		0.1039		0.0011		0.0002		0.0007		0.0042	
Haloperidol 12 mg vs placebo			0.0468		0.0001		0.0001		0.0001		0.0001		0.0001	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9805		0.8894		1.0000		0.9957		1.0000		1.0000	

*Best quetiapine dosage overall.

TABLE Trial 0013 - Mean change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Observed case analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine 75 mg	52	4.90	52	-0.20	47	-0.37	25	-0.79	22	-0.62	17	-1.03	16	-1.03
150 mg	48	5.00	48	-0.11	46	-0.23	37	-0.51	25	-0.74	23	-0.95	21	-1.10
300 mg	51	5.08	51	-0.28	48	-0.49	41	-0.70	32	-1.02	29	-1.06	24	-1.21
600 mg	51	4.88	51	-0.03	42	-0.49	35	-0.79	30	-1.16	29	-1.14	27	-1.19
750 mg	54	5.00	54	-0.17	48	-0.35	36	-0.67	31	-0.93	30	-0.78	29	-0.75
Haloperidol 12 mg	50	5.02	50	-0.36	45	-0.67	36	-0.82	24	-1.07	20	-1.35	18	-1.35
Placebo	51	4.92	51	-0.07	46	0.04	30	-0.04	26	-0.21	22	-0.13	17	-0.34
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.8494		0.1052		0.0173		0.4179		0.0143		0.1957	
150 mg vs placebo			0.9991		0.4403		0.1642		0.1705		0.0159		0.0990	
300 mg vs placebo			0.4219		0.0173		0.0166		0.0060		0.0024		0.0357	
600 mg vs placebo			0.9987		0.0219		0.0075		0.0011		0.0009		0.0381	
750 mg vs placebo			0.9205		0.1341		0.0332		0.0203		0.0559		0.5341	
Haloperidol 12 mg vs placebo			0.0468		0.0002		0.0015		0.0026		0.0001		0.0066	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9805		0.7658		0.9808		0.9998		0.7048		0.9896	

*Best quetiapine dosage overall.

TABLE Trial 0013 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Last observation carried forward analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine 75 mg	52	3.84	52	-0.35	52	-0.46	52	-0.29	52	-0.29	52	-0.34	52	-0.38
150 mg	48	3.95	48	-0.27	48	-0.52	48	-0.57	48	-0.68	48	-0.70	48	-0.74
300 mg	51	3.77	51	-0.31	51	-0.71	51	-0.84	51	-0.93	51	-0.81	51	-0.87
600 mg	51	3.54	51	-0.38	51	-0.54	51	-0.77	51	-0.76	51	-0.70	51	-0.73
750 mg	53	3.63	53	-0.32	53	-0.47	53	-0.72	53	-0.68	53	-0.60	53	-0.58
Haloperidol 12 mg	50	3.63	50	-0.39	50	-0.74	50	-0.81	50	-0.72	50	-0.80	50	-0.74
Placebo	51	3.74	51	-0.24	51	-0.20	51	-0.07	51	-0.05	51	-0.02	51	0.05
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.9521		0.5886		0.8062		0.7417		0.5157		0.2446	
150 mg vs placebo			0.9998		0.4064		0.1164		0.0318		0.0216		0.0061	
300 mg vs placebo			0.9913		0.0553		0.0035		0.0007		0.0040		0.0007	
600 mg vs placebo			0.8678		0.3353		0.0095		0.0100		0.0177		0.0064	
750 mg vs placebo			0.9896		0.5170		0.0178		0.0264		0.0564		0.0379	
Haloperidol 12 mg vs placebo			0.3875		0.0091		0.0013		0.0045		0.0011		0.0013	
Quetiapine 300 mg" vs haloperidol 12 mg			0.9901		0.9999		1.0000		0.8072		1.0000		0.9741	

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

"Best quetiapine dosage overall.

TABLE Trial 0013 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission)

Observed case analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine 75 mg	52	3.84	52	-0.35	46	-0.55	25	-0.95	22	-1.02	17	-1.48	16	-1.52
150 mg	48	3.95	48	-0.27	46	-0.55	37	-0.75	25	-1.03	23	-1.06	21	-1.08
300 mg	51	3.77	51	-0.31	49	-0.71	40	-1.00	32	-1.45	29	-1.22	24	-1.61
600 mg	51	3.54	51	-0.38	42	-0.62	35	-1.11	30	-1.43	29	-1.30	27	-1.39
750 mg	53	3.63	53	-0.32	48	-0.46	36	-1.01	31	-1.07	30	-0.96	29	-0.99
Haloperidol 12 mg	50	3.63	50	-0.39	45	-0.76	35	-1.03	24	-1.12	19	-1.43	18	-1.42
Placebo	51	3.74	51	-0.24	46	-0.27	30	-0.37	26	-0.52	21	-0.60	17	-0.68
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.9521		0.5933		0.2114		0.4232		0.0994		0.1651	
150 mg vs placebo			0.9998		0.5995		0.5016		0.3772		0.5758		0.7331	
300 mg vs placebo			0.9913		0.1626		0.0850		0.0121		0.2416		0.0647	
600 mg vs placebo			0.8678		0.3986		0.0393		0.0160		0.1560		0.2012	
750 mg vs placebo			0.9896		0.8587		0.0885		0.2584		0.7296		0.8452	
Haloperidol 12 mg vs placebo			0.3875		0.0292		0.0237		0.0809		0.0385		0.0859	
Quetiapine 300 mg# vs haloperidol 12 mg			0.9901		0.9994		1.0000		0.7303		0.9605		0.9791	

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.
#Best quetiapine dose overall.

TABLE Trial 0013 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Last observation carried forward analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine 75 mg	46	14.59	45	-0.10	46	-0.45	46	-0.17	46	-0.32	46	-0.40	46	-0.62
150 mg	45	14.73	44	-0.27	45	-0.50	45	-0.72	45	-0.42	45	-0.85	45	-0.78
300 mg	49	14.24	49	-0.46	49	-1.53	49	-1.92	49	-1.67	49	-1.47	49	-1.56
600 mg	49	14.35	48	-0.11	48	-0.46	49	-1.06	49	-1.23	49	-0.88	49	-0.98
750 mg	48	15.46	47	-0.18	47	-0.41	47	-0.82	47	-0.84	48	-0.57	48	-0.50
Haloperidol 12 mg	50	14.72	47	-0.84	50	-1.77	50	-1.79	50	-1.60	50	-1.75	50	-1.83
Placebo	50	13.88	50	0.82	50	0.68	50	0.88	50	0.80	50	1.12	50	0.76
2-sided p-values for pairwise comparisons														
Quetiapine 75 mg vs placebo			0.3107		0.2707		0.3627		0.3604		0.1155		0.2068	
150 mg vs placebo			0.1702		0.2405		0.0667		0.2855		0.0230		0.1371	
300 mg vs placebo			0.0667		0.0024		0.0001		0.0018		0.0009		0.0059	
600 mg vs placebo			0.2798		0.2589		0.0131		0.0147		0.0168		0.0618	
750 mg vs placebo			0.2253		0.3054		0.0407		0.0754		0.0599		0.2771	
Haloperidol 12 mg vs placebo			0.0020		0.0001		0.0001		0.0006		0.0001		0.0003	
Quetiapine 300 mg* vs haloperidol 12 mg			0.9301		0.9952		0.9998		1.0000		0.9932		0.9950	

*Best quetiapine dosage overall.

TABLE Trial 0013 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Observed case analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Quetiapine 75 mg	46	14.6	45	-0.10	41	-0.77	21	-1.52	16	-2.08	14	-2.10	13	-3.22
150 mg	45	14.7	44	-0.27	41	-0.74	35	-1.28	25	-1.01	23	-2.15	21	-2.02
300 mg	49	14.2	49	-0.46	47	-1.53	38	-2.39	32	-2.38	29	-2.30	24	-3.14
600 mg	49	14.2	48	-0.11	40	-0.89	34	-1.64	29	-2.80	28	-2.05	27	-2.67
750 mg	48	15.5	47	-0.18	46	-0.45	34	-1.47	28	-1.09	29	-0.82	27	-0.85
Haloperidol 12 mg	50	14.7	50	-0.84	45	-1.98	34	-2.55	23	-2.37	19	-3.27	16	-3.46
Placebo	50	13.9	50	0.82	42	0.38	27	0.68	23	0.54	19	1.29	16	-0.61

2-sided p-values for pairwise comparisons

Quetiapine 75 mg vs placebo	0.3107	0.3162	0.0445	0.0518	0.0058	0.0672
150 mg vs placebo	0.1702	0.3345	0.0414	0.3081	0.0011	0.4248
300 mg vs placebo	0.0667	0.0186	0.0003	0.0047	0.0003	0.0317
600 mg vs placebo	0.2798	0.2323	0.0114	0.0012	0.0009	0.0956
750 mg vs placebo	0.2253	0.5970	0.0217	0.2407	0.0630	0.9989
Haloperidol 12 mg vs placebo	0.0020	0.0007	0.0001	0.0047	0.0001	0.0100
Quetiapine 300 mg* vs haloperidol 12 mg	0.9301	0.9422	0.9995	1.0000	0.6690	0.9964

*Best quetiapine dosage overall.

Appendix 7.2.4

STUDY 0012 INVESTIGATORS (ADAPTED FROM SPONSOR'S ELECTRONIC STUDY REPORT)

INVESTIGATOR AND CENTER LIST

(Centers that recruited patients)

Center number	Investigator	Address	Number of patients entered
002	Dr D J King (Principal investigator)	Queen's University of Belfast United Kingdom	9
001	Prof S R Hirsch	Department of Psychiatry	31
		Charing Cross Hospital	
		United Kingdom	
003	Dr B G Ferguson	Department of Psychiatry, Mapperley Hospital	10
		Nottingham United Kingdom	
004	Dr R Didi	C.H.S. La Chartreuse	4
		France	
005	Dr T K Szulecka	Department of Psychiatry	17
		Doncaster Royal Infirmary, U.K.	
006	Dr J Lynch	Department of Psychiatry	15
		St Michael's Hospital	
		Clonmel Ireland	
007	Dr S B Mahapatra	Department of Psychiatry	9
		The General Hospital	
		Hartlepool U.K.	
008	Dr D J MacFarlane	Department of Psychiatry	3
		Ards Hospital Northern Ireland	
011	Dr W Kissling	Psychiatrische Klinik der Tu Muenchen	7
		Munich	
012	Dr S Shaw	Stanley Royd Hospital	2
		West Yorkshire U.K.	
013	Dr P S Meats	Department of Psychiatry	1
		King's Mill Hospital	
		Sutton-In-Ashfield U.K.	
014	Prof G W Fenton	Department of Psychiatry	4
		University of Dundee U.K.	
015	Prof T Burns	Department of Mental Health Sciences	6
		Cranmer Terrace	
		London U.K.	
016	Dr R Erkwoh	Psychiatrische Klinik der RWTH	4
		Aachen	
		Germany	
017	Dr F M Corrigan	Department of Psychiatry	3
		Argyll and Bute Hospital	
		Argyll U.K.	
019	Dr C S Thomas	Department of Psychiatry	5
		University Hospital of South Manchester	
		Manchester U.K.	
020	Prof R Priest	Department of Psychiatry	2
		St Mary's Hospital Medical School	
		London U.K.	
021	Dr F Mesotten	Medisch Centrum St Jozef	8
		Belgium	
022	Dr J M Martens	Sint Lucaskliniek	2
		Belgium	

023	Dr G Beckers	Medister	6
		Jagersdreef 100	
		Belgium	
024	Dr G Dierick	Ziekenhuis Reigerlo	3
		Belgium	
025	Dr Y Schroeder	Psychiatrische Universitaetsklinik	6
		Heidelberg	
		Germany	
027	Prof W W Fleischhacker	Department of Psychiatry	4
		Innsbruck University Clinics	
		Austria	
028	Dr C Geretsegger	Landes-Nervenklinik Salzburg	3
		Austria	
029	Dr J Stoessl	Psychiatrisches Krankenhaus der Stadt Wien	12
		Vienna	
		Austria	
030	Prof G Darcourt	C.H.R. Hopital Pasteur	7
		Nice Cedex	
		France	
031	Prof M Patris	C.H.U. Clinique Psychiatrique	7
		Strasbourg	
		France	
032	Dr P H Bern	Hotel Dieu	3
		France	
033	Prof J M Azorin	C.H.U. La Timone	3
		Clinique de Psichiatrie	
		13385 Marseille Cedex 4	
		France	
034	Dr F Ruyer	C.H.S. d'Evereux	6
		27022 Evreux Cedex	
		France	
035	Prof J Tignol	C.H.S. Charles Perrens	7
		33076 Bordeaux Cedex	
		France	
036	Dr M Marie-Cardine	C.H.S. Le Vinatier	11
		69677 Bron Cedex	
		France	
037	Dr A Braconnier	Centre de l'Eau Vive	3
		91450 Soisy-sur-Seine	
		France	
038	Dr C Gaussares	C.H.S. Charles Perrens	4
		33076 Bordeaux Cedex	
		France	
039	Dr J Daumer	C.H.S. Charcot	1
		56854 Caudan	
		France	
040	Dr G Clerc	C.H.S. de Pontorson	12
		50170 Pontorson	
		France	
041	Dr J P Chabannes	C.H.S. de Bassens	5
		B P 1126	
		73011 Chambery Cedex	
		France	
042	Dr G E Duboc	C.H.S. de Navarre	3

		27022 Evreux Cedex	
		France	
043	Dr F Caroli	Hopital Sainte Anne	7
		75674 Paris Cedex 14	
		France	
044	Dr R de Beaurepaire	C.H.S. Le Bon Sauveur	5
		14012 Caen	
		France	
045	Prof R H Belmaker	Psychiatric Center	19
		Beer Sheva	
		Israel	
046	Dr M Avnon	Psychiatric Center	14
		Shaar Menashe	
		Israel	
047	Prof A Weizman	Psychiatric Department	12
		Geha Psychiatric Hospital	
		Israel	
048	Dr J P Malanowski	Psychiatric Clinic Beverin	1
		Cazis	
		Switzerland	
049	Dr S P Kutcher	Department of Psychiatry	4
		Sunnybrook Health Sciences Center	
		Toronto	
		Ontario M4N 3M5	
		Canada	
050	Prof G Buchkremer	Psychiatrische Universitatskliniik Tubingen	5
		72076 Tubingen	
		Germany	
051	Prof R Michaelis	Krankenhaus Itzehoe	6
		Abt Psychiatrie	
		25524 Itzehoe	
		Germany	
052	Dr M Krausz	Psychiatrische und Nervenklinik	6
		Poliklinik der Universitat Hamburg	
		Germany	
053	Prof E Ruther	Psychiatrische Klinik der Gottingen Universitat	6
		Germany	
054	Prof R Uebelhack	Humboldt-Universitat Berlin	3
		Abteilung Psychiatrie	
		Germany	
055	Prof U H Peters	Med Einrichtung der Universitat Koln	2
		Fachabteilung Psychiatrie	
		Germany	
056	Dr D Ebert	Psychiatrische Klinik und Poliklinik	6
		91054 Erlangen	
		Germany	
057	Prof G A Rudolf	Klinik und Poliklinik fur Psychiatrie der Wilhelms Universitaet Muenster	7
		Germany	
059	Dr E Stip	Centre de Recherche	12
		Fernard - Seguin	
		Quebec H1N 3V2	
		Canada	
060	Dr R Manchanda	Department of Psychiatry	8
		University Hospital	
		London	
		Ontario N6A 5A5	

		Canada	
061	Dr A Malla	Department of Psychiatry	7
		Victoria Hospital Corporation	
		London	
		Ontario N6G 4G5	
		Canada	
062	Dr J Beau	Centre Hospitalier Malartic	8
		Malartic	
		Quebec J0Y 1Z0	
		Canada	
063	Dr P Silverstone	Department of Psychiatry	20
		University of Alberta Hospital	
		Edmonton	
		Alberta T6G 2B7	
		Canada	
064	Dr A Parashos	Aristotelian University of Thessaloniki	10
		Thessaloniki	
		Greece	
065	Prof E Smeraldi	DSNP Ospedale S Raffaele	10
		29-20127 Milan	
		Italy	
066	Prof L Ravizza	Universita di Torino	6
		15-10126 Turin	
		Italy	
067	Dr G Covelli	Ospedale Bolognini	9
		1-24068 Seriate	
		Italy	
068	Prof A Ermentini	Universita di Brescia	9
		Ospedale Civile	
		Italy	
069	Prof L Pavan	Universita di Padova	4
		Italy	
070	Dr C A Robotti	Servizio di Psichiatria	7
		Ospedale Maggoire di Borgotrento	
		1-37126 Verona	
		Italy	
072	Prof P Pancheri	Universita di Roma	3
		Italy	
073	Dr P Laddomada	Primario Servizio Psichiatrico	6
		Ospedale Sirai	
		Italy	
074	Dr M Bassi	Servizio di Salute Mentale	4
		153-43036 Fidenza	
		Italy	
075	Prof G Invernizzi	Universita Degla Studi di Milano	8
		Ospedale Maggiore Policlinico	
		Italy	
076	Dr R Longoni	Unita Operativa di Psichiatria	3
		Ospedale Civile	
		Milan	
		Italy	
077	Prof M Casacchia	Universita dell'Aquila	8
		Ospedale Santa Maria D Collemaggio	
		Italy	
078	Prof V Rapisarda	Universita di Catania	11
		Ospedale Policlin	
		Italy	
079	Prof F Rinaldi	Universita di Napoli	14

		Italy	
080	Prof A P Palha	Casa de Saude de Bom Jesus	13
		Nougueiro	
		4719 Braga	
		Portugal	
081	Dr M J Paes de Sousa	Hospital de Santa Maria	6
		Servicio de Psiquiatria	
		1600 Lisboa	
		Portugal	
082	Dr L M Ferreira	Hospital Magalhaes Lemos	8
		Servico Povoa Vila do Conde	
		4100 Porta	
		Portugal	
083	Dr P Sirota	Department 6A	12
		Abarbanel Mental Health Center	
		Bat-Yam	
		Israel	
084	Dr A Chinchilla	Servicio De Psiquiatria	23
		Hospital Ramon y Cajal	
		Madrid	
		Spain	
085	Dr T Palomo	Servicio de Psiquiatria	8
		Hospital 12 de Octubre	
		Madrid	
		Spain	
086	Dr S Cervera	Servicio de Psiquiatria	7
		Clinica Universitaria de Navarra	
		31080 Pamplona	
		Spain	
087	Dr M Gutierrez	Servicio de Psiquiatria	9
		Hospital Santiago	
		Vitoria	
		Spain	
088	Dr J Izquierdo de la Torre	Servicio de Psiquiatria	7
		Hospital Clinico de Salamanca	
		Spain	
089	Prof A Vaz Serra	Hospitais da Universidade de Coimbra	12
		Servico de Psiquiatria	
		Portugal	
091	Dr G Bartko	Department of Psychiatry	11
		South-Pest Hospital	
		Budapest	
		Hungary	
092	Dr C Banki	Department of Psychiatry	13
		Regional Neuropsychiatric Institute	
		Nagykallo	
		Hungary	
093	Dr G Ostorharics	Department of Psychiatry	13
		Petz A Hospital	
		Gyor, Vasvari P U 2	
		Hungary	
097	Dr L Mauas	Department A	7
		Shalvata Mental Health Center	
		Hod-Hasharon	
		Israel	
098	Dr H Silver	Mazra Psychiatric Hospital	7
		Akko, Israel	

Appendix Table 7.2.4.1 Trial 0012 - Demographic characteristics (adapted from sponsor's electronic submission)

Treatment groups	n	Age (years)		Sex (n [%])		Race (n [%])				
		Mean	Range	Male	Female	Caucasian	Black	Hispanic	Asian/ Oriental	Other
Quetiapine										
150 mg TID	209	34		128 (61)	81 (39)	195 (93)	6 (3)	2 (1)	5 (2)	1 (1)
225 mg BID	200	37		135 (68)	65 (33)	191 (96)	3 (2)	1 (1)	2 (1)	3 (2)
25 mg TID	209	36		146 (70)	63 (30)	201 (96)	3 (1)	0 (0)	2 (1)	3 (1)

Appendix TABLE 7.2.4.2 Trial 0012 - Patient completion rates (adapted from sponsor's electronic submission)

Treatment groups	Number randomized	Intent-to-treat sample*	Number (%) of patients completing					
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Quetiapine								
225 mg BID	200	195	195 (100)	180 (92.3)	142 (72.8)	121 (62.1)	108 (55.4)	103 (52.8)
150 mg TID	209	204	204 (100)	177 (86.8)	145 (71.1)	133 (65.2)	122 (59.8)	114 (55.9)
25 mg BID	209	198	198 (100)	175 (88.4)	134 (67.7)	117 (59.1)	100 (50.5)	94 (47.5)

*Patients who had at least one efficacy assessment on medication, omitting patients from excluded sites.

TABLE Trial 0012 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Last observation carried forward analysis

Quetiapine Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
225 mg BID	195	42.14	195	-3.74	195	-6.08	195	-7.79	195	-8.66	195	-9.49	195	-9.98
150 mg TID	204	42.74	203	-2.00	204	-4.36	204	-6.43	204	-7.09	204	-8.49	204	-8.59
25 mg BID	197	41.68	197	-1.99	197	-3.18	197	-4.68	197	-4.75	197	-5.54	197	-5.41
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.0811		0.0239		0.0307		0.0100		0.0140		0.0055	
150 mg TID vs 25 mg BID			0.9926		0.3545		0.2184		0.1199		0.0636		0.0503	
225 mg BID vs 150 mg TID			0.0804		0.1745		0.3395		0.2938		0.5274		0.3943	

TABLE Trial 0012 - Mean change from baseline in BPRS total score (adapted from sponsor's electronic submission)

Observed case analysis

Quetiapine Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
225 mg BID	195	42.14	195	-4.10	180	-8.12	141	-13.15	121	-16.66	108	-19.33	103	-21.15
150 mg TID	204	42.74	203	-2.38	177	-6.57	145	-12.24	133	-14.67	122	-18.36	114	-19.62
25 mg BID	197	41.68	197	-2.33	174	-5.63	134	-10.51	117	-13.29	100	-16.52	94	-17.21
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.0776		0.0487		0.0766		0.0323		0.0977		0.0273	
150 mg TID vs 25 mg BID			0.9612		0.4561		0.2433		0.3672		0.2650		0.1682	
225 mg BID vs 150 mg TID			0.0836		0.2181		0.5302		0.1908		0.5507		0.3667	

TABLE Trial 0012 - Grouped change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission) Last observation carried forward analysis

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Quetiapine 225 mg BID														
Baseline severity scores														
moderate (4)	51	26												
marked (5)	92	47												
severe (6)	44	23												
most severe (7)	8	4												
Change from baseline														
-3 or less			1	1	4	2	8	4	17	9	22	11	22	11
-2			8	4	16	8	23	12	18	9	21	11	23	12
-1			31	16	54	28	57	29	64	33	59	30	59	30
0			139	71	101	52	86	44	73	37	68	35	66	34
+1 or greater			16	8	20	10	21	11	23	12	25	13	25	13
Quetiapine 150 mg TID														
Baseline severity scores														
moderate (4)	54	26												
marked (5)	87	42												
severe (6)	58	28												
most severe (7)	6	3												
Change from baseline														
-3 or less					2	1	6	3	9	4	12	6	16	8
-2			4	2	9	4	24	12	29	14	30	15	29	14
-1			38	19	56	27	49	24	52	25	54	26	51	25
0			136	67	112	55	98	48	84	41	79	39	77	38
+1 or greater			26	13	26	13	28	14	31	15	30	15	32	16

TABLE Trial 0012 - Grouped change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission) (continued)

Last observation carried forward analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Quetiapine 25 mg BID														
Baseline severity scores														
moderate (4)	62	31												
marked (5)	85	43												
severe (6)	45	23												
most severe (7)	6	3												
Change from baseline														
-3 or less			1	1			3	2	5	3	7	4	10	5
-2			5	3	13	7	13	7	16	8	22	11	19	10
-1			23	12	46	23	60	30	55	28	49	25	52	26
0			148	75	110	56	88	44	85	43	81	41	78	39
+1 or greater			21	11	29	15	34	17	37	19	39	20	39	20

2-sided p-values for pairwise comparisons

225 mg BID vs 25 mg BID	0.6130	0.1230	0.0790	0.0160	0.0070	0.0290
150 mg TID vs 25 mg BID	0.2330	0.4140	0.1530	0.1800	0.3310	0.3440
225 mg BID vs 150 mg TID	0.2260	0.4490	0.6520	0.0920	0.2140	0.4450

TABLE Trial 0012 - Grouped change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission)

Observed case analysis														
	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment groups	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Quetiapine 225 mg BID														
Baseline severity scores														
moderate (4)	51	26												
marked (5)	92	47												
severe (6)	44	23												
most severe (7)	8	4												
Change from baseline														
-3 or less			1	1	4	2	7	5	15	12	19	18	19	18
-2			8	4	16	9	22	16	16	13	18	17	20	19
-1			31	16	54	30	49	35	53	44	44	41	42	41
0			139	71	1	51	58	41	33	27	23	21	20	19
+1 or greater			16	8	15	8	6	4	4	3	4	4	2	2
Quetiapine 150 mg TID														
Baseline severity scores														
moderate (4)	54	26												
marked (5)	87	42												
severe (6)	58	28												
most severe (7)	6	3												
Change from baseline														
-3 or less					2	1	6	4	9	7	12	10	16	14
-2			4	2	9	5	23	16	28	21	28	23	26	23
-1			38	19	54	31	45	31	45	34	47	39	42	37
0			136	67	96	54	61	42	42	32	31	25	26	23
+1 or greater			26	13	16	9	10	7	9	7	4	3	4	4

TABLE Trial 0012 - Grouped change from baseline in CGI - Severity of Illness score (adapted from sponsor's electronic submission) (continued)

Observed case analysis

Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Quetiapine 25 mg BID														
Baseline severity scores														
moderate (4)	62	31												
marked (5)	85	43												
severe (6)	45	23												
most severe (7)	6	3												
Change from baseline														
-3 or less			1	1			3	2	5	4	7	7	10	11
-2			5	3	11	6	12	9	14	12	20	20	17	18
-1			23	12	46	26	49	37	41	35	30	30	32	34
0			148	75	100	57	57	43	50	43	39	39	33	35
+1 or greater			21	11	18	10	13	10	7	6	4	4	2	2

2-sided p-values for pairwise comparisons

225 mg BID vs 25 mg BID	0.5960	0.1480	0.1560	0.0230	0.0170	0.1110
150 mg TID vs 25 mg BID	0.2230	0.5430	0.2110	0.0920	0.1530	0.2860
225 mg BID vs 150 mg TID	0.2280	0.5590	0.8790	0.1070	0.4300	0.8370

TABLE Trial 0012 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission) : Last observation carried forward analysis

Quetiapine Treatment Groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
225 mg BID	195	3.55	195	-0.37	195	-0.63	195	-0.79	195	-0.86	195	-0.92	195	-0.96
150 mg TID	204	3.52	203	-0.23	204	-0.47	204	-0.65	204	-0.68	204	-0.81	204	-0.86
25 mg BID	197	3.47	197	-0.25	197	-0.41	197	-0.53	197	-0.52	197	-0.61	197	-0.62
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.1445		0.0286		0.0194		0.0054		0.0157		0.0090	
150 mg TID vs 25 mg BID			0.7700		0.5862		0.2711		0.1708		0.1063		0.0649	
225 mg BID vs 150 mg TID			0.0780		0.0951		0.2054		0.1468		0.4066		0.4239	

TABLE Trial 0012 - Mean change from baseline in mean BPRS psychosis score* (adapted from sponsor's electronic submission): Observed case analysis

Quetiapine Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
225 mg BID	195	3.55	195	-0.40	180	-0.78	141	-1.16	121	-1.43	108	-1.64	103	-1.79
150 mg TID	204	3.52	203	-0.25	177	-0.62	145	-1.07	133	-1.23	122	-1.55	114	-1.70
25 mg BID	197	3.47	197	-0.27	174	-0.58	134	-0.93	117	-1.13	100	-1.42	94	-1.49
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.1419		0.0532		0.0750		0.0339		0.1237		0.0476	
150 mg TID vs 25 mg BID			0.7932		0.7068		0.2737		0.4622		0.3529		0.1722	
225 mg BID vs 150 mg TID			0.0815		0.1176		0.4765		0.1460		0.5070		0.4994	

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

TABLE Trial 0012 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Last observation carried forward analysis

Quetiapine Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
225 mg BID	189	14.38	188	-0.52	189	-0.80	189	-1.15	189	-1.36	189	-1.53	189	-1.68
150 mg TID	197	14.69	194	-0.14	197	-0.76	197	-1.05	197	-1.32	197	-1.30	197	-1.37
25 mg BID	190	14.38	188	-0.10	190	-0.39	190	-0.81	190	-0.74	190	-0.81	190	-0.85
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.0553		0.1382		0.2647		0.0698		0.0415		0.0216	
150 mg TID vs 25 mg BID			0.8712		0.1764		0.4413		0.0829		0.1563		0.1425	
225 mg BID vs 150 mg TID			0.0768		0.8854		0.7220		0.9237		0.5212		0.3929	

TABLE Trial 0012 - Mean change from baseline in SANS summary score (adapted from sponsor's electronic submission)

Observed case analysis

Quetiapine Treatment groups	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
225 mg BID	189	14.38	188	-0.59	176	-1.11	139	-1.89	119	-2.53	106	-3.02	100	-3.56
150 mg TID	197	14.69	194	-0.21	171	-1.19	138	-2.29	127	-3.01	117	-3.34	110	-3.73
25 mg BID	190	14.38	188	-0.16	166	-0.75	130	-1.76	116	-1.83	97	-2.66	93	-2.75
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID			0.0524		0.2034		0.6984		0.0724		0.3929		0.0591	
150 mg TID vs 25 mg BID			0.8347		0.1276		0.1125		0.0023		0.0962		0.0212	
225 mg BID vs 150 mg TID			0.0807		0.7900		0.2195		0.2089		0.4121		0.6886	

APPENDIX TABLE 8.1.1.1 Deaths during or after trial treatment ended* (adapted from sponsor's electronic submission) Cutoff date: 3/1/96

Trial/center/ subject number	Age (y)	Sex	Dose# (mg/day)	Duration (days)	Cause of Death and Comments
Quetiapine					
0012/0023/2303	47	F	50	11	Suicide
0012/0091/9103	56	M	50	6	Progressive cerebral ischemic lesions consistent with a progressive basilar artery thrombosis, autopsy showed new basilar artery thrombus, severe cerbral atherosclerosis, and encephalomalacia
0012OLE/0045/4502	56	M	500	52+	Cardiopulmonary arrest following several days of worsening angina
0012OLE/0062/6203	35	M	700	155+	Patient escaped hospital, stole car, died in Automobile accident
0012OLE/0080/8013	62	F	500	398	Died 3 days after a cerebrovascular accident; history of hypertension
0015OLE/0005/0514	56	M	300	700	Metastatic cancer from unkown primary
0048/0007/0703	92	M	150	191	Respiratory failure, Bronchopneumonia on autopsy (following transurethral resection of prostate)
0012OLE/0087/8702$	46	m	52@	107	Committed suicide 11 weeks after d/c quetiapine
0048/0017/1703$	81	m	50	15	Pneumonia after 15 days of quetiapine treatment; died 31 days after d/c quetiapine
0048/0007/0708	89	M	125	58	Aspiration Pneumonia; patient had Alzheimer's dementia and dysphagia
Placebo					
None	NA	NA	NA	NA	NA
Haloperidol					
0014/0043/4304	51	M	8	7	Sudden death, autospy report: acute heart failure
Chlorpromazine					
None	NA	NA	NA	NA	NA
Blinded treatment**					
0031/0021/2104	50	M	UNK	55	Accidental drowning (autopsy: drowning)

*Additionally, two subjects (0014/0012/9002 and 0015/0012/9001) died (committed suicide) before randomization to trial treatment

$ died more than 30 days after discontinuation of quetiapine treatment .

#The last full day's dose at time of death or withdrawal from the trial.

+Includesdouble-blind plus open-label treatment.

**Quetiapine or chlorpromazine

@ mean daily dose

NA = Not applicable; UNK = Unknown

Table 8.1.1.1a Deaths that were not part of the NDA submission or safety update (From IND safety reports and interim IND safety summary presented in 9/20/96 submission) Note: case report forms or other detailed information were not available for these cases

Trial/center/ subject number	Age (y)	Sex	Dose (mg/day)	Duration	Cause of Death and Comments
0402/015-003 Japan	40	m	Haloperidol		Found dead, possible water intoxication; no autopsy
H-15-13 Japan 0201/013-001	27	f	blinded		suicide by hanging
0015 OLE No subject number listed	69	m	500	2 years	Hospitalized for treatment of deep vein thrombosis; found to have metastatic pancreatic cancer and died one month later (no autopsy)
0048/?/ 0310	77	m	500	295 d	Myocardial Infarction
0048 /0007/0712	64	m	100	205 d	Respiratory failure, aspiration in setting of progressive supranuclear palsy
0048/?/1306	65	f	175	328	Sepsis, esophageal cancer
0048/?/1310	81	f	75	190	Possible cardiopulmonary arrest

TABLE 8.1.1.2 Overall mortality in the integrated Phase II-III clinical program

	Number of subjects	Subject-years exposure*	Number of deaths#	Crude mortality rate	Mortality per 100 subject-years
Quetiapine	2387	865.3	8	0.34	0.92
Haloperidol	320	42.5	1	0.31	2.35
Chlorpromazine	100	9.2	0	0.00	0
Placebo	206	14.6	0	0.00	0

*Subject-years is defined as the sum of all subjects' days on treatment (duration) divided by 365 days.
#Deaths occurring within 30 days after trial treatment ended (excludes one death from Trial 0031, for which treatment assignment remains blinded).

TABLE 8.1.5.3 Adverse events reported for at least 1% of quetiapine-treated subjects and for a higher percentage of quetiapine-treated subjects than subjects who received placebo in short-term, placebo-controlled Phase II-III trials (studies 0004, 0006, 0008, and 0013)
Adapted from sponsor's electronic ISS submission and draft labeling

Body system and COSTART Term	Number of subjects with adverse events (%)		p-value*
	Quetiapine (n = 510)	Placebo (n = 206)	
Whole body			
Headache	99 (19.4)	36 (17.5)	0.5150
Asthenia	18 (3.5)	6 (2.9)	0.7438
Abdominal pain	16 (3.1)	1 (0.5)	0.0236
Back pain	10 (2.0)	1 (0.5)	0.1928
Fever	8 (1.6)	2 (1.0)	0.5350
Chest pain	9 (1.8)	3 (1.5)	0.9053
Cardiovascular system			
Postural hypotension	36 (7.1)	5 (2.4)	0.0648
Tachycardia	36 (7.1)	10 (4.9)	0.3693
Hypertension	9 (1.8)	3 (1.5)	0.5763
Digestive system			
Constipation	44 (8.6)	10 (4.9)	0.0637
Dry mouth	33 (6.5)	6 (2.9)	0.0149
Dyspepsia	32 (6.3)	5 (2.4)	0.0816
Diarrhea	10 (2.0)	4 (1.9)	0.9926
GGT increased	8 (1.6)	1 (0.5)	0.0775
Hemic and lymphatic system			
Leukopenia	8 (1.6)	0	0.0938
Metabolic and nutritional disorders			
SGPT increased	31 (6.1)	3 (1.5)	0.0003
SGOT increased	18 (3.5)	2 (1.0)	0.0065
Weight gain	10 (2.0)	0	0.0471
Musculoskeletal system			
Myalgia	6 (1.2)	1 (0.5)	0.3714
Nervous system			
Somnolence	89 (17.5)	22 (10.7)	0.0005
Dizziness	49 (9.6)	9 (4.4)	0.0178
Anxiety	16 (3.1)	6 (2.9)	0.6636
Respiratory system			
Rhinitis	17 (3.3)	1 (0.5)	0.0680
Skin and appendages			
Rash	22 (4.3)	6 (2.9)	0.4106
Dry skin	6 (1.2)	2 (1.0)	0.7798
Special senses			
Ear pain	6 (1.2)	0	0.1371
Urogenital system			
Urinary tract infection	7 (1.4)	1 (0.5)	0.2799

*p-value from Cochran-Mantel-Haenszel test, adjusting for trial. NC = Not calculated
Events for which the quetiapine incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, hostility, accidental injury, hypotension, nausea, vomiting, agitation, insomnia, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, amblyopia.

TABLE 8.1.5.4

Other Events Observed During the Clinical Trial Evaluation of SEROQUEL: During its clinical trial assessment, multiple doses of SEROQUEL (quetiapine) were administered to 2162 patients in Phase 2 and 3 studies. The conditions and duration of exposure to SEROQUEL varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term and longer-term exposure.[136] In most studies, untoward events were obtained by spontaneous report and recorded by clinical investigators in terminology of their own choosing. Consequently, it is impossible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the listings that follow, spontaneously reported adverse events were classified using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) preferred terms. The frequencies presented, therefore, represent the proportion of the 2162 patients exposed to multiple doses of SEROQUEL who experienced an event of the type cited on at least one occasion while receiving SEROQUEL. All reported events are included except those already listed in the 1% table (appendix table 8.1.5.3), those events for which causality has not been established, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of descending frequency according to the following definitions: frequent adverse events are those reported in at least 1/100 patients; infrequent adverse events are those reported in 1/100 to 1/1000 patients; rare events are those reported in less than 1/1000 patients

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Nervous System: Frequent: insomnia, agitation, nervousness, akathisia, hypertonia, tremor, depression, extrapyramidal syndrome, paraesthesia; *Infrequent:* abnormal dreams, thinking abnormal, vertigo, speech disorder, movement disorder, tardive dyskinesia, amnesia, dyskinesia, psychosis, cogwheel rigidity, confusion, hyperkinesia, dysarthria, hallucinations, hypokinesia, paranoid reaction, convulsion, dystonia, incoordination, libido increased, urinary retention, delusions, myoclonus, schizophrenic reaction, apathy, depersonalization, oculogyric crisis, personality disorder; abnormal gait, ataxia, catatonic reaction, drug dependence, hemiplegia, stupor; *Rare:* akinesia, buccoglossal syndrome, cns neoplasia, delirium, euphoria, grand mal convulsion, libido decreased, manic reaction, neurosis aphasia, choreoathetosis, diplopia, emotional lability, facial paralysis, hypotonia, neuralgia, sleep disorder, subdural hematoma, torticollis, trismus

Body as a Whole: Frequent: pain, infection, accidental injury, flu syndrome, hostility; *Infrequent:* overdose, neck rigidity, neck pain, suicide attempt, cellulitis, malaise, pelvic pain, photosensitivity reaction, chills, intentional injury, abscess, cyst, face edema, sepsis; *Rare:* moniliasis, neuroleptic malignant syndrome, abdomen enlarged, accidental overdose, allergic reaction, cataract, granuloma, halitosis, hernia, injection site reaction, neoplasm.

Digestive System: Frequent: nausea, vomiting; *Infrequent:* increased salivation, anorexia, increased appetite, periodontal abscess, flatulence, rectal disorder, gastroenteritis, gingivitis, tooth disorder, gastritis, dysphagia, gastrointestinal disorder, stomatitis, thirst, rectal hemorrhage, tongue edema, tooth caries; *Rare:* fecal incontinence, glossitis, gum hemorrhage, melena, mouth ulceration, tongue disorder; biliary pain, cholecystitis, colitis, duodenal ulcer hemorrhage, hematemesis, hepatomegaly, intestinal obstruction, pancreatitis, peptic ulcer, ulcerative stomatitis.

Cardiovascular System: Frequent: hypotension, palpitation, syncope; *Infrequent:* vasodilatation, electrocardiogram abnormal, migraine, arrhythmia, cerebral ischemia; *Rare:* AV block first degree, bradycardia, deep vein thrombophlebitis, QT interval prolonged, ST segment elevated, supraventricular extrasystoles, angina pectoris, atrial fibrillation, bundle branch block, congestive heart failure, EKG abnormal, heart arrest, myocardial infarct, pallor, pericarditis, phlebitis, sinus bradycardia, T wave inverted, thrombophlebitis, ventricular extrasystoles

Respiratory System: Frequent: pharyngitis, cough increased, bronchitis; *Infrequent:* dyspnea, epistaxis, sinusitis, asthma, pneumonia; *Rare:* hiccup, hyperventilation, laryngitis, yawn.

Metabolic and Nutritional Disorders: Frequent: peripheral edema; *Infrequent:* weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, hypercholesterolemia; *Rare:* edema, gout, hyperglycemia, hypoglycemia, albuminuria, bilirubinemia, creatine phosphokinase increased, dehydration, healing abnormal, hyperkalemia, hypokalemia, lactic dehydrogenase increased, water intoxication.

Skin and Appendages: Frequent: sweating; *Infrequent:* pruritus, acne, fungal dermatitis, eczema, maculopapular rash, contact dermatitis, seborrhea; *Rare* herpes simplex, herpes zoster, nail disorder, psoriasis, alopecia, cutaneous moniliasis, exfoliative dermatitis, furunculosis, hirsutism, pustular rash, skin discoloration, vesiculobullous rash.

Urogenital System: Infrequent: urinary incontinence, dysmenorrhea, impotence, vaginitis, dysuria, cystitis, metrorrhagia, urinary frequency, abnormal ejaculation, urination impaired; *Rare:* orchitis, polyuria, vaginal moniliasis, acute kidney failure, anorgasmia, anuria, bladder stenosis, breast abscess, breast carcinoma, breast enlargement, breast pain, cervical carcinoma, female lactation, gynecomastia, menstrual disorder, nocturia, pyuria, urine abnormality, vaginal hemorrhage, vulvovaginitis.

Special Senses: Frequent: amblyopia; *Infrequent:* conjunctivitis, cataract specified, otitis media, abnormal vision, dry eyes, blepharitis, otitis externa, taste perversion, tinnitus, eye pain; *Rare* abnormality of accommodation, glaucoma, deafness, eye hemorrhage, hyperacusis, lacrimation.

Musculoskeletal System: Infrequent: pathological fracture, myasthenia, joint disorder, twitching, arthralgia, leg cramps, bone pain, arthritis; *Rare:* arthrosis, osteoporosis, ptosis, tendon disorder, tenosynovitis, tetany.

Hemic and Lymphatic System: Infrequent: leukocytosis, anemia, eosinophilia, ecchymosis, hypochromic anemia; *Rare:* cyanosis, hemolysis, lymphadenopathy, thrombocytopenia, iron deficiency anemia, petechiae, white blood cells abnormal

Endocrine System: Infrequent: hypothyroidism, diabetes mellitus; *Rare:* hyperthyroidism, thyroid disorder, thyroiditis

TABLE 8.1.6.1 Clinical laboratory assessments by trial, Phase II-III trials (adapted from sponsor's electronic iss)

	Phase II-III trial										
	0004	0005	0006	0007	0008	0012	0013	0014	0015	0048	OLE
Hematology											
Hematocrit	X	X	X	X	X		X		X	X	US only
Hemoglobin	X	X	X	X	X	X	X	X	X	X	X
RBC	X	X	X	X	X		X		X	X	US only
Reticulocytes	X	US only									
WBC	X	X	X	X	X	X	X	X	X	X	X
Differential	X	X	X	X	X	X	X	X	X	X	X
Neutrophils	X	X	X	X	X	X	X	X	X	X	X
Bands	X										
Lymphocytes	X	X	X	X	X	X	X	X	X	X	X
Monocytes	X	X	X	X	X	X	X	X	X	X	X
Eosinophils	X	X	X	X	X	X	X	X	X	X	X
Basophils	X	X	X	X	X	X	X	X	X	X	X
Platelets	X	X	X	X	X	X	X	X	X	X	X
Chemistry											
Sodium	X	X	X	X	X				X	X	US only
Potassium	X	X	X	X	X				X	X	US only
Chloride	X	US only	X		US only				X	X	US only
Glucose	X	X	X	X	X				X	X	US only
BUN	X	X	X	X	US only				X	X	US only
Creatinine	X	X	X	X	X				X	X	US only
Phosphorus	X	US only	X		US only						
Calcium	X	US only	X		US only				X	X	US only
Cholesterol	X	US only	X		US only						
Triglycerides	X	US only	X		US only						
ALT (SGPT)	X	X	X	X	X	X	X	X	X	X	X
AST (SGOT)	X	X	X	X	X	X	X	X	X	X	X
GGT	X	X	X	X	X						
Alk phos	X	X	X	X	X	X	X	X	X	X	X
Total bilirubin	X	X	X	X	X	X	X	X	X	X	X
Total protein	X	X	X	X	X						
Albumin	X	X	X	X	X				X	X	US only

TABLE
Clinical laboratory assessments by trial (continued)

	0004	0005	0006	0007	0008	0012	0013	0014	0015	0048	OLE
Chemistry (cont)											
Total T_4	X	X	X	X	X		X		X		
Total T_3	X	X	X	X	X		X		X		
Free T_4						X	X	X	X	X	X
TSH	X	X	X	X	X	X	X	X	X	X	X
TBG							X		X		
Reverse T_3							X		X		
Prolactin		X	X	X	X	X	X	X	X		
Urinalysis											
Specific gravity	X	X	X		US only					X	
pH	X	X	X		US only					X	
RBC	X		X		US only					X	
WBC	X		X		US only					X	
Glucose	X		X		US only					X	
Protein										X	
Albumin	X		X		US only						
Ketones	X		X		US only					X	
Casts	X		X		US only					X	

Table 8.1.6.3.1a Mean change from baseline for hematology values, short term placebo controlled trials (reproduced from sponsor's electronic submission)

	SEROQUEL						PLACEBO					
	NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE		NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE	
		MEAN	SD	MEAN	SD	MEAN	SD		MEAN	SD	MEAN	SD	MEAN	SD
WHITE CELL COUNT (X10**9/L)	479	7.51	2.36	7.50	2.40	-0.21	2.14	195	7.74	2.71	7.86	2.79	0.12	2.68
NEUTROPHIL, SEGS (X10**9/L)	472	4.75	1.91	4.60	1.96	-0.15	1.90	194	4.72	2.22	4.82	2.42	0.11	1.91
NEUTROPHIL, SEGS (%)	472	59.68	9.89	59.24	10.07	-0.24	9.66	192	59.24	10.71	59.48	11.20	0.25	9.56
NEUTROPHIL, BANDS (X10**9/L)	8	0.01	0.04	0.00	0.00	-0.01	0.04	4	0.00	0.00	0.00	0.00	0.00	0.00
NEUTROPHIL, BANDS (%)	8	0.10	0.40	0.00	0.00	-0.10	0.40	4	0.00	0.00	0.00	0.00	0.00	0.00
LYMPHOCYTES (X10**9/L)	472	2.29	0.79	2.25	0.77	-0.05	0.59	194	2.36	0.77	2.42	0.82	0.06	0.64
LYMPHOCYTES (%)	472	30.28	9.65	30.64	9.90	0.27	8.25	192	31.81	9.48	32.12	9.74	0.21	8.25
MONOCYTES (X10**9/L)	472	0.45	0.22	0.44	0.20	-0.01	0.20	194	0.39	0.17	0.38	0.19	-0.01	0.17
MONOCYTES (%)	472	6.06	2.91	6.04	2.68	-0.02	2.59	192	5.41	2.20	5.13	2.27	-0.28	2.04
EOSINOPHILS (X10**9/L)	469	0.24	0.22	0.22	0.20	-0.01	0.14	192	0.20	0.19	0.18	0.15	-0.02	0.15
EOSINOPHILS (%)	468	3.12	2.47	3.14	2.49	0.02	1.95	191	2.76	2.48	2.45	2.27	-0.28	1.91
BASOPHILS (X10**9/L)	467	0.06	0.05	0.06	0.05	0.00	0.06	191	0.06	0.05	0.06	0.05	0.00	0.05
BASOPHILS (%)	466	0.79	0.67	0.85	0.61	0.06	0.58	190	0.82	0.66	0.82	0.62	0.01	0.67
RED CELL COUNT (X10**12/L)	480	4.87	0.47	4.81	0.46	-0.06	0.22	195	4.87	0.42	4.88	0.45	0.00	0.22
HEMOGLOBIN (G/DL)	480	14.65	1.21	14.47	1.25	-0.19	0.91	195	14.75	1.24	14.77	1.28	0.02	0.85
RETICULOCYTE COUNT (X10**9/L)	8	61.42	28.71	62.21	20.03	1.79	24.04	4	42.40	20.21	61.15	15.84	18.75	24.12
HEMATOCRIT (VOL FRACTION)	475	0.44	0.05	0.42	0.05	-0.01	0.04	193	0.45	0.04	0.44	0.04	-0.00	0.04
PLATELET COUNT (X10**9/L)	479	260.45	66.91	264.50	66.78	4.05	47.82	194	262.09	67.38	261.26	62.78	-1.82	42.95

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Table 8.1.6.3.1b Mean Change from Baseline for chemistry values, short term placebo controlled trials (reproduced from sponsor's submission)

	SEROQUEL							PLACEBO						
	NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE		NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE	
		MEAN	SD	MEAN	SD	MEAN	SD		MEAN	SD	MEAN	SD	MEAN	SD
CALCIUM (MMOL/L)	166	2.27	0.10	2.26	0.12	-0.01	0.12	110	2.29	0.10	2.28	0.10	-0.01	0.10
PHOSPHORUS INORGANIC (MMOL/L)	166	1.27	0.12	1.27	0.21	-0.00	0.20	110	1.28	0.10	1.23	0.22	-0.05	0.20
UREA NITROGEN (MMOL/L)	226	4.42	1.71	4.54	1.58	0.12	1.45	145	4.55	1.28	4.50	1.51	-0.06	1.46
CREATININE (UMOL/L)	226	87.94	15.70	86.26	15.04	-1.59	11.28	145	87.53	16.00	85.84	17.36	-1.74	12.64
GGT (U/L)	225	29.98	21.58	22.09	22.00	2.11	17.84	145	21.92	22.17	26.85	20.85	-2.97	12.28
AST/SGOT (U/L)	484	22.26	10.97	26.16	20.17	2.38	19.26	196	22.84	11.46	26.57	20.21	2.72	29.06
ALT/SGPT (U/L)	482	27.83	21.71	35.24	40.58	7.36	28.22	194	30.94	22.45	36.85	38.71	5.91	77.66
PROTEIN, TOTAL SERUM (G/L)	226	70.47	5.02	70.54	5.95	0.06	5.26	146	71.25	5.29	71.27	5.17	0.02	4.81
ALBUMIN (G/L)	222	42.67	2.21	42.42	2.51	-0.24	3.20	144	44.05	2.11	44.16	2.55	0.11	3.22
BILIRUBIN, TOTAL (UMOL/L)	484	8.97	2.47	8.74	2.50	-0.23	2.49	195	9.00	4.16	9.21	4.09	0.21	3.11

ALKALINE PHOSPHATASE (U/L)	481	100.58	44.21	100.29	45.62	-0.51	22.95	195	112.85	62.15	106.96	57.12	-5.39	22.79
GLUCOSE (MMOL/L)	220	5.44	1.24	5.61	1.56	0.18	1.47	142	5.21	1.22	5.22	1.19	0.02	1.21
CHOLESTEROL, TOTAL (MMOL/L)	166	5.02	1.22	5.59	1.22	0.56	0.92	110	5.18	1.05	5.14	1.07	-0.04	0.91
TRIGLYCERIDES (MMOL/L)	166	1.94	1.28	2.27	1.51	0.32	1.12	110	2.12	1.09	1.87	0.99	-0.25	1.05
SODIUM (MMOL/L)	225	140.58	2.07	140.92	2.84	0.04	2.58	145	140.89	2.58	141.17	2.28	0.28	2.15
POTASSIUM (MMOL/L)	226	4.25	0.40	4.21	0.45	-0.04	0.50	146	4.28	0.45	4.27	0.25	-0.11	0.52
CHLORIDE (MMOL/L)	166	101.49	2.18	101.10	2.88	-0.29	2.61	110	101.09	2.16	101.28	2.78	0.29	2.21
TOTAL T4 (THYROXINE) RIA (NMOL/L)	442	106.79	25.96	85.68	24.07	-21.11	27.52	184	105.49	22.20	102.67	25.48	-1.82	21.84
TOTAL T3 (TRIIODOTHYRONINE) (NMOL/L)	422	2.07	0.44	2.00	0.47	-0.07	0.45	178	2.07	0.44	2.11	0.49	0.04	0.29

TSH, HIGHLY SENSITIVE (MIU/L)	441	1.71	2.25	1.99	4.74	0.09	5.12	181	1.61	1.27	1.49	1.27	-0.12	1.24
PROLACTIN RIA (UG/L)	292	21.95	21.12	11.94	12.26	-10.01	28.75	122	24.92	20.92	14.82	17.22	-10.09	25.10
T3 UPTAKE (UPTAKE)	8	0.20	0.05	0.20	0.05	0.00	0.00	4	0.25	0.06	0.25	0.06	0.00	0.00
FREE T-4 (PMOL/L)	212	22.41	7.62	18.05	6.52	-4.26	5.41	44	22.12	4.59	21.26	4.81	-0.86	5.18
THYROXINE-BINDING GLOBULIN (NMOL/L)	212	26444.2	6621.11	26925.9	7418.12	491.72	7099.15	45	27027.9	6220.84	26741.9	6240.95	-286.00	6165.45
REVERSE T3 (NMOL/L)	199	0.22	0.09	0.17	0.09	-0.04	0.11	45	0.22	0.05	0.22	0.10	0.00	0.12

Table 8.1.6.3.1c Mean change from baseline for urinalysis values, short term placebo controlled trials (reproduced from sponsor's submission)

	SEROQUEL							PLACEBO						
	NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE		NUMBER OF PATIENTS*	BASELINE		END OF TREATMENT		CHANGE	
		MEAN	SD	MEAN	SD	MEAN	SD		MEAN	SD	MEAN	SD	MEAN	SD
SPECIFIC GRAVITY	162	1.02	0.01	1.02	0.01	0.00	0.01	109	1.02	0.01	1.02	0.01	0.00	0.01
REACTION PH	162	5.56	0.65	5.52	0.70	-0.03	0.83	109	5.56	0.59	5.48	0.82	-0.07	0.89

TABLE 8.1.6.3.2 Definition of clinically significant clinical laboratory values (adapted from sponsor's electonic ISS)

Hematology parameter	Significant value
Hematocrit	males ≤ 0.37 ≥ 0.50 vol fraction; females ≤ 0.32 ≥ 0.55 vol fraction
Hemoglobin	males ≤ 11.5 g/dl; ≥ 18.5 g/dl; females ≤ 9.5 g/dl; ≥ 16.5 g/dl
RBC	≤ 3 X 10^{12} cell/L ; ≥ 6 x 10^{12} cell/L
Platelet count	≤ 75 X 10^{9} cells/L ≥ 700 x 10^{9} cells/L
WBC	≤ 2.8 X 10^{9} cells/L; ≥ 16.0 x 10^{9}/L
Neutrophils - percent	≤15%
- absolute	≤ 1.5 X 10^{9} cells/L
Eosinophils	≥ 10%
Basophils	> 3%
Lymphocytes	≤10%
Monocytes	> 20%

Chemistry parameter	Significant value
SGPT/ALT	≥ 165 U/L
SGOT/AST	≥ 150 U/L
Alkaline phosphatase	≥ 3 x ULN
GGT	females ≥ 135 U/L; males ≥ 195 U/L
LDH	≥ 1125 U/L
CPK	≥ 3 x ULN
Total bilirubin	≥ 34.2 mol/L (2 mg/dl)
Uric acid	f ≥ 505.58 µmol/L (8.5 mg/dl); m ≥ 624.54 µmol/L (10.5 mg/dl)
Albumin	≤ 25 g/L
Total protein	≤ 50 g/L
Calcium	≤ 1.7465 mmol/L (7 mg/dl); ≥ 2.994 mmol/L (12 mg/dl)
Phosphorus	≤ 0.4833 mmol/L (1.5 mg/dl); ≥ 1.7759 mmol/L (5.5 mg/dl)
Sodium	≤ 129 mmol/L; ≥ 160 mmol/L
Glucose	≤ 2.4979 mmol/L (45 mg/dl); ≥ 13.8775 mmol/L (250 mg/dl)
BUN	≥ 10.68 mmol/L (30 mg/dl)
Creatinine	≥ 176.8 µmol/L (2 mg/dl)
Potassium	< 0.9 x LLN; > 1.1 x ULN
Chloride	< 0.9 x LLN; > 1.1 x ULN
CO	< 0.9 x LLN; > 1.1 x ULN
Triglycerides	< 0.5 x LLN; > 2 x ULN
Cholesterol	< 0.5 x LLN; > 2 x ULN
Total T_4, Total T_3, Free T_4, TSH, Reverse T_3, and TBG	< 0.8 x LLN; > 1.2 x ULN
Prolactin	> 100 ug/L

Urinalysis parameter	Significant value
Specific gravity	≤ 1.001; ≥ 1.035
pH	≤ 4.6; > 8
RBC	males > 1/hpf; females > 5/hpf
WBC	> 5/hpf
Protein	increase of ≥ 2 units
Glucose	increase of ≥ 2 units
Casts	increase of ≥ 2 units
Ketones	≥ 2+
Bilirubin	≥ 2+
Nitrite	≥ 2+
Leukocyte esterase	≥ 2+

Table 8.1.6.3.2a Hematology: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS low value		CS high value	
	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	n	Number (%) with CS high values	p-value*	Odds ratio	p-value*	Odds ratio
Hematocrit	469	16 (3.4)	361	56 (15.5)	192	1 (0.5)	161	22 (13.7)	0.0576	5.056	0.3429	0.756
Hemoglobin	478	1 (0.2)	480	1 (0.2)	194	0 (0.0)	194	1 (0.5)	0.6547	NC	0.8229	0.689
Red cell count	480	0 (0.0)	474	6 (1.3)	195	0 (0.0)	194	3 (1.5)	NC	NC	0.9270	0.925
Platelet count	478	1 (0.2)	479	0 (0.0)	194	0 (0.0)	194	0 (0.0)	0.6554	NC	NC	NC
White cell count	479	3 (0.6)	478	8 (1.7)	195	0 (0.0)	191	5 (2.6)	0.1989	NC	0.4659	0.611
Neutrophils - percent	472	2 (0.4)	NA	NA	193	0 (0.0)	NA	NA	0.2158	NC	NA	NA
Neutrophils - absolute	470	12 (2.6)	NA	NA	191	2 (1.0)	NA	NA	0.2415	2.480	NA	NA
Eosinophils	NA	NA	458	14 (3.1)	NA	NA	185	5 (2.7)	NA	NA	0.8566	0.896
Basophils	NA	NA	464	4 (0.9)	NA	NA	188	2 (1.1)	NA	NA	0.9808	1.022
Lymphocytes	469	9 (1.9)	NA	NA	192	1 (0.5)	NA	NA	0.2041	4.537	NA	NA
Monocytes	NA	NA	471	1 (0.2)	NA	NA	193	0 (0.0)	NA	NA	0.4679	NC

CS Clinically significant
NA Not applicable
NC Not calculated
*CMH test

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Table 8.1.6.3.2b Chemistry: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS low value		CS high value	
	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	n	Number (%) with CS high values	p-value*	Odds ratio	p-value*	Odds ratio
SGPT/ALT	NA	NA	483	29 (6.0)	NA	NA	194	3 (1.5)	NA	NA	0.0051	5.533
SGOT/AST	NA	NA	484	6 (1.2)	NA	NA	196	1 (0.5)	NA	NA	0.4467	2.290
Alkaline phosphatase	NA	NA	482	1 (0.2)	NA	NA	195	0 (0.0)	NA	NA	0.6534	NC
GGT	NA	NA	234	3 (1.3)	NA	NA	145	0 (0.0)	NA	NA	0.2150	NC
Total bilirubin	NA	NA	484	0 (0.0)	NA	NA	195	0 (0.0)	NA	NA	NC	NC
Uric acid												
Albumin	232	0 (0.0)	NA	NA	144	0 (0.0)	NA	NA	NC	NC	NA	NA
Total protein	236	0 (0.0)	NA	NA	146	1 (0.7)	NA	NA	0.1573	0.000	NA	NA
Calcium	166	0 (0.0)	166	0 (0.0)	110	0 (0.0)	110	0 (0.0)	NC	NC	NC	NC
Phosphorus	166	0 (0.0)	163	6 (3.7)	110	0 (0.0)	110	2 (1.8)	NC	NC	0.4975	1.806
Sodium	234	2 (0.9)	235	0 (0.0)	145	0 (0.0)	145	0 (0.0)	0.2211	NC	NC	NC
Glucose	230	5 (2.2)	230	3 (1.3)	143	2 (1.4)	143	0 (0.0)	0.4202	1.920	0.2174	NC
Urea	NA	NA	232	1 (0.4)	NA	NA	145	1 (0.7)	NA	NA	0.8214	0.686
Creatinine	NA	NA	236	0 (0.0)	NA	NA	145	1 (0.7)	NA	NA	0.3220	0.000
Potassium	236	0 (0.0)	236	6 (2.5)	146	0 (0.0)	145	0 (0.0)	NC	NC	0.0458	NC
Chloride	166	0 (0.0)	166	0 (0.0)	110	0 (0.0)	110	0 (0.0)	NC	NC	NC	NC
CO_2												
Triglycerides	166	0 (0.0)	152	40 (26.3)	110	0 (0.0)	98	8 (8.2)	NC	NC	0.0002	4.323
Cholesterol	166	0 (0.0)	165	0 (0.0)	110	0 (0.0)	110	0 (0.0)	NC	NC	NC	NC
Total T_4	441	20 (4.5)	440	2 (0.5)	183	1 (0.5)	183	2 (1.1)	0.0093	8.791	0.3428	0.433
Total T_3	429	7 (1.6)	429	4 (0.9)	177	1 (0.6)	177	3 (1.7)	0.2968	3.010	0.5781	0.685
TSH	427	24 (5.6)	434	4 (0.9)	174	10 (5.7)	177	1 (0.6)	0.8741	1.063	0.6373	1.712
Free T_4	209	14 (6.7)	209	0 (0.0)	44	0 (0.0)	44	0 (0.0)	0.0779	NC	NC	NC
TBG	209	4 (1.9)	211	3 (1.4)	45	2 (4.4)	45	0 (0.0)	0.3116	0.420	0.4220	NC
Reverse T_3	199	0 (0.0)	185	3 (1.6)	45	0 (0.0)	42	5 (11.9)	NC	NC	0.0011	0.122
Prolactin	NA	NA	286	0 (0.0)	NA	NA	118	0 (0.0)	NA	NA	NC	NC

CS Clinically significant
NC Not calculated
NA Not applicable

*CMH test

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Table 8.1.6.3.2c Urinalysis: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS low value		CS high value	
	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	n	Number (%) with CS high values	p-value*	Odds ratio	p-value*	Odds ratio
Specific gravity	162	1 (0.6)	161	6 (3.7)	109	0 (0.0)	108	3 (2.8)	0.3126	NC	0.6215	1.445
Reaction pH	162	0 (0.0)	162	1 (0.6)	109	1 (0.9)	109	1 (0.9)	0.3220	0.000	0.6000	0.429

CS Clinically significant
NC Not calculated
*CMH test

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Table 8.1.7.1 Vital signs and weight assessments by trial (integrated Phase II-III trials) Reproduced from sponsor's electronic ISS

	Phase II-III trials										
	0004	0005	0006	0007	0008	0012	0013	0014	0015	0048	OLE
Pulse	X	X	X	X	X	X	X	X	X	X	X
Blood pressure[a]	X	X	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X		X						
Temperature	X	X	X	X	X		X		X	X	US only
Weight	X	X	X	X	X	X	X	X	X	X	X

[*] All measures were taken while subjects were seated.
[a] Unless otherwise noted, readings were taken for both supine and standing systolic and diastolic blood pressures.
[*] Only supine readings were taken for Trials 0002, 0007, 0025, and 0026.
[**] Respiration readings were taken while subjects were in the supine position unless otherwise noted.

Table 8.1.7.3.2 Definitions of clinically significant vital signs and weight (reproduced from sponsor's electronic ISS)

Vital sign	Criterion value	Change from baseline
Systolic blood pressure	≥ 180 mmHg	increase ≥ 20 mmHg
	≤ 90 mmHg	decrease ≥ 20 mmHg
Diastolic blood pressure	≥ 105 mmHg	increase ≥ 30 mmHg
	≤ 50 mmHg	decrease ≥ 20 mmHg
Pulse	120 bpm	increase ≥ 15 bpm
	50 bpm	decrease ≥ 15 bpm
Temperature	≥ 38.3°C	change ≥ 1.11°C
Weight	—	change ≥ 7% body weight
Orthostatic changes		
Systolic blood pressure	decrease ≥ 30 mmHg from supine to standing	
Diastolic blood pressure	increase ≥ 30 mmHg from supine to standing	
Pulse	increase ≥ 20 bpm from supine to standing	
Combined	decrease ≥ 30 mmHg in systolic blood pressure from supine to standing and increase ≥ 20 bpm in pulse from supine to standing	

Table 8.1.7.3.1 Mean and mean change values for vital signs variables at baseline and end of treatment with quetiapine or placebo in the Phase II-III short-term, placebo-controlled trials (adapted from sponsor's electronic ISS)

Variable	Quetiapine				Placebo			
	Number of subjects*	Base-line mean (±SD)	End-of- treat-ment mean (±SD)	Change mean (±SD)	Number of subjects*	Base-line mean (±SD)	End-of - treatment mean (±SD)	Change mean (±SD)
Systolic BP								
Supine (mmHg)	474	119 (16)	119 (15)	-0.2 (16)	186	121 (15)	119 (14)	-2.1 (14.5)
Standing (mmHg)	466	117 (16)	117 (15)	-0.1 (16.5)	180	118 (15)	117 (15)	-1.1 (14.9)
Diastolic BP								
Supine (mmHg)	474	75 (11)	76 (11)	0.8 (11.4)	186	78 (12)	76 (11)	-1.8 (13.6)
Standing (mmHg)	466	78 (11)	78 (11)	0.3 (12.1)	180	79 (11)	78 (11)	-0.8 (12.9)
Pulse								
Supine (bpm)	466	81 (12)	84 (12)	3.3 (14.5)	183	79 (12)	80 (13)	0.8 (14.9)
Standing (bpm)	447	88 (14)	92 (15)	3.9 (16.8)	179	87 (13)	88 (15)	1.6 (15.2)
Temperature (C)	450	36.5 (0.4)	36.5 (0.5)	-0.0 (0.6)	179	36.5 (0.5)	36.5 (0.5)	0.0 (0.6)
Weight (kg)	391	78 (16)	80 (17)	2.3 (3.9)	178	78 (16)	78 (16)	0.1 (3.1)
Postural changes								
Systolic BP (mmHg)	448	-1.9 (11.7)	-1.9 (10.4)	-0.1 (13.9)	176	-2.4 (11)	-1.7 (9)	0.7 (12.6)
Diastolic BP (mmHg)	448	2.3 (8.8)	1.9 (8.6)	-0.4 (11.2)	176	1.8 (10)	2.4 (9)	0.6 (13.2)
Pulse (bpm)	430	7.5 (11.2)	8.1 (11.1)	0.6 (14.1)	174	7.5 (11)	8.4 (12)	0.9 (13.8)

*Number of subjects is based on number of subjects with both baseline and end-of-treatment assessments.
*This table presents supine-to-standing values; the T Tables present standing-to-supine values; therefore the positive and negative signs will be opposite to that presented in the intext tables.
SD = Standard deviation
BP = Blood pressure

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Table 8.1.7.3.2b Vital signs: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS high value		CS low value	
	n	Number (%) with CS high values	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	p-value*	Odds ratio	p-value*	Odds ratio
Supine systolic blood pressure	495	4 (0.8)	487	77 (15.8)	202	1 (0.5)	198	26 (13.1)	0.7300	1.507	0.1671	1.403
Supine diastolic blood pressure	492	16 (3.3)	490	50 (10.2)	197	8 (4.1)	201	14 (7.0)	0.5451	0.746	0.1588	1.551
Standing systolic blood pressure	489	4 (0.8)	470	96 (20.4)	197	2 (1.0)	190	30 (15.8)	0.8916	1.121	0.1351	1.421
Standing diastolic blood pressure	488	37 (7.6)	486	44 (9.1)	193	12 (6.2)	197	13 (6.6)	0.5625	1.232	0.2631	1.439
Supine pulse rate	489	28 (5.7)	491	4 (0.8)	201	5 (2.5)	201	2 (1.0)	0.1042	2.295	0.5450	1.641
Standing pulse rate	472	101 (21.4)	482	4 (0.8)	195	23 (11.8)	196	1 (0.5)	0.0036	2.116	0.2352	2.952
Temperature	482	4 (0.8)	NA	NA	200	1 (0.5)	NA	NA	0.7151	1.542	NA	NA
Weight	391	89 (22.8)	391	11 (2.8)	178	11 (6.2)	178	9 (5.1)	0.0000	4.301	0.0855	0.457

	n	Number (%) with CS values	n	Number (%) with CS values	p-value*	Odds ratio
Orthostatic pulse	415	256 (61.7)	165	93 (56.4)	0.2335	1.262
Orthostatic diastolic blood pressure	484	16 (3.3)	195	8 (4.1)	0.9160	0.951
Orthostatic systolic blood pressure	482	34 (7.1)	194	13 (6.7)	0.7091	1.134
Orthostatic pulse/systolic blood pressure	473	15 (3.2)	194	5 (2.6)	0.5325	1.369

CS Clinically significant *CMH test
NA Not applicable

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ON ORIGINAL

Table 8.1.8.1 Electrocardiogram assessments by trial (integrated Phase I and Phase II-III trials) (adapted from sopnsor's electronic ISS)

	Phase I trials																
	0002	0007	0008	0016	0017	0018	0019	0020	0024	0025	0026	0027	0029	0035	0045	0046	0047
Heart rate					X			X	X	X	X	X		X	X	X	X
PR					X			X	X		X	X		X	X	X	X
QRS					X			X	X	X	X	X		X	X	X	X
QT					X			X	X	X	X	X		X	X	X	X
QT_c					X			X	X	X	X	X		X	X	X	X
PQ										X							

	Phase II-III trials										
	0004	0005	0006	0007	0008	0012	0013	0014	0015	0048	OLE
Heart rate	X	X	X	X	X		X		X	X	US only
PR	X	X	X	X	X		X		X	X	US only
QRS	X	X	X	X	X		X		X	X	US only
QT	X	X	X	X	X		X		X	X	US only
QT_c	X	X	X	X	X		X		X	X	US only

Table 8.1.8.3.2a Zeneca-defined electrocardiogram (ECG) abnormalities considered clinically significant (adapted from sponsor's electronic submission)

Heart rate	> 120 bpm and an increase of ≥ 15 bpm from the baseline value < 50 bpm and a decrease of ≥ 15 bpm from the baseline value
PR	≥ 0.210 sec
QRS	≥ 0.150 sec ≤ 0.050 sec
QT	≥ 0.500 sec ≤ 0.200 sec
QT_c	50 sec ≥ 0.4

TABLE 8.1.8.3.1 Mean and mean change values for electrocardiogram variables at baseline and end of treatment with quetiapine and placebo in the short-term (≤ 6 weeks), placebo-controlled Phase II-III clinical trials (adapted from sponsor's electronic ISS)

Variable	Quetiapine				Placebo			
	Number of subjects*	Baseline mean (±SD)	End of treatment mean (±SD)	Change mean (±SD)	Number of subjects*	Baseline mean (±SD)	End of treatment mean (±SD)	Change mean (±SD)
Ventricular rate (bpm)	405	79 (14)	86 (14)	7 (15)	158	79 (15)	81 (16)	1 (16)
PR interval (sec)	405	0.15 (0.02)	0.15 (0.03)	–0.00 (0.03)	160	0.15 (0.02)	0.15 (0.02)	–0.00 (0.02)
QRS interval (sec)	405	0.09 (0.01)	0.09 (0.01)	–0.00 (0.01)	160	0.08 (0.01)	0.08 (0.01)	–0.00 (0.01)
QT interval (sec)	395	0.36 (0.04)	0.35 (0.03)	–0.01 (0.03)	155	0.36 (0.04)	0.36 (0.04)	–0.01 (0.04)
QT_c interval (sec)	393	0.41 (0.03)	0.41 (0.03)	0.00 (0.03)	153	0.41 (0.04)	0.41 (0.03)	–0.00 (0.04)

*Based on number of subjects with both baseline and end-of-treatment assessments.

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Table 8.1.8.3.2b ECG: proportion of patients meeting clinically significant criteria, short term placebo controlled trials

Variable	Quetiapine				Placebo				CS high value		CS low value	
	n	Number (%) with CShigh values	n	Number (%) with CS low values	n	Number (%) with CS high values	n	Number (%) with CS low values	p-value*	Odds ratio	p-value*	Odds ratio
Heart rate												
Atrial	403	4 (1.0)	401	1 (0.2)	159	1 (0.6)	157	0 (0.0)	0.6411	1.542	0.4980	NC
Ventricular	403	4 (1.0)	401	1 (0.2)	157	1 (0.6)	155	0 (0.0)	0.6513	1.524	0.5026	NC
PR	402	1 (0.2)	406	0 (0.0)	160	1 (0.6)	160	0 (0.0)	0.3802	0.234	NC	NC
QRS	405	0 (0.0)	403	3 (0.7)	160	0 (0.0)	159	2 (1.3)	NC	NC	0.5808	0.592
QT	395	0 (0.0)	393	1 (0.3)	154	0 (0.0)	154	0 (0.0)	NC	NC	0.4924	NC
QT_c	377	18 (4.8)	393	0 (0.0)	144	5 (3.5)	153	0 (0.0)	0.4817	1.473	NC	NC

CS Clinically significant *CMH test
NC Not calculated

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ON ORIGINAL

February 5, 1997

Report: Neutropenic Episodes Associated With the Use of Seroquel™ (Quetiapine) in Clinical Trials by Stanton L Gerson, MD, Professor of Medicine, Division of Hematology/Oncology, BRB 3-West, 10900 Euclid Avenue, Cleveland, OH 44106-4937.

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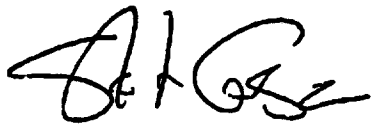

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Summary

Quetiapine has been administered to 2,387 patients who have accumulated over 865 patient years of exposure. A total of 88 neutropenic and 43 leukopenic episodes have been recorded, including episodes of severe neutropenia. A number of these episodes were reported as adverse events requiring cessation of therapy by the physician. Review of these episodes indicates that most are transient, some oscillating in nature but none progressive and none leading to a severe episode of agranulocytosis. There is no clear pattern in onset or duration and in most instances, patients were continued on quetiapine without symptoms related to neutropenic or leukopenic events. Thus, it appears that although neutropenia is observed in patients receiving quetiapine, it can be safely administered without an expectation of progression of the neutropenia to more severe neutropenia or to episodes of agranulocytosis. Nonetheless, given the relatively small patient base of exposures, a rare episode of agranulocytosis could possible occur in a much larger exposed population.

Database

Zeneca Pharmaceuticals asked for my review of the cumulative episodes of reported and recorded neutropenia and leukopenia. I reviewed this data first in the integrated summary of safety hematology values for the phase II and III clinical trials program, including the controlled and uncontrolled, short-term placebo controlled, short-term comparitor controlled trials and the long-term controlled clinical trials. This data was originally provided in June of 1996 with an update in November of 1996 consisting of the 4 month safety update of the previous trials. I also had the opportunity to review other significant adverse hematology values, such as leukocytosis thrombocytopenia and eisinophenia. Given the nature of the case identification, adverse event reportings and clinically significant values were identified. Comprehensive patient summaries were not provided and I did not have access to concurrent drug lists or intercurrent illnesses in the patient base.

Case Definitions

Standard definitions were used:

Leukopenia	(<	3.0 X 10^9 cells per L
Neutropenia		
Agranulocytosis	(<	0.5 (X 10^9 cells per L) with symptoms)
Severe Neutropenia	(<	0.5 (X 10^9 cells per L) without symptoms)
Moderate Neutropenia	(≥	0.5 and < 1.0 (X 10^9 cells per L))
Mild Neutropenia	(≥	1.0 and < 1.5 (X 10^9 cells per L))

These values reflect convention for reporting clinically significant values of neutropenia.

It appears that the laboratory reporting included the WBC and neutrophil, segs (for segmented neutrophils) for each individual patient. In most, if not all instances, the data was recorded and reported as absolute values and not as percent neutrophils. This reduces the probability of erroneous reports, although there are apparently some episodes suggesting irregularity by the reporting laboratory.

APPENDIX A

Listings of abnormal ANC and WBC values A1 to A

Number of patients with abnormal WBC and ANC values

	Quetiapine (n=2387)		Placebo (n=206)		Active control (n=420)	
	transient n (%)	Persistent N (%)	transient n (%)	Persistent N (%)	transient n (%)	Persistent N (%)
Neutropenia						
agranulocytosis (<0.5 with symptoms)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
severe neutropenia (<0.5 without symptoms)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
moderate neutropenia (≥0.5 and <1.0)	15 (0.6)	4 (0.2)*	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
mild neutropenia (≥1.0 and <1.5)	59 (2.5)	6 (0.3)	2 (1.0)	1 (0.5)	6 (1.4)	0 (0.0)
Leukopenia						
severe leukopenia (<3.0 x 10^9 cells/L)	37 (1.6)	5 (0.2)#	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)

Units for neutrophil and leukocyte counts are x 10^9 cells/L

*These 4 patients had persistent mild neutropenia with an occasional data point falling into the moderate neutropenic range.

#Three of the 5 patients had treatment values that were similar to baseline values.

Case Distribution
Patients in Quetiapine Clinical Trials with Neutropenia or Leukopenia

APPENDIX A

1 Quetiapine

1.1 Agranulocytosis ..... A

None

1.2 Severe neutropenia. ..... A

1.2.1 Transient severe neutropenia

Patient 0006/0008/0814
Patient 0005/0017/0002
Patient 0012/0011/1106
Patient 0012/0045/4508 ..... A

1.2.2 Persistent severe neutropenia

None ..... A

1.3 Moderate neutropenia ..... A

1.3.1 Transient moderate neutropenia

Patient 0008/0044/1701
Patient 0007/0017/0002
Patient 0007/0017/0003
Patient 0015/0018/1815
Patient 0005/0017/0001
Patient 0005/0018/0001
Patient 0048/0002/0210
Patient 0012/0089/8943
Patient 0012/0035/3504
Patient 0012/0039/3901
Patient 0012/0047/4712
Patient 0014/0044/4405
Patient 0014/0067/6707
Patient 0015/0005/0502
Patient 0015/0005/0507 ..... A

1.3.2 Transient moderate neutropenia with persistent mild neutropenia

Patient 0048/0015/1504
Patient 0014/0001/0141
Patient 0013/0004/0402
Patient 0015/0027/2706 ..... A

1.3.3 Persistent moderate neutropenia

None

1.4 **Persistent mild neutropenia** ..... A

Patient 0007/0004/0006
Patient 0007/0030/0005
Patient 0012/0005/0508
Patient 0013/0007/0711
Patient 0014/0001/0103
Patient 0015/0034/3408 ..... A

1.5 **Severe leukopenia...** ..... A

1.5.1 **Transient severe leukopenia**

None

1.5.2 **Transient severe leukopenia with persistent mild to miderate leukopenia**

Patient 0012/0036/3609
Patient 0015/0034/3409 ..... A

1.5.3 **Persistent severe leukopenia**

Patient 0007/0030/0005
Patient 0012/0005/0508
Patient 0012/0042/4203
Patient 0013/0004/0402
Patient 0014/0045/4508 ..... A

2. **Placebo** ..... A

2.1 **Agranulocytosis** ..... A

None

2.2 **Severe neutropenia.** ..... A

2.2.1 **Transient severe neutropenia**

None

2.2.2 **Persistent severe neutropenia**

None

2.3 **Moderate neutropenia** ..... A

2.3.1 **Transient moderate neutropenia**

None

NUMBER OF PATIENTS WITH ABNORMAL WBC AND ANC VALUES
While on Quetiapine
SEVERE NEUTROPENIA
TRANSIENT SEVERE NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0006/0008/0814	2.8	0.28	2	Disproportionately low single value of ANC. Followup preceding and followup values at 7 and 28 days were normal. No neutropenic symptoms. Not clinically significant.
0005/0017/0002	6.4/7.6	0.51/0.48	3/4	Laboratory evidence of severe neutropenia on 2 occasions with no mention of symptoms. Disproportion between the WBC and ANC suggests abnormality in ANC measurement and the real possibility of laboratory error. There are no followup values. It is very unusual to have no change in the WBC with sudden onset of drug associated neutropenia. Doubt an association with drug use.
0012/0045/4508	3.1	0.43	6	Single low value with preceding and post values of WBC and ANC normal. Downward trend in WBC pre and post nadir are noted, but are within the range of subsequent values. Patient had 2 infections remote to the time of the reported neutropenia, unassociated with the neutropenic episode. This is possibly associated with drug use, but may well have been some other intercurrent process. Non progressive, asymptomatic single reported abnormal value.
0012/0011/1106	2.4	0.27	3	Single low value with normal values the week before and the week after in both WBC and ANC could represent significant severe neutropenia. No evidence of symptoms. Nonprogressive and resolved spontaneously. Could be intercurrent illness, concomitant drug use or laboratory error.

MODERATE NEUTROPENIA
TRANSIENT MODERATE NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0008/0044/1701	5.4	0.76	2	Surprising drop in ANC without significant change in WBC associated with numerous unrelated complaints. Nonprogressive, asymptomatic.
0007/0017/0002	3.4, 3.3, 4.1	1.0, 0.79, 1.44	1,2,5	Repeated mild to moderate neutropenia. Nonprogressive. No apparent symptoms. Moderately low WBC to start with proportionate ANC/WBC percentages. This is probably drug related case of neutropenia which resolved while on treatment.
0007/0017/0003	3.4, 2.5	1.09, 0.95	1, 2	Patient discontinued for leukopenia 4 days later. Had a WBC of 4.0 an ANC of 3.1. Possibly drug related since it resolved quickly off drug. Clinically asymptomatic.
0015/0018/1815	3.3/3.7	0.92/1.10	2	Repeated value showing low ANC 2 days after first value shown suggesting represents probable drug related neutropenia resolving spontaneously without symptoms.
0005/0017/0001	5.7, 6.4	0.58, 0.73	0, 1	Asymptomatic moderate neutropenia continued on treatment for 4 weeks subsequent WBCs all normal, no differentials after week 2. Not drug related and atypical because of the disproportionately low ANC/WBC ratio.
0005/0018/0001	2.8/3.0	0.9/1.3	4/5	Final value on study. WBC 3.1 ANC 1.9 appears to represent mild to moderate neutropenia resulting spontaneously, not associated with symptoms. May be drug related.
0048/0002/0210	5.5	0.88	24	Single value at apparent end of study in an elderly individual who had normal WBC and ANC throughout the first 20 weeks of treatment. In the absence of a change in WBC, the low ANC may represent artifact. This episode is not associated with symptoms and in this age group suggests perhaps an intercurrent illness or concomitant medication. Of doubtful clinical significance.

MODERATE NEUTROPENIA
TRANSIENT MODERATE NEUTROPENIA (CONT.)

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0012/0089/8943	2.9/3.4	1.02/1.98	20/24	A 23 y/o male on study for 55 weeks two episodes of leukopenia and neutropenia. No apparent symptoms, non progressive and maintained on drug with recovery period, possible drug related process.
0012/0035/3504	9.5	0.66	13	Repeat value the next day: WBC 6.4, ANC 4.35; laboratory artifact.
0012/0039/3901	2.5	0.91	1	A 24 y/o male on study 4 weeks. Subsequent week, values normal. Nonprogressive, no associated symptoms, unlikely clinical significance, possible drug related.
0012/0047/4712	3.2, 3.1, 3.3	1.2, 1.27, 0.94	1, 16, 17	Oscillating neutropenia with moderately low WBC and ANC. Nonprogressive process with recurrent episodes of mild to moderate neutropenia occurring at the beginning and end of study. Possible drug related.
0014/0044/4405	2.7	0.75	8	Single episode week 7, week 10 values normal. Most likely intercurrent event or concomitant drug lab abnormality is also possible. No evidence of progression. Clinically insignificant, possible drug related.
0014/0067/6707	4.2	0.67	2	Mild drop in WBC at occurrence of ANC nadir. Transient nonprogressive, possible drug related. Note: suicide attempt by overdose of valium plus quetiapine without evidence of neutropenia.
0015/0005/0502	2.5	0.60	61	Leukopenia observed one month later with a WBC of 3.0 and an ANC of 2.01. Since two low values were observed in this 64 y/o female, this is probably drug related. Of note is the diagnosis of breast cancer on the 44th week of treatment and a variety of other intercurrent illnesses which could account for the neutropenic event. The question is raised whether this woman was on systemic therapy for breast carcinoma, such as adjuvant chemotherapy or had received radiation therapy as a result of her initial diagnosis. Given these facts, it is unlikely to be quetiapine related.

MODERATE NEUTROPENIA
TRANSIENT MODERATE NEUTROPENIA (CONT.)

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0015/0005/0507	3.4, 3.1, 2.0	1.29, 1.1, 0.94	8, 22, 27	34/35 y/o male with no clear symptoms associated with episodic neutropenia and associated with leukopenia. Most WBC counts are less than 5,000, suggesting a chronic leukopenic process not likely to be drug related. Nonprogressive, asymptomatic.

MODERATE NEUTROPENIA
TRANSIENT MODERATE NEUTROPENIA WITH PERSISTENT MILD NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0048/0015/1504	3.5-2.7	1.0, 0.82, 1.13	-5-40	Chronic persistent leukopenia and neutropenia in a 78 y/o woman appears to have preceded the onset of quetiapine therapy. Not drug related.
0014/0001/0141	2.6-4.5	0.86-1.17	2-18	A 30 y/o male with chronic persistent leukopenia and neutropenia while on therapy. Had numerous repeat values verifying the presence of neutropenia. Since this patient did not have followup it is difficult to determine whether this is drug related but with the information obtained since the baseline WBC (5.5) or, ANC (2.48) for normal. This is likely drug related. Note, however, drug dependency, use of cannabis and alcohol. Suggesting alcohol as a comorbid condition and perhaps etiology of the persistent neutropenia and leukopenia.
0013/0004/0402		1.35, 0.84 (nadir), 1.13	7-115	A 39 y/o man with recurrent gastritis, gastroenteritis, periodontal abscess, E or I skin ulcers. Treated successfully for 113 weeks without progressive neutropenia. It may well be that other intercurrent illnesses in this individual were responsible for the low ANC and WBC. However, drug effect needs to be considered since the WBC and ANC were in the normal range for the first 6 weeks of treatment. There is no followup to define whether the WBC normalizes with this continuation of quetiapine.
0015/0027/2706	4.0, 3.5-4.0	1.27, 1.31, 1.25, 0.72, 1.50	2, 12-24	A 30 y/o male with a normal WBC/ANC at baseline with repeated mild neutropenic values in one neutropenic episode at week 20, which resolved on week 24. However, all WBC/ANC values are at the low end of the normal range, suggesting preexisting cause for mild leukopenia/neutropenia. Only one transient episode at week 20 and note the accidental inhalation of javex on week 21, suggests the possibility of other concurrent medications or drug abuse as the cause of this transient episode. Not likely drug related.

MODERATE NEUTROPENIA
PERSISTENT MILD NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0007/0004/0006	3.5-0.9	1.35-1.31	0-4	Leukopenia at baseline. No associated symptoms, nonprogressive. Unlikely to be drug related since present at baseline.
0007/0030/0005	2.9-3.0	1.18-1.26	1-3	34 y/o female, no baseline value. Nonprogressive asymptomatic. Possible drug related, although no baseline value available. No followup available either. For posttreatment normalization. Nondrug relationship.
0012/0005/0508	2.7-2.9	1.23-1.20	9-30	25 y/o female. Oscillating mild neutropenia with some normal values. All values including at baseline (WBC 3.5) are below a WBC of 5.0. Nonprogressive oscillating neutropenia taken off study on week 3 for ANC of 1.07 on repeat value 2.9 with a WBC with an ANC of 1.2. Possibly drug related, but given baseline low values, this could be a chronic neutropenia due to another cause.
0013/0007/0711	3.6-3.2	1.5-1.15	2-9	43 y/o male. Persistent mild neutropenia, nonprogressive. No other cause of neutropenia, likely drug related.
0014/0001/0103	3.7-5.1	1.34-1.10 (nadir), 1.73	1-22	30 y/o male. Nonprogressive mild neutropenia. Baseline values 4.9 WBC, 2.63 ANC. Numerous other medical complaints. Nonprogressive mild neutropenia. Of note, week 18 is the only time with repeated values, WBC 3.8, 4.3; ANC 1.0, 2.02. Mild neutropenia no clinical symptoms, nonprogressive. Possible drug related.
0015/0034/3408	4.5-2.8 (week 75)-3.1	1.5-1.19 (nadir)-1.35	-1-85	Chronic persistent neutropenia preceding drug onset not associated with symptoms or progression. Unlikely to be related to drug as it appears to be preexisting.

SUMMARY OF NEUTROPENIC CASES

Of the total of88 neutropenic episodes, none are progressive, none were associated with symptoms and none led to neutropenic febrile episodes. There is no pattern in onset, which ranged from week 1 to 61. Given the number of patients exposed, however, most episodes occurred in less than 6 weeks, strongly biased by the duration at exposure. Many episodes are probably not drug related, and only a few (6 cases, underlined) appear to be associated with drug use in a clear fashion and only some of these appear to be persistent. Furthermore, there is no evidence that therapy exacerbates baseline neutropenia. Thus the conclusion can be drawn that quetiapine has a low incidence of nonprogressive transient neutropenia, infrequent episodes of persistent neutropenia and no episodes of progressive neutropenia leading to agranulocytosis.

SEVERE LEUKOPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0012/0036/3609	2.8	1.86	12	Transient episode of severe leukopenia with persistent mild to moderate leukopenia. This is nonprogressive. Had associated lymphopenia. Not clinically significant.
0015/0034/3409	2.9	1.6	72	Chronic persistent mild leukopenia, nonprogressive in a patient on drug for 78 weeks. Clinically asymptomatic. Possibly related.
0007/0030/0005	2.9-3.0	1.18-1.26	1-3	No baseline values. Severe leukopenia with mild neutropenia. Nonprogressive. Unlikely to be drug associated in a 34 y/o female and no followup. Not clinically significant.
0012/0005/0508		1.23, 1.07	9, 30	Chronic persistent mild to moderate leukopenia with episodes of severe leukopenia and 3 episodes of mild neutropenia. Nonprogressive. Note that this occurred in a 24 y/o woman with a baseline WBC 3.5, ANC 1.77 probably unrelated to drug exposure on a background of chronic mild leukopenia.
0012/0042/4203	2.9	1.33	14	34 y/o female on drug for 14 weeks who reported adverse events of leukopenia and neutropenia at week 14, based on a single value. Followup 6 days later at an ANC of 2.58 and WBC of 3.5. This is possibly drug related, occurring late and nonprogressive and rapidly reversible. No other etiology to the leukopenia and neutropenia.
0013/0004/0402	2.9	1.1-1.7	85, 91, 95	39 y/o male on drug for 115 weeks with chronic intermittent recurrent leukopenia and neutropenia. Patient reported to have multiple bacterial infections, LFT abnormalities suggesting a variety of intercurrent illnesses to explain the mild to moderate leukopenia.
0014/0045/4508	2.5	1.10	7	Patient developed chronic leukopenia and neutropenia while on quetiapine. Repeat values during week 7 showed an episode of moderate to severe leukopenia. Adverse event was reported and the patient was taken off study. There was no evidence of progression. the WBC recovered to 5.1, 14 days off drug, suggesting that this may well have been a drug related episode of lymphopenia and mild neutropenia.

This group of individuals represents patients with severe leukopenia, some of which is persistent and associated with mild to moderate neutropenia. Some of these events appear to be drug related (3 cases) because there is no other obvious etiology. Etiology of leukopenia without neutropenia can be obscure but is rarely clinically significant in the absence of severe lymphopenia with immunodeficiency as with HIV infection. Otherwise, isolated leukopenia is usually not clinically significant.

Adverse events reports of neutropenia and leukopenia.
The following cases were also adverse reports:

0007/0017/0003
0007/0017/0002
0012/0039/3901
0015/0005/0507
0015/0027/2706

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ON ORIGINAL

APPENDIX B

Listings of adverse events classified as neutropenia or leukopenia (COSTART Term Leukopenia) related to abnormal ANC and WBC values ..... B1 to B

Summary of adverse events and withdrawals classified by severity

	Quetiapine			
	Patients with adverse events because of leukopenia*		Withdrawn for adverse events of leukopenia*	
	transient*	persistent*	transient*	persistent*
Neutropenia				
agranulocytosis (<0.5 with symptoms)	0	0	0	0
severe neutropenia (<0.5 without symptoms)	0	0	0	0
moderate neutropenia (≥0.5 and <1.0)	5	0	1	0
mild neutropenia (≥1.0 and <1.5)	10	2	4	1
Leukopenia				
severe leukopenia (<3.0)	6	0	3	0
mild to moderate leukopenia (≥3.0 and <4.0)	18	0	5	0
Normal or ANC>1.5 and WBC >4.0	7			

*The incidences (14) of withdrawal because of the adverse event of leukopenia are included in the columns describing patients with adverse events of leukopenia.
Units for neutrophil and leukocyte counts are x 10^9 cells/L

ADVERSE REPORTS OF TRANSIENT MILD NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0012/0035/3506		1.4	3	Asymptomatic mild.
0012/0064/6406		1.32	8	Transient mild neutropenia.
0012/0065/6503		1.12	26	Mild leukopenia. Transient with mild leukopenia.
0014/0031/3101	3.7, 3.6, 3.2	1.9, 1.6, 1.2	3, 18-26	Intermittent neutropenia on both haloperidol and on quetiapine. Moderate leukopenia and mild neutropenia that may be drug related despite its mild nature.
0014/0051/5101	4.1	1.41	3	Nonprogressive mild neutropenia.
0012/0005/0502	2.4	1.4	6	Single episode of transient neutropenia on week 6. Noncumulative transient cytopenia etiology.
0013/0021/2119	3.0	1.27	3	Two values of mild neutropenia on week 3 and 4. Nonprogressive asymptomatic.
0013/0022/2206	4.0-3.6	1.44, 1.32, 1.27	5-11	Mild persistent neutropenia with mild leukopenia.
0014/0004/0401	3.1	1.27	32	Repeat 3 weeks later, normal. Transient leukopenic episode unclear etiology.
0015/0029/2912	3.3	1.9	50	Repeat on week 51, normal. Single episode of transient leukopenia and neutropenia. Unclear etiology associated with dermatitis in a 36 y/o female. Possible comorbid condition.

ADVERSE REPORTS OF PERSISTENT MILD NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0012/0005/0508	3.2, 2.7, 2.9	1.23, 1.07, 1.20	9, 13, 30	Repeat value on week 30 confirmed mild leukopenia, persistent mild leukopenia. This led to withdrawal of the patient with repeat value 10 days later showing WBC 5.0, ANC 2.8. Probable association with drug administration, late onset persistent neutropenia.
0014/0001/0103	2.9-3.9	1.1-1.48	1, 4, 6, 7, 10, 18	Persistent mild leukopenia without progression associated with a low normal neutrophil count. Presence on week 1 suggests prior abnormality.

ADVERSE REPORTS OF SEVERE LEUKOPENIA WITHOUT NEUTROPENIA

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0013/0022/2212	2.7-3.7	1.52-2.57	1-8	Asymptomatic mild leukopenia noted repeatedly as an adverse event, not apparently associated with any abnormality.
0012/0062/6205	2.9	1.7	16	Single episode of mild leukopenia widely fluctuating WBC and ANC, no evidence of progression or symptoms.
0013/0014/1401	2.8-3.7	1.54-1.68	7-9, 14, 15	Nonprogressive, tolerated continued therapy. Not drug related.
0012/0036/3609				See above review.
0012/0042/4203				See above review.
0014/0045/4508				See above review.

MILD TO MODERATE LEUKOPENIA
TRANSIENT MILD TO MODERATE LEUKOPENIA LEADING TO WITHDRAWAL

Patient Number	WBC Nadir	ANC Nadir	Week of Nadir	Comments
0008/0008/0007	3.7		3	Transient episode found 2 days after a WBC of 5.0 leading to withdrawal, repeat 3 days later. WBC 6.7. Possible drug effect.
0012/0044/4404	3.4		3	Transient, repeat 7 days later, WBC 5.1. Unclear drug association.
0005/0003/0010	3.6		3	Withdrawal, no followup values. Unclear drug etiology.
0013/0019/1909	3.0	1.7	18	Associated with URI. Transient nonprogressive, probably nonrelated.
0014/0006/0005	3.4		14	Terminated on week 15, 5 days later WBC 3.9. Unrelated to drug given baseline WBC of 4.0.

PLEASE NOTE: Patient Number 0014/0006/0005 is a typographical error. This Patient Number is 0014/0006/0605.

TRANSIENT MILD TO MODERATE LEUKOPENIA NOT LEADING TO WITHDRAWAL

Patient Number	Comments
0008/0001/0018	
0008/0001/0032	
0008/0015/0009	
0013/0007/0701	
0005/0011/0005	Episodes of transient mild to moderate leukopenia or mild nonprogressive. Most occurred early with very
0014/0001/0144	minimal changes in WBC and not associated with neutropenic episodes. In most instances, the WBC fell
0012/0036/3604	from less than 6,000 to greater than 3,000. Most patients had WBCs in the range of 4,000-5,000 persistently.
0012/0050/5002	None of these can be ascribed to be progressive symptomatic or indicative of definitive drug effect.
0013/0019/1904	
0013/0022/2203	
0013/0022/2207	
0014/0035/3506	
0014/0035/3507	

Summary of adverse drug events

Many of these adverse drug events could be classified as severe neutropenias or mild to severe leukopenias and could be used to generate an overall incidence of episodes. There is no characteristic which separates the reported adverse events from those not reported in terms of absolute values or progression of WBC and ANC.

In summary, quetiapine has an association of episodes with mild to severe nonprogressive asymptomatic neutropenia and no cases of agranulocytosis. No patients were removed for adverse events due to symptomatic neutropenia and the breadth of the data does not indicate any clinically significant adverse outcome due to the presence of neutropenia. It appears that this drug can be safely administered and there is no population at risk for development of sustained and neutropenic episodes including those patients with benign neutropenia or leukopenia at the time of onset of treatment.

Medical Officer's Review of NDA 20-639
Ophthalmology Consult

NDA # 20-639
Consult

Submission:	7/29/96
Consult Request:	2/3/97
Review completed:	3/9/97

Name: Seroquel (quetiapine fumarate tablets)

Applicant: Zeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437

Proposed Indication(s): For the management of the manifestations of psychotic disorders

Reviewer's Comments: Comments in this review are limited to areas of ophthalmic concern.

Non-clinical: (From Integrated Summary of Safety, Vol 285, page 53)

"The lens was the principal organ affected by quetiapine in the dog. Opacities were first noted after 3 months of dosing at 100 mg/kg/day with posterior subcapsular triangular cataracts appearing after 6 months. These did not progress to diffuse cataracts. Histologic changes included anterior and posterior fiber swelling and variations in staining intensity."

Reviewer's Comments: *Based on the animal studies, quetiapine fumarate should be considered potentially cataractogenic in man until studies are performed to demonstrate otherwise.*

APPEARS THIS WAY
ON ORIGINAL

Clinical:
(From Integrated Summary of Safety, Vol 286, page 6-10)

Number and percent of subjects with unchanged, improved, or worsened LOCS III scores from baseline to final evaluation during treatment with quetiapine in trials 12, 13 and 15.

	Number of patients		
	Improved	No Change	Worsened
Cortical cataract	5	77	8
Posterior subcapsular	0	86	4
Nuclear opalescence	15	57	17
Nuclear color	15	60	15

Reviewer's Comments:

The number of patients demonstrating a worsening was higher than the number of patients demonstrating improvement. If the changes were due to observational mis-classification, the groups would be expected to be balanced. The small number of subjects in the haloperidol and placebo groups makes their use of limited value.

APPEARS THIS WAY
ON ORIGINAL

Number and percent of subjects with no change, improved, or worsened LOCS III scores from baseline to final evaluation during treatment with quetiapine in uncontrolled trials including open label extension of trials 12, 13 and 15.

	Number of patients		
	Improved	No Change	Worsened
Cortical cataract	6	45	9
Posterior subcapsular	0	54	6
Nuclear opalescence	13	27	19
Nuclear color	8	39	13

Reviewer's Comments:

The number of patients demonstrating a worsening was higher than the number of patients demonstrating improvement. If the changes were due to observational mis-classification, the groups would be expected to be balanced.

APPEARS THIS WAY
ON ORIGINAL

Patients with clinically significant changes [From Volume 1.171, pages 132-139]

007/00702 34 ♀	Seroquel 75 mg	Normal baseline, clinically significant change in right eye at week 12	Cataract unusual for this age
013/01308 43 ♂	Seroquel 75 mg	Normal baseline and week 12. Lens changes at week 24.	Cataract unusual for this age
013/01309 43 ♀	Seroquel 300 mg	Normal baseline, lens changes at week 12 and continuing. Visual acuity loss from 20/15 to 20/25.	Cataract unusual for this age
023/02301 23 ♂	Seroquel 600 mg	Normal baseline, posterior subcapsular cataracts noted at week 12.	Cataract unusual for this age
029/02902 51 ♀	Seroquel 600 mg	Normal baseline and week 12. Central lens opacity at week 24.	Cataract
006/00601 24 ♂	Seroquel 75 mg	Posterior subcapsular opacities with decreased vision during study	Decreased vision

Reviewer's Comments: *Cataracts in patients under the age of 50-60 is very unusual.*

From Consultant's Report [Volume 1.178, pages 62-67]:

"Study 5077IL/0015 -Relapse Prevention Clinical Trial

The requirement for retro-illumination photography of the crystalline lens was removed from the protocol on October 23, 1994. This technique had been included to allow a small group of cataract graders, masked to visit, drug status, and other parameters, to grade in a standardized manner all of the photographs after the trial was completed. Its omission means that cataract classification will be done at the slit-lamp by several graders, and that there will be less likelihood that cataract classification criteria will be employed uniformly to all instances lens specification and cataracts."

Reviewer's Comments: *The deletion of retro-illumination photography specifically undermines the ability to detect the development of cataracts.*

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

"Patients completing the trial:

'... the overall proportion of patients who completed the trial was low.' 16%-34% in the Seroquel and Haloperidol groups. This inevitably reduces the power of the study to detect significant adverse effects of Seroquel on the lens."

Reviewer's Comments: *Concur.*

"On page 102 are the specific data for the ophthalmologic and slit-lamp examinations and LOCS III data for the 139 U.S. and 21 Canadian patients.

In the narratives on p 103 one can read the specific ophthalmologic problems observed. It should be noted however that the protocol does not attempt to standardize either the observational methods used to examine the lens or the terminology used to describe the lens findings. Therefore the precise meaning of the terms used below is unknown. Also whether or not the examiner was describing a normal age-related change or finding in the lens is not clear."

Reviewer's Comments: *The methods used also undermine the ability to detect the development of cataracts. Many of the patients failed to have both visual acuity measurements and slit lamp examinations.*

"(Canadian Data) 4/21 Canadian patients had normal baseline and at least one abnormal exam of the ocular lens. Three of these 4 were deemed to be clinically significant (in the Seroquel) group. It is not possible to draw any conclusions about the effect of Seroquel on the lens from such a small sample."

Reviewer's Comments: *Disagree. This represents a 15% rate of clinically significant changes and is unusual for any trial.*

Applicant's Summary:

Overall, the results of the slit-lamp examinations of the ocular lens support the view that Seroquel has no clinically relevant effect on the ocular lens. Ocular changes noted were of a very minor nature, were noted in all treatment groups, and were not related to the dose of Seroquel administered. The LOCS III data support the slit lamp examination results, that Seroquel had no clinically relevant effect on the ocular lens.

Reviewer's Comments:

The applicant's summary should be regarded as either false or very misleading. Few patients had complete examinations, abnormal findings were dismissed even when listed as clinically significant and tests to detect cataract changes were deleted from the protocols.

Reviewer's Conclusions:

The non-clinical study results are suggestive of a drug product which is capable of increasing the development of cataracts. The applicant has had the opportunity to study the issue, but failed to adequately follow patients and/or perform the necessary examinations. The ocular adverse experiences which have been observed, have been inappropriately minimized by the applicant and are not balanced between groups (higher in the Seroquel groups).

Reviewer's Recommendations:

1. If the application is approved, the package insert should include a statement in the WARNINGS section that "Seroquel has the potential to increase the development of cataract formation. Periodic slit lamp examinations (approximately every 6 months) are recommended."

2. Prior to any modifications of the above warning, an additional study should be performed to further evaluate the cataract potential of Seroquel. The study should be controlled, include at least 300 patients on treatment for at least 12 months with standardized slit lamp examinations and best corrected distance visual acuity measurements performed at baseline, months 3, 6, 9 and 12. Retro-illumination photography would be helpful, but alternative standardized grading systems are also acceptable.

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-639
HFD-120
HFD-120/Mosholder
HFD-105
HFD-550/Consult File
HFD-550/Chambers