Table 63 Glucose regulation laboratory data, change from randomization to end of treatment (Randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 336	PLA+ LI/VAL N = 367	QTP+ LI N = 143	PLA+ LI N = 153	QTP+ VAL N = 193	PLA+ VAL N = 214
Glucose (mg/dL)							
N [a]		310	329	134	138	176	191
Randomization	Mean(SD)	93.97(21.261)	96.16(18.807)	95.71(18.117)	95.01(13.637)	92.64(23.337)	96.99(21.791)
End of treatment	Mean(SD)	97.97(20.142)	95.81(18.189)	100.35(21.577)	96.81(17.749)	96.16(18.838)	95.09(18.513)
Change	Mean(SD)	4.00(18.896)	-0.35(16.215)	4.64(16.951)	1.80(14.160)	3.52(20.286)	-1.90(17.422)
	Median	3.00	0.00	2.00	1.50	3.00	-1.00
	Min to Max	-132.00 to 84.00	-85.00 to 67.00	-68.00 to 72.00	-27.00 to 50.00	-132.00 to 84.00	-85.00 to 67.00
HbAlC (%)							
N [a]		307	338	130	137	177	201
Randomization	Mean(SD)	5.40(0.617)	5.39(0.530)	5.28(0.561)	5.23(0.480)	5.49(0.641)	5.51(0.535)
End of treatment	Mean(SD)	5.56(0.622)	5.44(0.557)	5.44(0.572)	5.28(0.477)	5.66(0.641)	5.54(0.583)
Change	Mean(SD)	0.17(0.403)	0.04(0.294)	0.16(0.285)	0.05(0.245)	0.17(0.472)	0.04(0.323)
	Median	0.10	0.00	0.20	0.00	0.10	0.00
	Min to Max	-1.60 to 3.80	-1.10 to 1.40	-0.90 to 1.10	-0.70 to 0.90	-1.60 to 3.80	-1.10 to 1.40
Insulin (pmol/L)							
N [a]		254	276	106	111	148	165
Randomization	Mean(SD)	110.04(125.974)	119.75(136.348)	93.89(84.008)	99.56(90.356)	121.61(148.151)	133.34(158.858)
End of treatment	Mean(SD)	130.67(149.765)	122.54(159.380)	125.21(140.838)	124.73(135.721)	134.58(156.199)	121.07(173.880)

Table 63 Glucose regulation laboratory data, change from randomization to end of treatment (Randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 336	PLA+ LI/VAL N = 367	QTP+ LI N = 143	PLA+ LI N = 153	QTP+ VAL N = 193	PLA+ VAL N = 214
Change	Mean(SD)	20.63(143.118)	2.79(166.281)	31.32(103.506)	25.17(134.958)	12.97(165.706)	-12.27(183.247)
	Median	7.00	0.00	20.00	7.00	0.00	-6.00
	Min to Max	-882.00 to 799.00	-895.00 to 1660.00	-243.00 to 611.00	-319.00 to 646.00	-882.00 to 799.00	-895.00 to 1660.00
HOMA-R							
N [a]		259	275	110	113	149	162
Randomization	Mean(SD)	4.16(7.615)	4.35(5.628)	3.38(3.803)	3.39(3.219)	4.73(9.469)	5.02(6.753)
End of treatment	Mean(SD)	4.54(5.683)	4.45(6.374)	4.18(4.221)	4.57(5.703)	4.81(6.558)	4.37(6.820)
Change	Mean(SD)	0.39(6.702)	0.10(6.630)	0.79(3.661)	1.18(5.642)	0.08(8.259)	-0.65(7.160)
	Median	0.22	0.01	0.44	0.22	0.16	-0.14
	Min to Max	-50.60 to 33.46	-29.01 to 62.54	-10.47 to 15.52	-12.27 to 29.09	-50.60 to 33.46	-29.01 to 62.54
QUICKI							
N [a]		259	275	110	113	149	162
Randomization	Mean(SD)	0.3387(0.0431)	0.3342(0.0430)	0.3416(0.0429)	0.3414(0.0426)	0.3366(0.0432)	0.3293(0.0427)
End of treatment	Mean(SD)	0.3316(0.0425)	0.3338(0.0425)	0.3321(0.0433)	0.3335(0.0431)	0.3312(0.0421)	0.3341(0.0423)
Change	Mean(SD)	-.0071(0.0385)	-.0004(0.0394)	-.0095(0.0376)	-.0079(0.0399)	-.0054(0.0392)	0.0048(0.0383)
	Median	-.006	-.001	-.008	-.007	-.005	.0027
	Min to Max	-0.1476 to 0.0959	-0.1279 to 0.1208	-0.1133 to 0.0897	-0.1152 to 0.0889	-0.1476 to 0.0959	-0.1279 to 0.1208

[a] Number of patients with assessment at randomization and at least one assessment after randomization.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. HbAlC Hemoglobin Alc.
HOMA [insulin (uU/ml) x glucose (mmol/l)]/22.5. QUICKI 1/[log10(insulin n(uU/ml) + log10(glucose e(mg/dl))].
/csre/prod/seroquel/d1447c00126/sp/output/tlf/t1103080416.rtf chem207.sas 17APR2007:09:19 luchen
Table corresponds to Table 11.3.8.4- 16.

There were increases in mean glucose and insulin levels for the quetiapine treatment group compared to the placebo group during randomized treatment. Glucose levels increased by a mean of 4.00 mg/dL (median 3.0) in the quetiapine group, compared with a –0.35 mg/dL decrease (median 0.0) in the placebo group. Insulin levels increased by a mean of 20.63 pmol/L (median 7.0)in the quetiapine treatment group, compared with an increase of 2.79 pmol/L (median 0.0) in the placebo group. The glucose and insulin data were highly variable in the treatment groups. There was also an increase in HbA_{1c} (mean 0.17%, median 0.10%) in quetiapine-treated patients compared to placebo-treated patients (mean 0.04%, median 0.00%).

Insulin resistance (HOMA-R) increased in the quetiapine-treated patients (mean 0.39, median 0.22) and remained stable in the placebo-treated patients (mean 0.10, median 0.01). The insulin sensitivity (QUICKI) decreased in the quetiapine group (mean -0.0071, median –0.006) and remained stable in the placebo group (mean 0.0004, median –0.001).

The mean change from baseline in glucose regulation laboratory data for patients with diabetes (defined as having baseline glucose ≥126 mg/dL or HbA1c above ULN or a history of diabetes), patients at risk for diabetes (defined as having a history of gestational diabetes or a BMI of ≥35 or impaired presumably fasting glucose ≥100 to <126 mg/dL), and patients with no known diabetic risk is summarized by treatment group in Table 64, and by mood stabilizer in Table 11.3.8.4- 18.

Table 64 Glucose regulation data, change from randomization, diabetic subgroups, by treatment group (Randomized safety population)

		QTP+LI/VAL N=336				PLA+LI/VAL N=367			
Parameter		**N[a]**	**Mean**	**SD**	**Median**	**N[a]**	**Mean**	**SD**	**Median**
Glucose, fasting (mg/dL)	Diabetic	23	-20.43	34.755	-18.00	33	-5.70	33.416	-6.00
	Diabetic risk	87	3.67	15.537	3.00	88	-4.14	13.122	-3.00
	Non diabetic	200	6.96	15.450	4.00	208	2.11	12.447	2.00
HbA1C (%)	Diabetic	23	-0.14	0.552	-0.10	33	-0.04	0.518	-0.10
	Diabetic risk	86	0.23	0.412	0.15	89	0.05	0.294	0.00
	Non diabetic	198	0.17	0.363	0.10	217	0.05	0.244	0.00
Insulin (pmol/L)	Diabetic	21	-46.57	140.639	-14.00	27	-33.63	81.113	-14.00
	Diabetic risk	69	15.61	196.189	0.00	77	-1.31	129.698	7.00
	Non diabetic	163	29.33	104.159	14.00	172	10.34	188.982	0.00
HOMA-R	Diabetic	21	-6.18	13.166	-1.58	27	-1.57	3.837	-0.61
	Diabetic risk	71	0.23	6.945	0.00	77	-0.23	5.392	0.20
	Non diabetic	167	1.28	4.725	0.47	171	0.52	7.411	0.01
QUICKI	Diabetic	21	0.0134	0.0281	0.0125	27	0.0043	0.0270	0.0073
	Diabetic risk	71	-0.0011	0.0350	-0.0000	77	0.0022	0.0331	-0.0028
	Non diabetic	167	-0.0122	0.0400	-0.0110	171	-0.0023	0.0434	-0.0009

[a] Number of patients with assessment at baseline and at least one after baseline.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
Note: Diabetics defined as having documented fasting glucose >=126 mg/dL or non-documented fasting glucose >=200 mg/dL at baseline or a history of diabetes, or HbAlc above ULN at baseline,
Diabetic risk defined as having a history of gestational diabetes or a BMI of >= 35 or impaired documented fasting glucose >=100 to <126 mg/dL;
Non-diabetic defined as not meeting criteria for diabetes or diabetic risk.
/csre/prod/seroquel/d1447c00126/sp/output/tlf/t1103080417.rtf chemm201.sas 17APR2007:09:19 luchen
Table corresponds to Table 11.3.8.4- 17.

Decreases in glucose regulation data were observed in diabetics during the randomized treatment phase in both treatment groups. Small decreases were also observed in patients at risk for diabetes in the placebo group. Non-diabetic patients remained relatively stable on most glycemic measures during randomized treatment. There was little change in measures of insulin resistance (HOMA-R) and insulin sensitivity (QUICKI) during randomized treatment.

There were relatively few diabetic patients (23 total in the quetiapine group and 33 total in the placebo group), thus comparisons of this subgroup are made with caution. Nonetheless, in diabetic patients glucose values decreased during randomized treatment in both treatment groups: a mean change of –20.43 mg/dL (median –18) in the quetiapine treatment group and –5.70 mg/dL (median –6.00) in the placebo group. $HbA1_C$ (measured in %) in diabetic patients decreased during randomized treatment by a mean change of –0.14 (median -0.10) in the quetiapine treatment group, and by –0.04 (median –0.10) in the placebo group. Insulin values decreased during randomized treatment in diabetic patients in both treatment groups: mean change of –46.57 pmol/L (median -14.00) in the quetiapine treatment group compared to –33.63 pmol/L (median –14.00) in the placebo group. Changes in measures of insulin resistance (HOMA-R) and insulin sensitivity (QUICKI) reflect the changes described above.

In patients at risk for diabetes there was a small increase in glucose values during randomized treatment in the quetiapine treatment group (mean increase of 3.67 mg/dL, median 3.00) and a small decrease (mean change of –4.14 mg/dL, median –3.00) in the placebo group. $HbA1_C$ (measured in %) in patients at risk for diabetes increased during randomized treatment by a mean change of 0.23 (median 0.15) in the quetiapine treatment group, and by a mean change of 0.05 (median 0.00) in the placebo group. Insulin values increased during randomized treatment in patients at risk for diabetes in the quetiapine treatment group (mean change 15.61 pmol/L; median 0.00), and decreased in the placebo group (mean change of –1.31 pmol/L, median 7.00). The results in insulin resistance (HOMA-R) and insulin sensitivity (QUICKI) reflects the results above.

There was a small increase in glucose values during randomized treatment in non-diabetic patients in the quetiapine treatment group (mean increase of 6.96 mg/dL, median 4.00) and in the placebo group (mean change of 2.11 mg/dL, median 2.00). $HbA1_C$ (measured in %) in increased during randomized treatment by a mean change of 0.17 (median 0.10) in the quetiapine treatment group, and by a mean change of 0.05 (median 0.00) in the placebo group. Insulin values increased in non-diabetics in the quetiapine treatment group (mean change 29.33 pmol/L; median 14.00) and in the placebo group (mean change of 10.34 pmol/L, median 0.00). The results in insulin resistance (HOMA-R) and insulin sensitivity (QUICKI) reflects these results.

A more detailed examination of the mean change from baseline in glucose regulation laboratory data for patients with diabetes, at risk for diabetes, and patients with no known diabetic risk is summarized by treatment group and mood stabilizer in Table 11.3.8.4- 19, Table 11.3.8.4- 20, and Table 11.3.8.4- 21, respectively. Change from randomization to Week 12, 28, 40, 52, 68, 84 and 104 in glucose regulation laboratory data (observed cases) is shown in Table 11.3.8.4- 22.

TABLE 27 Frequencies of clinically significant values of selected vital signs and weight (number and percentage of patients)

Assessment	SEROQUEL 450 mg (bid) (n = 192)			SEROQUEL 450 mg (tid) (n = 204)			SEROQUEL 50 mg (bid) (n = 196)		
	Number with significant value (%)		Mean % days with significant valuo	Number with significant value (%)		Mean % days with significant value	Number with significant value (%)		Mean %days with significant value
Postural changes in systolic BP	20	(10)	29	18	(9)	28	12	(6)	22
Postural changes in pulse rate	54	(28)	34	71	(35)	34	56	(29)	35
Postural changes in systolic BP and pulse rate	7	(4)	33	2	(1)	14	5	(3)	29
Supine pulse rate	10	(5)	27	16	(8)	21	3	(2)	23
Weight	26	(14)	n/a	27	(13)	n/a	13	(7)	n/a

n/a = not available

Postural changes in blood pressure and/or pulse rate occurred with similar incidence in each of the three treatment groups. Only 2% of all patients met the criteria for combined postural changes in systolic blood pressure and pulse and the incidence of these changes did not appear to be related to the dose of SEROQUEL.

The incidence of postural changes in systolic blood pressure was slightly higher in the two SEROQUEL 450 mg groups than in SEROQUEL 50 mg (bid) group. The mean time of onset was slightly later in the SEROQUEL 450 mg (bid) group (20 days) and in the SEROQUEL 450 mg (tid) group (19 days) compared with the SEROQUEL 50 mg (bid) group (16 days). The percentage of days on which a clinically significant postural change in blood pressure was present was also higher in the SEROQUEL 450 mg groups than in the SEROQUEL 50 mg (bid) group.

The majority of patients who had changes in vital signs that met the pre-defined criteria for clinical significance did not have adverse events (postural hypotension, tachycardia) associated with these alterations (Section 5.3.1).

These results support the conclusion that SEROQUEL is associated with mild or moderate postural changes in systolic blood pressure and supine pulse rate in a minority of patients, which are not generally associated with clinical symptomatology.

The incidence of clinically significant weight gain (an increase of 7% or more from baseline), was approximately 14% in the SEROQUEL 450 mg (bid) group and 13% in the SEROQUEL 450 mg (tid) group, compared with 7% in the SEROQUEL 50 mg (bid) group. These results suggest that SEROQUEL 450 mg (bid) and SEROQUEL 450 mg (tid) were associated with a higher incidence of clinically significant weight gain than SEROQUEL 50 mg (bid).

In summary, these results suggest that SEROQUEL was associated with mild or moderate postural changes in blood pressure or pulse which were not generally associated with adverse events. The incidence of these changes was not related to the dose of SEROQUEL and the incidence of combined postural changes in blood pressure and pulse rate was low. SEROQUEL 450 mg (bid) and SEROQUEL 450 mg (tid) were associated with a higher

incidence of clinically significant weight gain than SEROQUEL 50 mg (bid). There was little difference between the two SEROQUEL 450 mg groups in the incidence of weight gain.

5.7 Plasma concentrations of ICI 204,636

Summary tables: *plasma levels of ICI 204,636; T20.1 to T20.2*

Individual patients listings: *median trough plasma levels of ICI 204,636; G15*

Plasma samples were to be collected at selected centres for measurement of plasma concentrations of ICI 204,636 (Section 2.8.2). However, only five centres agreed to do this. A total of 17 patients from Centres 002, 045, 046, 050 and 083 had at least one plasma sample collected. (The other patients at these centres did not give consent to the extra blood samples required.) Due to small sample sizes, only descriptive statistics are presented for the median weekly trough plasma concentrations and for the median pre- and post-dose plasma concentrations (Table T20). No assessment of the relationship between plasma concentrations and response to treatment was made due to the extremely small sample sizes.

5.8 Overall evaluation of safety

Approximately half the patients in each of the SEROQUEL 450 mg treatment groups experienced at least one adverse event during the study; the proportion of patients was slightly lower in the SEROQUEL 50 mg (bid) group (44%). The most frequent adverse events in each of the three treatment groups were somnolence and insomnia.

Somnolence occurred with similar incidence in the two SEROQUEL 450 mg groups and with lower incidence in the SEROQUEL 50 mg (bid) group. It was generally mild or moderate in severity, although some patients only in the SEROQUEL 450 mg groups experienced severe somnolence. The onset of somnolence tended to occur on first exposure to treatment or during the dose-titration phase. These results suggest that SEROQUEL 450 mg (bid) and SEROQUEL 450 mg (tid) were associated with a higher incidence and more severe somnolence than SEROQUEL 50 mg (bid). SEROQUEL 450 mg (bid) was not associated with more somnolence than SEROQUEL 450 mg (tid).

Adverse events of dry mouth occurred with higher incidence in the two SEROQUEL 450 mg groups than in the SEROQUEL 50 mg (bid) group, suggesting that the higher dose of SEROQUEL may cause more anticholinergic effects.

Dizziness was reported with similar frequency in the two SEROQUEL 450 mg groups and less frequently in the SEROQUEL 50 mg (bid) group, suggesting it was related to the higher dose of SEROQUEL. Adverse events of postural hypotension occurred with similar incidence in each treatment group. These events tended to occur on first exposure or during the dose-escalation phase. SEROQUEL was also associated with mild or moderate postural changes in blood pressure or pulse in some patients, although these findings were generally not recorded as adverse events.

Symptoms of schizophrenia, such as anxiety, agitation and insomnia were commonly reported as adverse events and in some cases were severe. In the SEROQUEL 50 mg (bid) group, new cases of agitation were reported throughout the study, which may represent lack of efficacy of this dose.