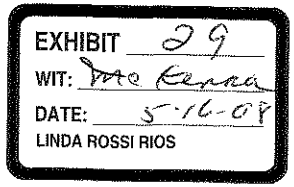
Seroquel and Glucose Dysregulation



Outline

- General considerations
- Clinical studies
- Epidemiology and other studies
- Post-marketing data
- Ongoing and future work

Definitions

- Diabetes
  - Fasting blood glucose ≥126 mg/dL (≥7.0 mmol/L)
  - Random blood glucose ≥200 mg/dL (≥11.1 mmol/L)
    - With symptoms such as polyuria, polydipsia
- Impaired glucose tolerance
  - 140 to 199 mg/dL (7.8 to 11.0 mmol/L) @ 2 hours
- Impaired fasting glucose
  - 100* to 125 mg/dL (5.6 to 6.9 mmol/L)

* Formerly 110 mg/dL (6.1 mmol/L)

Diabetes is common

- Prevalence approximately 10% in Japan (MHLW) and US (Mokdad 2001)
- More common in psychiatric patients
  - Schizophrenia
    - US: 11.1 to 14.9% (Dixon et al 2000)
      13% (Regenold 2002)
    - Italy 15.8% (Mukherjee et al 1996)
  - Bipolar disorder
    - US: 10% in bipolar disorder, manic or mixed compared to 3.4% in the general population(Cassidy 1999)
      10% in bipolar (manic + depressive) compared to 2% in the general population (Lilliker 1998)
      26% in bipolar I (Regenold 2002)
  - Major depression
    - US: 18% (Regenold 2002)

Glucose Metabolism in Schizophrenics

(Ryan et al 2003)

- Study population
  - 26: Drug naïve, first episode, schizophrenics
  - 26: Healthy control subjects, matched to age, exercise and dietary habits
- Impaired fasting glucose
  - 15.4% schizophrenics vs. 0% controls ($p<0.02$)

Diabetes is Progressive

Begins subclinically

↓

Impaired fasting glucose, glucose intolerance

↓

Diabetes

Type II may progress from insulin resistance/impaired secretion to beta cell failure (requiring insulin)

Clinical Studies

Clinical Studies

- Random Glucose Measurements
  - Schizophrenia
    - Short-term
    - Long-term
  - Bipolar Mania monotherapy
  - Elderly Dementia with Psychosis
- Fasting Glucose Measurements
  - Dementia with agitation
  - Bipolar depression
  - High dose

Short-Term Placebo-Controlled Schizophrenia Trials (Random glucose (mg/dL))

	N	LS Mean	Diff	LCL	UCL	p-value
Seroquel	230	3.6				
Placebo	143	-0.26				
Seroquel vs. Placebo			3.87	-0.97	8.71	0.1173

	Seroquel (N=323)	Placebo (N=143)	Chlorpromazine (N=92)
# of patients with baseline glucose <200 mg/dL	322	142	92
#(%) of patients with glucose >200 mg/dL post baseline	10 (3.1)	1 (0.7)	0
All patients irrespective of baseline glucose value	323	143	92
#(%) of patients with glucose >200 mg/dL post baseline	11 (3.4)	1 (0.7)	0
Incidence density	0.4	0.1	0

Trial IL/0041 - Short-Term Placebo-Controlled Schizophrenia Trials
Mean Change from Baseline in Plasma Glucose (mg/dL)

	Placebo	300 SR	600 SR	800 SR	300 IR	600 IR
N	60	73	69	66	69	60
Mean	2.9	4.4	6.7	3.1	-0.7	11.1
Median	0	2.0	0	1.0	1.8	8.5

Difference in mean change from baseline to end of treatment between Seroquel groups and Placebo group not statistically significant. SR=sustained release, IR=immediate release.

% of Patients with Potentially Clinically Significant Elevation of Plasma Glucose (>200 mg/dL)

	Placebo	300 SR	600 SR	800 SR	300 IR	600 IR
N	60	73	69	66	69	60
# of Patients	0	0	2	3	0	1
%	0	0	2.9	4.5	0	1.7

Trial US/0043 (Acute schizophrenia vs risperidone)
Mean Change from Baseline in Plasma Glucose

	Seroquel	Risperidone
N	222	234
Mean	4.5	4.6
Median	4.0	4.0

% of Patients with Potentially Clinically Significant Plasma Glucose Level (>200 mg/dL)

	Seroquel	Risperidone
N	222	234
# of Patients	4	5
% of Patients	1.8	2.1

Long-Term Controlled Schizophrenia Trials (Random glucose (mg/dL))

	N	LS Mean	Diff	LCL	UCL	p-value
Seroquel	170	4.53				
Haloperidol	35	4.01				
Seroquel vs. Haloperidol			0.52	-11.79	12.83	0.9333

	Seroquel (N=170)	Haloperidol (N=35)
# of patients with baseline glucose <200 mg/dL	167	32
#(%) of patients with glucose >200 mg/dL post baseline	2 (1.2)	1 (3.1)
All patients irrespective of baseline glucose value	170	35
#(%) of patients with glucose >200 mg/dL post baseline	5 (2.9)	3 (8.6)
Incidence density	0.1	0.2

Bipolar Mania Monotherapy Placebo-Controlled Trials
Change from baseline to endpoint
(Random glucose (mg/dL))

Glucose (mg/dL)	QTP	PLA
N	195	183
Mean Change	-3.35	-4.02

Treatment emergent, potentially clinically significant random glucose value at any time

	QTP			PLA		
	N	n	%	N	n	%
Endpoint Glucose ≥230 mg/dL	194	2*	1.0	183	0	

*One patient had high value occur after withdrawal (baseline=210.9 mg/dL, Day 21=199.9 mg/dL, Day 33=234.9 mg/dL [patient was withdrawn on Day 15])

Second patient had 9 kg wt gain as an AE, history of alcoholic fatty liver, and was concomitantly taking dexamethasone (baseline=171.1 mg/dL, Day 84=342.2 mg/dL).

Trial IL/0039 – Psychosis in Elderly Dementia
Change from Baseline in Blood Glucose (mmol/L)

	Seroquel	Haloperidol	Placebo
N	80	74	72
Mean	-0.15	-0.04	-0.01

Glucose Metabolism
Summary of Random Glucose Data

- No cases of DKA or hyperosmolar coma in clinical trial program
- 7 cases of diabetes
  - 5 in OLE: none considered related or led to withdrawal
  - 1 in double-blind comparison to risperidone; had diabetes/increased blood glucose prior to study drug
  - 1 in mania adjunct trial prior to study drug
- No increase in thirst, polyuria, or urinary frequency
- No consistent clinically significant effect on randomly collected blood glucose

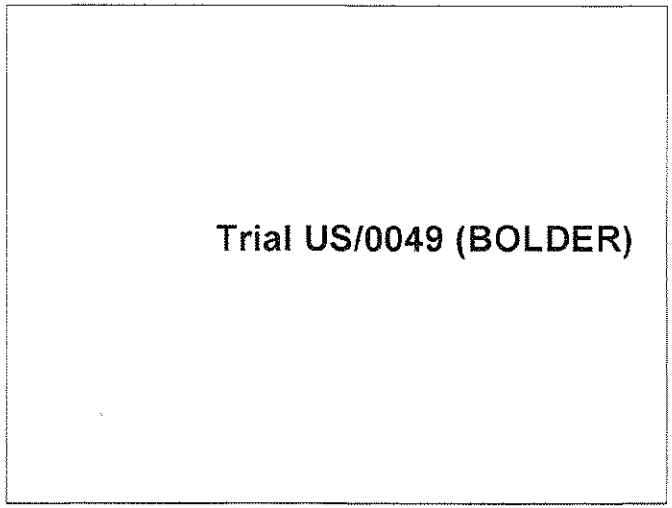
Trial US/0046 (STAR)

True Fasting Data

Trial US/0046

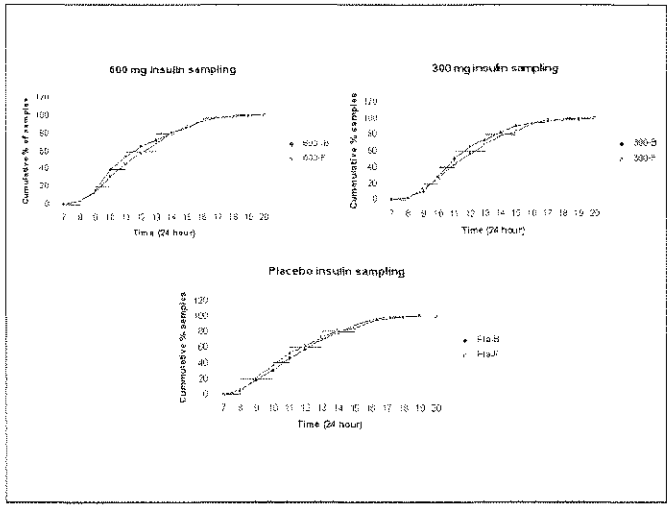
Fasting Glucose: Mean Change from Baseline (mg/dL)

Change in Glucose	Quetiapine 100 mg/day	Quetiapine 200 mg/day	Placebo
All: N Mean	97 -1.7	91 3.3	77 2.3
Diabetic: N Mean	17 2.0	13 -18.5	12 -11.7
Non-diabetic: N Mean	80 -2.5	78 6.9	65 4.9
Insulin (pmol/L) Median change	0.0	7.2	7.2
Weight change: N Mean	104 0.4	103 0.0	79 -0.8


Trial US/0049 (BOLDER)

Trial US/0049
Data Review

- Intended to be fasting, but probably not
- Screening/baseline vs. Week 8/withdrawal
  - Total cholesterol—no apparent effect
  - HDL—no apparent effect
  - LDL—no apparent effect
  - Triglycerides
  - Glucose
  - Insulin
    - HOMA-R


600 mg insulin sampling
Cumulative % of samples
Time (24 hour)
300 mg insulin sampling
Cumulative % samples
Time (24 hour)
300-S
300-P
Placebo insulin sampling
Cumulative % samples
Time (24 hour)
Plac-S
Plac-P

Trial US/0049
Fasting Status

- Sample times suggest it's unlikely that the patients were truly fasted.
  - Glucose, insulin, and triglycerides are very sensitive to fasting status.

Trial US/0049 - Triglycerides

	600 mg			300 mg			Placebo		
	Mean	Median	Max	Mean	Median	Max	Mean	Median	Max
Baseline	149.6	113.0	850.0	150.8	124.0	540.0	158.1	108.5	1240.0
Endpoint	171.2	135.0	1000.0	185.9	146.0	877.0	164.6	120.5	1930.0
Change	21.61	12.0	350.0	35.17	13.5	378.0	6.47	2.0	900.0

US/0049 – Fasting Glucose (mg/dL)

		300mg	600mg	Placebo
All Patients	N	156	147	152
	Mean	3.19	5.90	3.60
	Median	2.5	3.0	1.0
Diabetic	N	6	7	7
	Mean	2.67	4.71	24.57
	Median	9.0	-5.0	-9.0
Diabetic Risk	N	34	30	36
	Mean	2.56	5.87	1.25
	Median	2.5	0.5	0.0
Non-diabetic	N	116	110	109
	Mean	3.40	5.98	3.30
	Median	2.0	3.0	2.0

US/0049 – Fasting Insulin (ulU/ml)

		300mg	600mg	Placebo
All Patients	N	156	142	152151
	Mean	6.27	13.63	1.62
	Median	1.0	4.0	2.0
Diabetic	N	7	7	6
	Mean	-3.29	0.86	-42.33
	Median	-1.0	-4.0	-0.5
Diabetic Risk	N	34	27	36
	Mean	7.88	26.85	3.33
	Median	3.5	6.0	2.0
Non-diabetic	N	115	108	109
	Mean	6.37	11.15	3.48
	Median	1.0	4.0	2.0

US/0049 – HOMA-R

		300mg	600mg	Placebo
All Patients	N	144	137	144
	Mean	1.72	4.29	0.06
	Median	0.4	1.1	0.3
Diabetic	N	6	7	5
	Mean	-0.05	1.23	-25.14
	Median	-0.2	-1.2	1.1
Diabetic Risk	N	30	26	32
	Mean	1.91	10.70	1.40
	Median	1.2	1.5	0.2
Non-diabetic	N	108	104	107
	Mean	1.77	2.89	0.84
	Median	0.2	1.1	0.3

$$\text{HOMA - R} = \frac{\text{Insulin}(\mu\text{U/ml}) \times \text{Glucose (mmol/l)}}{22.5}$$

US/0049 - Summary

- Sample times suggest many samples are not fasted
- No apparent effect in diabetic patients, though small sample size
- Diabetic risk patients displayed small average increases in insulin and HOMA-R at both 300mg and 600mg
- Non-diabetics patients displayed small average increases in insulin and HOMA-R at 600mg, but not 300mg
- Future trials can include diabetics and draft proposals for monitoring of fasted glucose and insulin adequately insure patient safety

STACK
Canadian High-dose Study
(Ongoing)

STACK-Local Canadian Study

- Chronic schizophrenics titrated to 800 Seroquel
- At Day 29 non responders randomized 2:1 to increase dose to 1200/d Seroquel or continue on 800/d
- Fasting Assessments at screen, Day 29, 85

Median Values-All Patients

	N	Screen	N	Randomisation	N	Final
Glucose Mmol/L	108	5.10	78	5.15	50	5.15
Insulin ulu/ml	105	7.00	77	8.00	52	6.50
GTT (2 hour) Mmol/L	102	5.50	73	5.40	44	6.20
HbA1c	111	.053	77	.053	50	.054

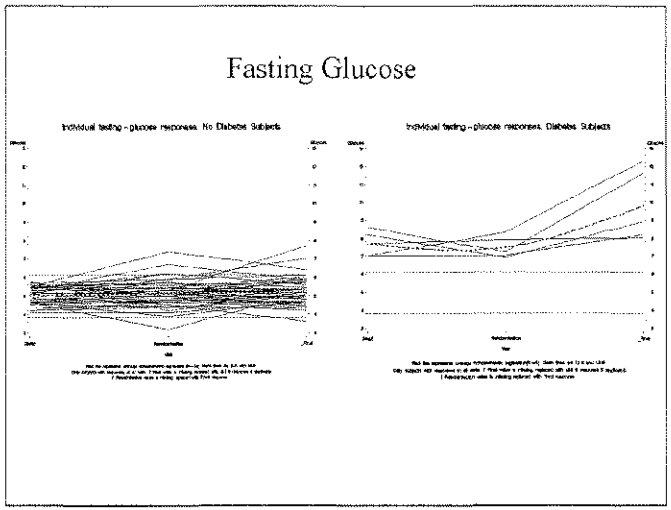
Median Values-Diabetics

	N	Screen	N	Randomisation	N	Final
Glucose Mmol/L	7	7.70	5	7.2	5	8.9
Insulin ulu/ml	7	11.57	5	10.00	5	15.00
GTT (2 hour) Mmol/L	6	13.55	3	17.10	4	19.85
HbA1c	7	.059	5	.061	5	.075

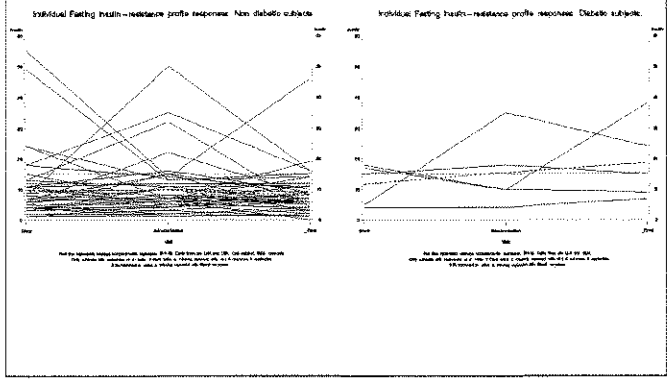
Median Values-Non-diabetics

	N	Screen	N	Randomisation	N	Final
Glucose Mmol/L	101	5.00	73	5.10	45	5.00
Insulin ulu/ml	98	7.00	72	8.00	47	6.00
GTT (2 hour) Mmol/L	96	5.35	70	5.35	40	5.75
HbA1c	104	.053	72	.053	45	.052

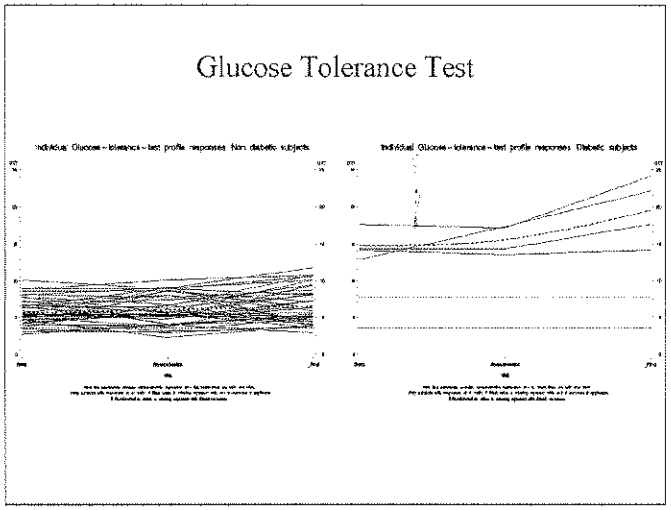
Fasting Glucose



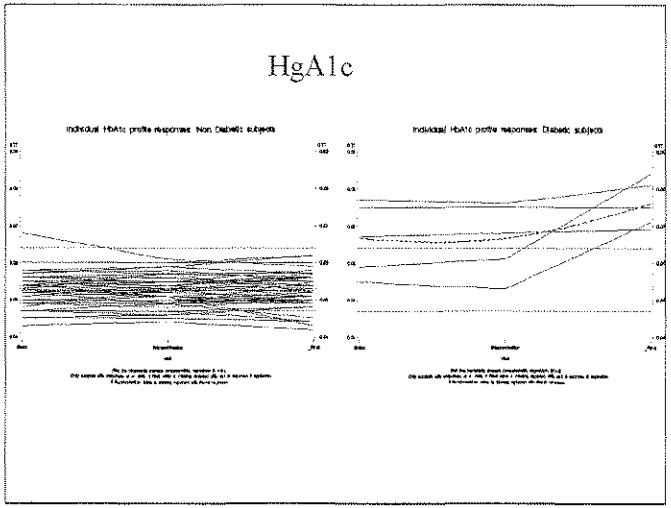
Insulin


Individual Fasting Insulin – resistance profile responses: Non diabetic subjects
Individual Fasting Insulin – resistance profile responses: Diabetic subjects

Glucose Tolerance Test



HgA1c


Individual HbA1c profile responses: Non Diabetic subjects
Individual HbA1c profile responses: Diabetic subjects

Clinical Data – Overall Summary

- Early studies confounded by lack of fasted sampling
  - No apparent, consistent effect
- 'Fasted' studies
  - No apparent effect in elderly demented patients
  - Inconsistent signals across diabetic sub-populations between US/0049 and STACK

Epidemiology

Epidemiology/others - Summary

- Inconsistent and conflicting results for Seroquel
  - Similar for risperidone
  - Majority of studies implicate olanzapine
  - Few data available for other atypicals
- Studies have limitations
  - Increased risk of diabetes in study population
  - Effect of previous antipsychotic, "channeling"
  - Other risk factors, e.g. weight, family history

Global Post-marketing Data

Global Spontaneous Reports through 16 March 2005

Number of diabetes related AE reports	416
Estimated population exposure	8,870,000
Reporting rate	0.005% Very rare

Seroquel and Glucose Related Reports 416 reports

- 40: Diabetic Ketoacidosis (DKA)
- 12: Coma related terms (*2 also counted in reports of DKA)
- 130: New onset Diabetes Mellitus (DM)
- 147: Hyperglycemia (no hx DM)
- 80: Exacerbation of DM
- 4: Glucose tolerance impaired (no hx)
- 5: Blood glucose fluctuation (all w/ hx of DM)

Post-marketing Reports Summary

- Reports of diabetes related adverse events very rare (< 0.01%)
- Interpretation complicated by:
  - Incomplete information or
  - Confounding by Risk Factors for Diabetes
    - Indication (schizophrenia risk for diabetes)
    - Weight
    - Family History
    - Other
  - Common and progressive nature of diabetes

Ongoing work

Trial 125

- 24 Week randomised comparison of the effect of Seroquel, risperidone and olanzapine on glucose metabolism
- Chronic patients not previously on atypicals, randomized 1:1:1
- Patients hospitalized overnight at baseline, 12 weeks and 24 weeks
- Variables: Fasting glucose, insulin, triglycerides, LDL, HDL; 2hr GTT, weight, HgA1c
- Minimum 95 patients in all 3 groups with week 24 assessment
- LPI 10 May 05. Code break to inform business case launch

Diabetes Exclusion Criteria Current Clinical Trials

- A subject with Diabetes Mellitus (DM) fulfilling one of the following criteria:
  - Unstable DM defined as enrolment Glycosylated Hemoglobin (HbA1c) >8.5%.
  - Admitted to hospital for treatment of DM or DM related illness in past 12 weeks.
  - Not under physician care for DM
  - Physician responsible for subject's DM care has not indicated that subject's DM is controlled.
  - Physician responsible for subject's DM care has not approved subject's participation in the study
  - Has not been on the same dose of oral hypoglycaemic drug(s) and/or diet for the four (4) weeks prior to randomisation. For thiazolidinediones (glitazones) this period should not be less than 8 Weeks.
  - Taking insulin whose daily dose on one occasion in the past 4 weeks has been more than 10% above or below their mean dose in the preceding 4 weeks

  Note: If a diabetic subject meets one of these criteria, the subject is to be excluded even if the treating physician believes that the subject is stable and can participate in the study

Additional Data Collected in Clinical Trials

- Clinical Trial Assessments-All Patients Irrespective of Diagnosis of Diabetes or Risk Factors
- Short Term Studies (8 weeks or less)
  - Fasting blood glucose at randomization, 4weeks and endpoint. HgA1c at baseline and endpoint (for studies of 6 weeks duration and longer)
- Long Term Studies and Extensions
  - Fasting blood glucose and HgA1c every 3 months
- Case Record Forms-Data to be Collected
  - Record time of blood draw, time since last consumption of food.
  - Identify patients with risk factors for diabetes – obesity (BMI>30), family history, history of diabetes including gestational diabetes