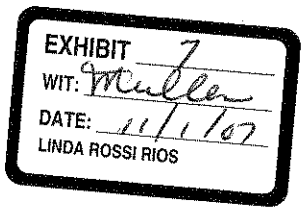
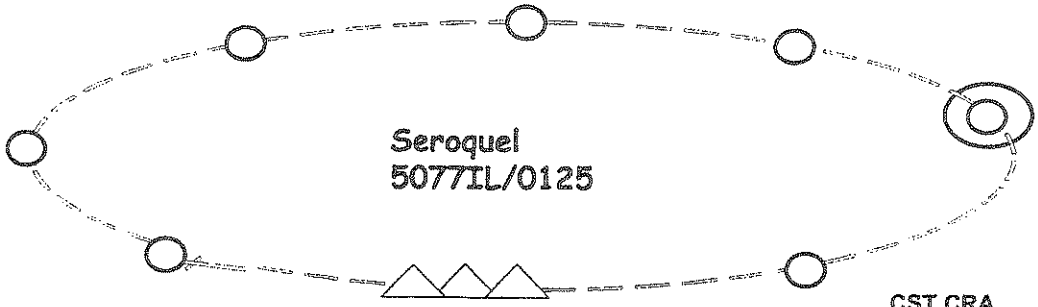
Seroquel study 125

D1441C00125

A 24-week, International, Multicenter, Open-label, Flexible-dose, Randomised, Parallel-group, Phase IV Study to Compare the Effect on Glucose Metabolism of Quetiapine, Olanzapine and Risperidone



125 Study Team



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Participating countries

- Czech Republic
- Denmark
- Finland
- Germany
- Norway
- Slovak Republic
- United Kingdom
- Romania
- Bulgaria
- South Africa

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Study Background:

- Recently much debate about metabolic effects of atypicals, and whether glucose dysregulation and pro-diabetogenic effects are 'class' effects.
- Most evidence concerns olanzapine and clozapine, but reports also on risperidone and quetiapine.
- Differential effects on weight with atypicals have been reported. Definitely an issue for olanzapine. Link to diabetes.
- During 2001-2003, several questions/"attacs" from health authorities on the weight/diabetes topic.

WE ARE LACKING GOOD METABOLIC DATA!

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Purpose of the study

1. **Regulatory purpose:**
   Produce data that will help us defend the Seroquel label.

2. **Commercial purpose:**
   Produce data that will enable us to generate commercially attractive and competitive messages in relation to diabetes & weight.

Business objectives / claims

- To demonstrate the superior safety / tolerability profile of Seroquel over olanzapine on glucose metabolism (and weight & lipids)
- To provide long-term satey / tolerability data on metabolism in patients with schizophrenia against comparators
- To support regulatory defense on glucose disturbances observed in schizophrenic patients treated with atypical antipsychotics

+ To show comparable effects on glucose and weight vs risperidone.
+ To show comparable safety / tolerability profile regarding EPS vs olanzapine, superior vs risperidone.
+ To show superior safety / tolerability profile on prolactin compared to risperidone, comparable with olanzapine.
+ To show maintained effect (CGI) Seroquel (comparable to risperidone and olanzapine).
+ To obtain Quality of Life data for Seroquel.

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Primary Objective

To compare the safety / tolerability effect profile of quetiapine and olanzapine on glucose metabolism in schizophrenic patients.

Primary outcome variable.

Evaluating the change from baseline to 24 weeks, measured by Area Under the Curve (0-2h) of plasma glucose following 2h-Oral Glucose Tolerance Test (OGTT).

Secondary objectives (I)
Glucose metabolism

➢To compare the safety / tolerability profile of quetiapine and risperidone on glucose metabolism measured by change from baseline to week 24 in Area Under the Curve (0-2h) of plasma glucose following 2h - Oral Glucose Tolerance Test (OGTT).

➢To further compare quetiapine, olanzapine and risperidone safety / tolerability profile on glucose metabolism by evaluating:

Plasma fasting glucose and insulin.

Indexes of insulin sensitivity (ISI):

- AUC (0-2h) plasma values of insulin following OGTT
- ISI derived from OGTT according to Matsuda et al.
- Homeostasis model assessment (HOMA = fasting plasma insulin (mmol/L) x fasting plasma glucose (uU/mL)/22.5)

Incidence of patients with hyperglycemia.

Incidence of patients with impaired fasting glucose or impaired glucose tolerance.

Evaluation of explorative measures

- Hb A1C
- Plasma C-peptide level.

Secondary Objectives / Variables (II)

To compare the safety / tolerability profile of quetiapine, olanzapin and risperidone from baseline to week 24 on

- Weight, BMI and waist circumference
- Lipid profile – cholesterol, HDL, LDL, TG
- Efficacy (CGI)
- Prolactin level
- Extra Pyramidal Syndrome (SAS*, BARS**, anticholinergic medication)
- Adverse events, blood pressure, pulse rate, ECG
- Patient rated QoL (PETiT scale***)
- Compliance questionnaire (ROMI****)

** Simpson-Angus Scale; ** Barnes-Akathisia Scale;*

Personal Evaluation of Transitions in Treatment ; * Rating of Medical Influences Scale*

Study Design - Population

- Sample size calculation based on weight as no data is available on AUC and it's variance.
- 600 screened, 570 randomised, 285 completed.
- Randomisation will be stratified on BMI and age using IVRS.
- 5% drop-out is expected between screening and randomisation, 50% drop-out during the 24 weeks.

Inclusion.

- In- or outpatients with schizophrenia.
- Male or female, 18-65 years old.
- Requiring a change in treatment due to tolerability or insufficient efficacy.

Exclusion.

- Known diabetes or fasting plasma glucose $\geq$ 126 mg/dl.
- Previous use of atypicals (3 months) or other medications that might influence glucose metabolism.

Method for Primary Variable Oral Glucose Tolerance Test

- Patients to be 8-14h overnight fasted. No smoking allowed.
- Requires hospitalization.
- In the morning, a venous catheter is put in place for determination of baseline plasma fasting glucose and insulin concentrations.
- The patient swallows 75 gr of liquid glucose (250-300 ml).
- 4 blood samples over 2 hours will be drawn (30, 60, 90 and 120 minutes). Plasma glucose and insulin are analysed for calulation of AUC.
- Central laboratory doing the analysis: Covence

Investigational products

- Open-label products
- Crosstitration period for 5 days
- 23 weeks of treatment with flexible dose
- Titration package and all quetiapine packed by IPS
- Comparators – use of local commercial supplies

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Study timetable

Final protocol	Aug 15, 2003
Investigator Meetings	Dresden 19-21 Nov
	Montreaux 20-22 Jan
First patient First visit:	November 2003
Recruitment period:	12 months (Nov 2003 to Dec 2004)
Last patient Last visit :	July 2005.

Potential issues

- Setup of IVRS – time (delays?), cost.
- Comments from Ethics committees, Regulatory.
- Slow recruitment / feasibility?
  - Many patient already on atypicals.
  - Few patients suitable / willing to switch.
  - Hospitalization x 3 + OGTT procedure.
- Regulatory requests during the study time?
- Budget
  - 600 patients, extensive labs, comparator drugs, IVRS

Study acronym

- STAGE
  - **S**chizophrenia **T**rial to evaluate **A**typical antipsychotic **G**lucose **E**ffects
- SEAHORSE
  - **SE**roquel **AH**ead of **O**lanzapine and **R**isperidone in **S**af**E**ty
- FATFARM
  - **F**lexible dose **A**pproach **T**rial **F**or **A**typical **R**esponses to **M**etabolism
- POLARIS
  - quetia**P**ine **OLA**nzapine **RIS**peridone
- METEOR
  - **MET**abolism quetiapin**E** **O**lanzapine **R**isperidone
- EQUATOR-GM
  - **E**ffect of **Qu**etiapine, **A**nd **T**hat of **O**lanzapine and **R**isperidone on **G**lucos **M**etabolism?
- **McGORS** study (after the famous Scottish McGors clan).
  - **M**etabolic comparison of **G**lucose: **O**lanzapine, **R**isperidone and **S**eroqu
- SOLAR
  - **S**eroquel, **OL**anzapine, **R**isperdal

International Principal Investigator (not yet appointed)

- Suggestions from MCs
  - Dr Wolfgang Gaebel, Germany
  - Dr Robin Elmsley, South Africa
  - Dr Henrik Lublin, Denmark

Inclusion Criteria

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Exclusion Criteria

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Exclusion Criteria

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Exclusion criteria (III)

18.

Exclusion criteria (IV)

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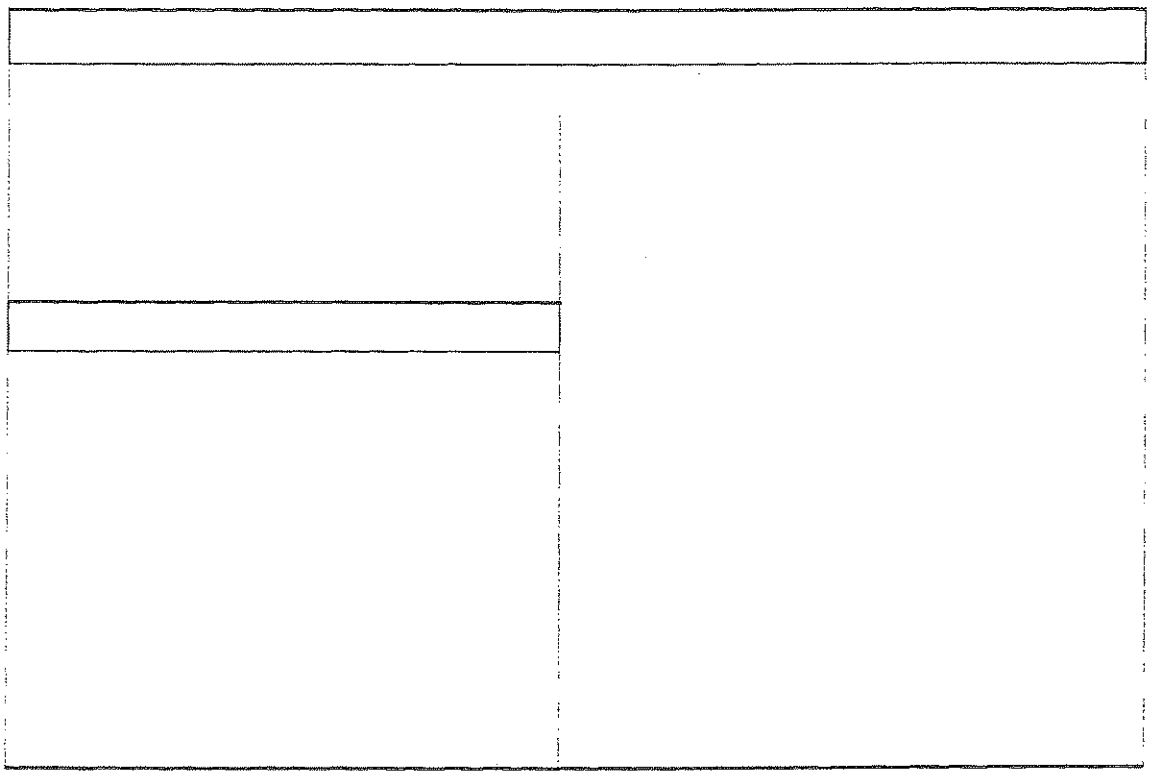
Laboratory variables at screening and final visit at week 24 or discontinuation



Laboratory analysis primary and secondary Variables

- Fasting plasma glucose — OGTT: baseline (0min), 30, 60, 90, 120 min
- Fasting plasma insulin — OGTT: baseline (0 min), 30, 60, 90, 120 min

- Lipid profile (TG, HDL, LDL, TC) in connection with OGTT baseline
- Hba1c in connection with OGTT baseline
- C-peptide in connection with OGTT baseline
- Prolactin in connection with OGTT baseline

All these variables are measured at randomisation, 12 weeks and 24 weeks.
AUC and indexes of insulin sensitivity calculated.

Statistical Methods (I) Populations for Analysis

Analysis sets based on 3 patient populations:

- Safety population including all randomised patients who were given study treatment classified according to the treatment they actually received.
- The Intention To Treat population (ITT) will include all randomised patients who were given study treatment, classified according to the treatment to which they were randomised.
- The Primary Analysis Population (PAP): all randomised patients who were given study treatment and who have baseline and week 24 assessments ($\pm$ 4 weeks)
- The per-protocol population (PP) excluding patients with significant protocol violations or deviations and non-compliants from PAP.

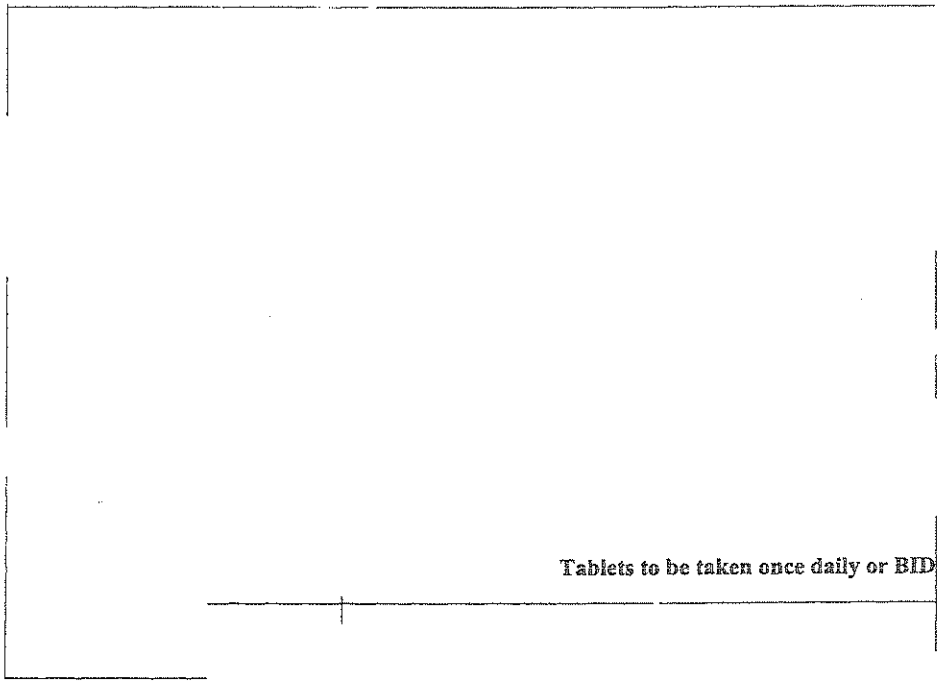
Statistical methods (II) Primary Analysis

- Analysis of covariance (ANCOVA): change from baseline in AUC plasma value of glucose following OGTT at week 24.
- Independent variables: baseline BMI group, age group, baseline AUC glucose measurement and treatment.
- Least square means, p-values and 95% CI.
- The contrast of primary interest: the quetiapine-treated group and the olanzapine-treated group.
- No p-values for the other two contrasts.
- Center not included in the model (too large number of centers).

Statistical methods (III) Determination of sample size

- No published data on the primary variable and its variance. Power calculation on change in weight since there is a fairly strong correlation between change in weight and change in plasma glucose levels.
- Based on the number of patients needed to find a difference of 3 kg in the mean change from baseline to week 24 between the quetiapine- and the olanzapine treated groups.
- 90% power for a 2-sided test, at the 5% alpha level, to demonstrate less weight gain with quetiapine compared to olanzapine.
- A total of 95 patients per treatment group (285 patients in total) with valid AUC (0-2 h) plasma glucose assessments following OGTT at baseline and at week 24.

Study Flowchart



Study Plan

- Insert Study plan from CSP