Clinical Trial Report Summary – Study 11286C

Title of Study
An exploratory study conducted as an add-on to clinical trial 11286, to evaluate the metabolic effect of up to 12 weeks treatment with sertindole and olanzapine in patients with schizophrenia

Study Centres
8 centres in China

Study Period
First patient first visit – 26 March 2007
Last patient last visit – 18 March 2008

Objectives
To evaluate the effects of sertindole and olanzapine on metabolic syndrome and its components in patients with schizophrenia, measured using the change from baseline by treatment and between treatments for each of the components of metabolic syndrome

Methodology
• Study 11286 was a randomised, double-blind, parallel-group, flexible-dose study evaluating the efficacy and safety of 12 weeks of treatment with sertindole or olanzapine in patients with schizophrenia in Asia. Study 11286 consisted of a 2- to 5-day antipsychotic-free run-in period, after which patients were randomised to 12 weeks of double-blind treatment with flexible doses of sertindole (12 to 20mg/day) or olanzapine (10 to 20mg/day). Patients randomised to the sertindole group were up-titrated over 16 days from 4 mg/day to 16 mg/day, after which the dose was flexible (12, 16, or 20mg/day) on the basis of response and tolerability as judged by the investigator. Patients randomised to the olanzapine group were up-titrated over 16 days from 10mg/day to 15mg/day, after which the dose was flexible (10, 15, or 20mg/day) on the basis of response and tolerability as judged by the investigator.
• Patients in China who participated in Study 11286 were asked to participate in this metabolic add-on study, Study 11286C.
• Metabolic data were collected at Weeks 6 and 12.

Number of Patients Planned and Analysed
• 250 patients were planned for enrolment: 125 in the sertindole group and 125 in the olanzapine group
• Patient disposition is tabulated below:

<table>
<thead>
<tr>
<th></th>
<th>SER</th>
<th>(%)</th>
<th>OLZ</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomised</td>
<td>124</td>
<td></td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Patients treated</td>
<td>122</td>
<td></td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Patients completed</td>
<td>89</td>
<td>(73)</td>
<td>99</td>
<td>(79)</td>
</tr>
<tr>
<td>Patients withdrawn</td>
<td>33</td>
<td>(27)</td>
<td>27</td>
<td>(21)</td>
</tr>
<tr>
<td>Primary reason for withdrawal:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adverse events (AEs)</td>
<td>18</td>
<td>(15)</td>
<td>7</td>
<td>(6 )</td>
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<tr>
<td>Lack of efficacy</td>
<td>5</td>
<td>(10)</td>
<td>10</td>
<td>(8 )</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>(8 )</td>
<td>10</td>
<td>(8 )</td>
</tr>
</tbody>
</table>

n = number of patients; % = percentage of patients within treatment group

Diagnosis and Main Selection Criteria
Patients with a primary diagnosis of schizophrenia according to DSM-IV-TR™ criteria (all subtypes except residual), who:
• signed the Informed Consent Form for Study 11286, and were eligible for participation in Study 11286, that is, fulfilled all inclusion criteria and did not meet any exclusion criteria
• signed the Informed Consent Form for Study 11286C
Investigational Product, Dose and Mode of Administration

Sertindole – 12 to 20mg/day; orally

Duration of Treatment
12-week double-blind treatment period, including a 16-day titration period

Reference Therapy, Dose and Mode of Administration

Olanzapine – 10 to 20mg/day; orally

Metabolic Assessments

- Weight/body mass index (BMI)
- Waist circumference
- Blood pressure
- Fasting serum lipid profile (triglycerides, total cholesterol, high-density lipoprotein [HDL]-cholesterol, low density lipoprotein [LDL]-cholesterol, and very low density lipoprotein [VLDL]-cholesterol)
- Fasting plasma glucose

Safety Assessments

Metabolic AEs

Statistical Methodology

- The following analysis sets were used:
  - all-patients-randomised set (APRS) – all patients randomised to add-on Study 11286C
  - all-patients-treated set (APTS) – all randomised patients who took at least one dose of investigational medicinal product (IMP)
  - per-protocol set (PPS) – all patients in the APTS who took IMP up until the Week 6 visit or later, who had an assessment at the Week 6 visit or later of each of the metabolic syndrome variables (that is, sufficient assessments to be able to determine the presence/absence of metabolic syndrome in accordance with the International Diabetes Federation [IDF] definition), and who did not take any concomitant medication at baseline or up to the Week 6 visit that could interfere with the assessment of metabolic variables (that is, no medications to treat lipid, glucose, or weight abnormalities, or hypertension)
  - per-protocol set waist circumference (PPSwaist) – all patients in the APTS who took IMP up until the Week 6 visit, who had at least one assessment of waist circumference at the Week 6 visit or later, and who did not take any medication to treat weight abnormalities at baseline or up to the Week 6 visit. The PPSwaist was also used for the analysis and reporting of weight and BMI.
  - per-protocol set blood pressure (PPSbp) – all patients in the APTS who took IMP up until the Week 6 visit or later, who had at least one assessment of blood pressure at the Week 6 visit or later, and who did not take any treatment for hypertension at baseline or up to the Week 6 visit
  - per-protocol set lipid (PPSlipid) – all patients in the APTS who took IMP up until the Week 6 visit or later, who had at least one fasting assessment of the lipid profile (triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol) at the Week 6 visit or later, and who did not take any treatment for lipid abnormalities at baseline or up to the Week 6 visit
  - per-protocol set glucose (PPSglucose) – all patients in the APTS who took IMP up until the Week 6 visit or later, who had at least one fasting plasma glucose assessment at the Week 6 visit or later, and who did not take any treatment for glucose abnormalities at baseline or up to the Week 6 visit
- The prevalence of patients in the PPS who met the definition of metabolic syndrome (as defined by the IDF) was summarised by visit and last assessment.
- For each of the five individual metabolic syndrome variables, the prevalence of patients who met each criterion was summarised by visit and last assessment for the respective per-protocol populations (PPSwaist, PPSbp, PPSlipid, PPSglucose).
- Absolute values and changes from baseline to each assessment in the metabolic variables (weight, BMI, waist circumference, blood pressure, fasting lipid profile, and fasting plasma glucose) were summarised for the respective per-protocol populations.
Statistical Methodology (continued)

- The mean change from baseline to Week 6, Week 12, and to last assessment in each of the metabolic variables was compared between treatment groups using analysis of covariance (ANCOVA) on the respective per-protocol populations, based on observed cases (OC). Estimated differences in mean changes from baseline between treatment groups (sertindole minus olanzapine) are presented with 95% confidence intervals (CIs).
- The incidences of metabolic AEs were summarised and tabulated by primary system organ class (SOC) and preferred term for the APTS.

Demography of Study Population

- Slightly more than half of the patients were men (52% in the sertindole group and 54% in the olanzapine group). The mean age at baseline was the same in the sertindole group (32 years, ranging from 18 to 58 years) and in the olanzapine group (32 years, ranging from 18 to 60 years). All the patients were Asian.
- At baseline, the mean weight (61 kg in the sertindole group and 62 kg in the olanzapine group), height (166 cm in both treatment groups), BMI (22 kg/m² in both treatment groups), and waist circumference (81 cm in both treatment groups) were similar in the two treatment groups.

Metabolic Results

- In both treatment groups, the prevalence of metabolic syndrome increased from baseline to Weeks 6 and 12. At last assessment, the prevalence of metabolic syndrome was 19% in the sertindole group and 26% in the olanzapine group; the difference was not statistically significant.
- For the individual metabolic syndrome criteria:
  - In both treatment groups, the prevalences of central obesity and elevated triglycerides were higher at last assessment than at baseline; the prevalence of elevated triglycerides increased more in the olanzapine group than in the sertindole group.
  - The prevalence of elevated blood pressure was lower at last assessment than at baseline in the sertindole group, but approximately the same at baseline and at last assessment in the olanzapine group.
  - The prevalence of low HDL-cholesterol was lower at last assessment than at baseline in the sertindole group, but higher at last assessment than at baseline in the olanzapine group.
  - The prevalence of elevated fasting glucose was approximately the same at last assessment and at baseline in the sertindole group, but higher at last assessment than at baseline in the olanzapine group.
- In both treatment groups, the mean weight, BMI, and waist circumference increased with time on IMP. At each assessment, there were greater absolute increases from baseline in weight, BMI, and waist circumference in the olanzapine group than in the sertindole group; for weight and BMI, these differences were statistically significant at each assessment and for waist circumference at Week 6.
- The proportion of patients who had potentially clinically significant (PCS) weight increases at least once during the study was higher in the olanzapine group than in the sertindole group (47% versus 36%). The proportion of patients who had PCS weight decreases was comparable between the sertindole group and the olanzapine group (1% versus 3%).
- In both treatment groups, the mean changes from baseline in blood pressure and sitting pulse rate were small and not clinically relevant. There were no statistically significant differences between the treatment groups in mean changes from baseline in systolic blood pressure, diastolic blood pressure, or sitting pulse rate, at any of the assessments.
- The proportion of patients who had PCS low systolic blood pressure at least once during the study was higher in the olanzapine group than in the sertindole group (6% versus 1%). There were no other PCS changes in blood pressure or sitting pulse rate during the study.
**Metabolic Results (continued)**

- In both treatment groups, the mean triglycerides, total cholesterol, LDL-cholesterol, VLDL-cholesterol, and plasma glucose increased with time on IMP. For total cholesterol, LDL-cholesterol, VLDL-cholesterol, and plasma glucose, the increases were similar in both treatment groups, whereas for triglycerides, the increase was greater in the olanzapine group than in the sertindole group (the only statistically significant differences between the treatment groups were in triglycerides and VLDL-cholesterol at Week 6). The mean HDL-cholesterol increased from baseline to last assessment in the sertindole group and decreased in the olanzapine group (the difference between the treatment groups was statistically significant at each assessment).

- The proportion of patients who had post-baseline PCS high total cholesterol values in the sertindole group and in the olanzapine group (9% versus 10%, respectively) and the proportion of patients who had post-baseline PCS high LDL-cholesterol values (7% versus 6%, respectively) were comparable between the treatment groups. The proportion of patients who had PCS low HDL-cholesterol values was higher in the olanzapine group (33%) than in the sertindole group (26%) and the proportion of patients who had PCS high triglyceride values was also higher in the olanzapine group (41%) than in the sertindole group (30%).

- In each treatment group, approximately 4% of the patients had PCS high fasting plasma glucose values.

**Safety Results**

- The proportion of patients with metabolic AEs was statistically significantly higher in the olanzapine group than in the sertindole group (48% versus 37%). The only metabolic AE reported in >5% of patients in either treatment group was weight increased (sertindole: 30%; olanzapine: 44%).

- None of the serious adverse events (SAEs) reported in Study 11286 were metabolic AEs.

- None of the AEs leading to withdrawal in Study 11286 were metabolic AEs.

**Publications**

None (as of the date of this report)

This study was conducted in compliance with the principles of *Good Clinical Practice*. 