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# REPORT SYNOPSIS

| Name of Sponsor/Company: Daiichi Sankyo Pharma Development | Individual Study Table Referring to Part of the Dossier Volume: Page: | *(For National Authority Use Only)* |
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| Name of Test Product: Rivoglitazone HCl (CS-011) | | |
| Name of Active Ingredient: Rivoglitazone HCl (CS-011) | | |

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| Title of Study: | A Randomized, Double-blind, Placebo and Active Comparator-controlled, Parallel-group Study of the Efficacy and Safety of Rivoglitazone as Monotherapy Treatment of Type 2 Diabetes Mellitus With an Optional 26-Week Active Comparator-controlled Extension Period |
| Phase of Development: | 3 |
| Study Period: | First subject first visit date: 23 Apr 2007<br>Last subject last follow-up date: 12 Feb 2009 |
| Investigators: | For a complete list of investigators, see Appendix 16.1.4. |
| Study Centers: | 254 study centers: Africa, 20; Asia, 35; Europe, 83; North America, 97; and South America, 19 |
| Publication (reference): | None |
| Study Objectives/ Hypothesis: | The hypothesis for the study was that rivoglitazone monotherapy for type 2 diabetes mellitus will be safe, well tolerated, and demonstrate non-inferior efficacy compared with pioglitazone.<br>The primary objective of the study was to compare the effects on mean change from baseline in hemoglobin $A_{1c}$ ($HbA_{1c}$) for rivoglitazone versus pioglitazone administered as monotherapy for treatment of type 2 diabetes over a 26-week treatment period.<br>The secondary objectives of the study were the following:<br>• To demonstrate the safety and tolerability of rivoglitazone as a treatment for type 2 diabetes mellitus;<br>• To demonstrate the lowering of fasting plasma glucose (FPG) with rivoglitazone versus placebo over 26 weeks in type 2 diabetics; |

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- To assess the effects of each rivoglitazone dose on the percentage of responders as defined by:
  - Subjects experiencing a decrease of ≥0.7% in $HbA_{1c}$;
  - Subjects achieving an $HbA_{1c}$ goal of <7.0%;
  - Subjects achieving an $HbA_{1c}$ goal of <6.5%;
- To assess the effect of rivoglitazone versus placebo on homeostasis model assessment (HOMA) index of insulin resistance and β-cell function in type 2 diabetics;
- To assess the effects of rivoglitazone on change from baseline and percent change from baseline in plasma lipids (including total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]), and on other parameters including adiponectin, high-sensitivity C-reactive protein (hsCRP), insulin, apolipoprotein (Apo) A-I, and Apo B; and
- To compare effects of rivoglitazone versus pioglitazone on secondary measures of glycemic control and lipid parameters.

The objective of the extension period was to demonstrate the long-term efficacy and safety of rivoglitazone as a treatment for type 2 diabetes mellitus. No formal hypothesis testing was performed on efficacy parameters during the extension period.

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Study Design/Methodology: This study was planned as a multicenter, randomized, double-blind, placebo and active comparator-controlled, parallel-group study in subjects with type 2 diabetes mellitus sub-optimally controlled with or without prior anti-hyperglycemic (non-thiazolidinedione [TZD]) monotherapy.

Subsequent to screening, the study had 4 periods as follows:

- Period A: 2-week stabilization/washout and single-blind, placebo run-in period;
- Period B: 26-week, double-blind, randomized treatment period;
- Period C: 2-week safety follow-up period for subjects not participating in Period D (the final safety visit occurred approximately 2 weeks after the last dose of double-blind medication); and
- Period D: Optional 26-week double-blind extension period (subjects could participate in up to three 26-week extension cycles, for a total of 78 weeks).

During the 2-week, single-blind, placebo run-in period (Period A), subjects were to discontinue any previous therapy with oral anti-hyperglycemic agents and were to self-administer single-blind, double-dummy, placebo medication consisting of over-encapsulated pioglitazone-matching placebo tablets and rivoglitazone-matching placebo tablets once daily.

During the double-blind period (Period B), subjects were randomized to receive 1 of the following 4 treatments:

- Placebo once daily,
- Rivoglitazone 1.0 mg once daily,
- Rivoglitazone 1.5 mg once daily, or

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- Pioglitazone 45 mg once daily.

Subjects were randomized at a ratio of 2:4:11:11, corresponding to the above groups, using a block size of 28.

During the 2-week, safety follow-up period (Period C), subjects who discontinued or completed the base study but did not enroll in the extension period had a post-study follow-up visit approximately 14 days after the last visit of Period B.

Subjects who completed the Week 26 visit without requirement for rescue medication were eligible to participate in Period D, an optional double-blind extension period consisting of up to three 26-week cycles. Subjects who completed the first 26 weeks (cycle 1) were potentially eligible to participate in a second 26-week cycle (cycle 2). A third 26-week cycle was planned; however for administrative reasons, the extension was terminated early by DSPD after the last subject in the base study completed the final treatment visit of the base study.

Subjects who were randomized to placebo in the base study were reassigned to receive pioglitazone 45 mg once daily in the extension period. Subjects randomized to base study treatment with rivoglitazone 1.0 mg, rivoglitazone 1.5 mg, or pioglitazone 45 mg continued on the same therapy during the extension period.

An independent Clinical Events Committee (CEC) adjudicated potential cardiovascular events that occurred during the course of the study. The CEC was provided a review of and adjudication for all potential clinical events according to the following established event definitions: death, myocardial infarction (including silent myocardial infarction), arterial revascularization (coronary, carotid, or peripheral), unstable angina requiring hospitalization, stroke, congestive heart failure (new onset or worsening congestive heart failure), and peripheral arterial event.

An independent Data Monitoring Committee (DMC) was utilized to assess study data and monitor subject safety

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| | throughout the study. Safety data was reviewed, ublinded where needed, on a twice yearly basis. The DMC was charged with making appropriate recommendations to ensure the highest quality of Good Clinical Practice while ensuring the safety of study participants. |
| Duration of Treatment for Individual Subject: | The total duration of the base study was 30 weeks, which included a 2-week stabilization/washout and single-blind, placebo run-in period, a 26-week treatment period, and a 2-week, post-treatment follow-up period.<br><br>The maximum planned duration of the extension period was 78 weeks (three 26-week extension cycles). The actual maximum duration of the extension period was 52 weeks, for a maximum treatment duration (base plus extension) of approximately 78 weeks. |
| Number of Subjects: | Planned: 1820 subjects<br><br>Screened: 5113 subjects<br><br>Randomized: 1912 subjects<br><br>Completed Base Study: 1482 subjects<br><br>Discontinued Base Study: 430 subjects<br><br>Entered Extension Period: 488 subjects<br><br>Completed cycle 1 of Extension: 152 subjects<br><br>Completed cycle 2 of Extension: 10 subjects<br><br>No subject entered cycle 3 of the Extension.<br><br>Discontinued Extension Period: 390 subjects<br><br>Note: The majority (>70%) of the subjects who did not complete the extension period discontinued due to the early termination of the extension by DSPD. |
| Diagnosis and Main Criteria for Study Entry: | The study population included subjects diagnosed with type 2 diabetes mellitus who were sub-optimally controlled with diet and exercise alone or with prior treatment using a single anti-hyperglycemic (non-TZD) agent. |

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Investigational Product and Comparator Information:

1. Dosage Form: rivoglitazone 1.0 mg
   Route of Administration: orally, once daily
   Lot No.: [redacted]
   Packaging Information: blister cards
2. Dosage Form: rivoglitazone 1.5 mg
   Route of Administration: orally, once daily
   Lot No.: [redacted]
   Packaging Information: blister cards
3. Dosage Form: rivoglitazone-matching placebo tablet
   Route of Administration: orally, once daily
   Lot No.: [redacted]
   Packaging Information: blister cards
4. Dosage Form: pioglitazone 45 mg over-encapsulated tablets
   Route of Administration: orally, once daily
   Lot No.: [redacted]
   Packaging Information: blister cards
5. Dosage Form: pioglitazone-matching placebo over-encapsulated tablets
   Route of Administration: orally, once daily
   Lot No.: [redacted]
   Packaging Information: blister cards

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the change in $HbA_{1c}$ from baseline to Week 26, and the secondary efficacy variable was the change in FPG from baseline to Week 26.

Additional efficacy variables included change in $HbA_{1c}$ and FPG over time; effects of each rivoglitazone dose on the percentage of responders; percent change in lipid parameters, Apo A-I, and Apo B at Weeks 12 and 26; change in HOMA indices, TC/HDL-C ratio, Apo B/Apo A-I ratio, adiponectin, fasting insulin, and C-peptide at Weeks 12 and 26; and changes in other biomarkers from baseline to Week 26.

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Changes in the above-listed efficacy variables were also summarized from baseline to the end of treatment during the extension period.

Safety:

Safety assessments included adverse events, clinical laboratory parameters (including serum chemistry, hematology, and urinalysis), vital signs, physical examinations, and 12-lead electrocardiogram (ECG) results.

Statistical Methods:

The primary analysis in the base study was stepwise comparison of non-inferiority with a subsequent test for superiority for each descending dose of rivoglitazone versus pioglitazone 45 mg, and superiority assessment for each descending dose of rivoglitazone versus placebo. An assessment of non-inferiority for rivoglitazone 1.5 mg versus pioglitazone 45 mg was evaluated first, and if significant, a superiority analysis for rivoglitazone 1.5 mg versus pioglitazone 45 mg was performed. Next, if superiority was shown for rivoglitazone 1.5 mg versus pioglitazone 45 mg then non-inferiority analysis for rivoglitazone 1.0 mg versus pioglitazone 45 mg, as well as superiority analysis for rivoglitazone 1.5 mg versus placebo, was tested. Lastly, superiority was evaluated for both rivoglitazone 1.0 mg versus pioglitazone 45 mg and rivoglitazone 1.0 mg versus placebo conditional on observing non-inferiority for rivoglitazone 1.0 mg versus pioglitazone 45 mg and superiority for rivoglitazone 1.5 mg versus placebo, respectively. Testing hypotheses in this pre-specified tree-structured hierarchically ordered manner preserved the family-wise type I error rate at 0.05. Multiplicity-adjusted p-values were computed based on the Bonferroni test using the decision matrix approach.

The efficacy analyses were adjusted for the effects of stratification factors, background diabetes treatment status, and global regions using the generalized Cochran-Mantel-Haenszel method for categorical variables and Analysis of Covariance method for continuous variables.

No formal hypothesis testing was performed during the extension period on the efficacy variables.

Summary:

Efficacy Results:

The largest least-squares (LS) mean reduction in $HbA_{1c}$ from baseline to Week 26 with last observation carried forward (LOCF) was observed in the rivoglitazone

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1.5 mg group (0.7%), followed by the pioglitazone 45 mg group (0.6%) and the rivoglitazone 1.0 mg group (0.4%). The placebo group had an LS mean increase in $HbA_{1c}$ of 0.2% from baseline to Week 26 with LOCF.

Rivoglitazone 1.5 mg was both statistically non-inferior to pioglitazone 45 mg ($p<0.0001$) and statistically significantly superior to pioglitazone 45 mg ($p=0.0339$).

The effect of rivoglitazone 1.0 mg on $HbA_{1c}$ was statistically non-inferior to pioglitazone 45 mg ($p=0.0339$). Pioglitazone 45 mg was statistically significantly superior to rivoglitazone 1.0 mg ($p=0.0339$). The effect of both doses of rivoglitazone on $HbA_{1c}$ was clinically and statistically significantly superior to placebo.

During the base study, changes in FPG among the active treatment groups were consistent with the results observed in $HbA_{1c}$.

Treatment with rivoglitazone 1.0 mg, rivoglitazone 1.5 mg, and pioglitazone 45 mg reduced LS mean FPG levels from baseline to Week 26 (with LOCF) by 25.3 mg/dL, 34.3 mg/dL, and 31.0 mg/dL, respectively. The treatment comparisons of LS mean change in FPG between the rivoglitazone 1.5 mg group and the pioglitazone 45 mg group were statistically significant at all time points except for Week 26 (-3.3 mg/dL, $p=0.0505$). The treatment comparison between the rivoglitazone 1.0 mg group and the pioglitazone 45 mg group was statistically significant at Week 26 (5.7 mg/dL, $p=0.0126$).

Analysis of $HbA_{1c}$ categorical response was consistent with the results observed for mean change in $HbA_{1c}$. The rivoglitazone 1.5 mg group had the largest percentage of subjects with reduction in $HbA_{1c}$ $\geq$0.7% (46.5%) followed by the pioglitazone 45 mg group (41.8%) and the rivoglitazone 1.0 mg group (38.7%). The rivoglitazone 1.5 mg group had the largest percentage of subjects with $HbA_{1c}$ <7.0% at endpoint (49.2%) followed by the pioglitazone 45 mg group (46.4%) and the rivoglitazone 1.0 mg group (44.4%). The rivoglitazone 1.5 mg group had the largest percentage of subjects with $HbA_{1c}$ <6.5% at endpoint (21.0%) followed by the pioglitazone 45 mg group (18.1%) and the rivoglitazone 1.0 mg group (13.5%).

In general, analysis of the other efficacy parameters showed a numerically more favorable response in the rivoglitazone 1.5 mg group, followed by the pioglitazone 45 mg group and the rivoglitazone 1.0 mg group, in descending order of positive efficacy response.

The key efficacy results observed from baseline to Week 26 of the base study were, in general, maintained throughout the extension period.

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Safety Results:

During the base study, 1065 (56.5%) subjects had a treatment-emergent adverse event (TEAE): 154 (57.2%) subjects in the rivoglitazone 1.0 mg group, 434 (58.6%) subjects in the rivoglitazone 1.5 mg group, 408 (55.2%) subjects in the pioglitazone 45 mg group, and 69 (50.4%) subjects in the placebo group. Overall, the most frequently reported TEAEs were peripheral edema (6.9%), nasopharyngitis (5.3%), and urinary tract infection (4.7%).

During the base study, 343 (18.2%) subjects had a TEAE that was considered by the investigators to be related to study medication: 50 (18.6%) subjects in the rivoglitazone 1.0 mg group, 144 (19.4%) subjects in the rivoglitazone 1.5 mg group, 134 (18.1%) subjects in the pioglitazone 45 mg group, and 15 (10.9%) subjects in the placebo group. Overall, the most frequently reported drug-related TEAEs were peripheral edema (5.7%), increased weight (2.1%), and pitting edema (1.5%).

Two subjects died during the base study (myocardial infarction and pancreatic cancer). The SAEs for these subjects were considered unrelated to study medication. Two subjects died during the extension period: 1 subject died from unknown causes, which was considered possibly related to study medication, and 1 subject died from respiratory failure, which was considered unlikely related to study medication.

Sixty-three (3.3%) subjects had an SAE during the base study: 10 (3.7%) subjects in the rivoglitazone 1.0 mg group, 22 (3.0%) subjects in the rivoglitazone 1.5 mg group, 28 (3.8%) subjects in the pioglitazone 45 mg group, and 3 (2.2%) subjects in the placebo group. Seven (0.4%) subjects had an SAE that was considered related to study medication: 4 (0.5%) subjects in the rivoglitazone 1.5 mg group (1 subject with renal failure, 1 subject with atrioventricular block and cardiac failure, 1 subject with congestive cardiac failure, and 1 subject with spinal compression fracture), 2 (0.3%) subjects in the pioglitazone 45 mg group (1 subject with congestive cardiac failure and 1 subject with a suicide attempt), and 1 (0.7%) subject in the placebo group (hand fracture).

The incidence of SAEs during the extension period was low and similar among treatment groups.

Seventeen subjects had an adjudicated cardiovascular event during the base study: 11 subjects had an event of congestive heart failure, 3 subjects had an event of arterial revascularization, 3 subjects had an event of stroke, 2 subjects had an event of unstable angina, 1 subject had an event of myocardial infarction, and 1 subject died. The incidence of congestive heart failure was numerically higher in the rivoglitazone groups compared to the pioglitazone 45 mg group. Four subjects had an adjudicated

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cardiovascular event during the extension period. Of these 4 subjects, 2 subjects died, 1 subject had an event of arterial revascularization, and 1 subject had an event of congestive heart failure.

During the base study, 73 (3.9%) subjects discontinued study medication due to a TEAE: 10 (3.7%) subjects in the rivoglitazone 1.0 mg group, 30 (4.0%) subjects in the rivoglitazone 1.5 mg group, 30 (4.1%) subjects in the pioglitazone 45 mg group, and 3 (2.2%) subjects in the placebo group. For 56 of the 73 subjects, the TEAE that led to discontinuation was considered related to study medication: 7 (2.6%) subjects in the rivoglitazone 1.0 mg group, 27 (3.6%) subjects in the rivoglitazone 1.5 mg group, 20 (2.7%) subjects in the pioglitazone 45 mg group, and 2 (1.5%) subjects in the placebo group. The most frequently reported drug-related TEAE that led to discontinuation was peripheral edema (12 subjects).

The incidence of study medication discontinuations during the extension period due to a TEAE was low and similar for the treatment groups.

The incidence of edema/fluid retention was higher in the active treatment groups than in the placebo group. The increased incidence of edema resulted in a hemodilution effect, which was manifested in numerically larger decreases in hematocrit, hemoglobin, red blood cell count, and white blood cell count compared with the placebo group. The hemodilution effect also resulted in numerically larger reductions in alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase among the active treatment groups compared with the placebo group. The increased edema among the active treatment groups coincided with increases in weight, body mass index, and waist and hip circumference compared with the placebo group.

No clinically meaningful trends in other safety laboratory parameters or ECG parameters were observed across treatment groups.

Conclusions:

On the basis of these results, rivoglitazone as monotherapy appears to be safe and efficacious for the treatment of type 2 diabetes mellitus in patients who are sub-optimally controlled with diet and exercise with or without prior treatment with a single anti-hyperglycemic (non-TZD) agent.

- Treatment with rivoglitazone 1.5 mg resulted in a larger mean reduction in $HbA_{1c}$ than pioglitazone 45 mg, whereas the reduction in $HbA_{1c}$ following treatment with rivoglitazone 1.0 mg was less than that for pioglitazone 45 mg.

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- The effect of rivoglitazone 1.5 mg in terms of reducing $HbA_{1c}$ was both statistically non-inferior and significantly superior to the effect of pioglitazone 45 mg.
- Analysis of $HbA_{1c}$ categorical response was consistent with the results observed with change in $HbA_{1c}$ for the active treatment groups.
- Treatment with rivoglitazone 1.5 mg resulted in the largest mean reductions in FPG, followed by treatment with pioglitazone 45 mg, then treatment with rivoglitazone 1.0 mg.

No new TZD-associated safety issues were identified during the study.

- The overall incidences of TEAEs, SAEs, and discontinuations were similar among active treatment groups.
- Known side effects of TZDs including edema, fluid retention, weight gain, and hemodilution occurred with similar frequency among active treatment groups and with lower frequency in the placebo group.
- There were no unexpected, clinically important differences between the treatment groups with respect to changes in safety laboratory parameters, vital signs, or physical findings.

Date of the Report: 06 Nov 2009