The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

2.0 SYNOPSIS

Title of Study:

A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate Weekly Treatment with SYR-472 in Subjects with Type 2 Diabetes

Name of Sponsor:

Takeda Global Research & Development Center, Inc.
Takeda Global Research & Development Center (Europe), Ltd.

Name of Active Ingredient:

SYR-472

Name of Finished Product:

SYR-472

Investigators:	**Study Sites:**
Lead Investigator: Text redacted to protect personally identifiable All participating investigators are listed in Appendix 16.1.4.	Lead site: Compass Research Orlando, Florida 90 total sites in 12 countries (see Appendix 16.1.4).).

Publication (reference):

None

Study Period (years):	**Phase of Development:**
21 March 2007 to 12 March 2008	Phase 2

OBJECTIVES

Primary:

The primary objective of the study was to evaluate the efficacy of SYR-472 treatment on glycosylated hemoglobin (HbA1c) change from Baseline in subjects with type 2 diabetes mellitus (T2DM) who had not previously achieved adequate glycemic control with either lifestyle modification (diet/exercise) or metformin oral antidiabetic monotherapy.

Secondary:

The secondary objectives of this study were to evaluate the treatment effects of SYR-472 on other parameters of glycemic control, pancreatic function, and lipid metabolism, as well as the safety/tolerability of the drug. A sparse sampling approach was used to determine SYR-472 plasma concentration pharmacokinetics and the percentage of inhibition of dipeptidyl peptidase-4 (DPP-4) activity pharmacodynamics.

METHODOLOGY

This was a phase 2, double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to evaluate the efficacy and safety of 4 dose levels of SYR-472 versus placebo. Subjects were men and women; 18 to 80 years of age, inclusive; with T2DM who were experiencing inadequate glycemic control with either lifestyle modification (diet/exercise) or metformin oral antidiabetic monotherapy; and who were receiving no current antidiabetic therapy other than metformin or lifestyle modification.

The study included a Screening Period of up to 2 weeks, a 4-week Run-in/Stabilization Period, a 12-week Treatment Period followed by an End-of-Treatment visit, and a 2-week Follow-up Period.

During the Run-in/Stabilization Period, eligible subjects continued with their current treatment with either lifestyle modification or oral metformin monotherapy. Compliance with the metformin regimen during the Run-in/Stabilization Period was documented by a subject diary. Subjects who were less than 75% compliant during the Run-in/Stabilization Period were not randomly assigned to treatment.

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At the conclusion of the Run-in/Stabilization Period, subjects were randomly assigned to 1 of 5 treatment groups in a 1:1:1:1:1 ratio as follows: placebo, 25 mg SYR-472, 50 mg SYR-472, 100 mg SYR-472, or 200 mg SYR-472. Subjects were stratified at randomization using the following stratification factors: 1) HbA1c at Week -1 (HbA1c <8.0% versus ≥8.0%), 2) geographic region, and 3) Baseline antidiabetic medication usage (lifestyle modification or metformin oral monotherapy).

Number of Subjects:

Planned: Approximately 300 subjects (60 per treatment group).

Analyzed: Randomized-369 subjects; Full Analysis Set (FAS)-358 subjects; Safety Set-368 subjects.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been diagnosed with T2DM; aged 18 to 80 years, inclusive; able to comprehend and willing to sign an informed consent form and comply with study procedures; had received no current antidiabetic therapy except lifestyle modification or had received metformin monotherapy for at least 8 weeks before Screening and maintained a stable daily dose of metformin for at least 12 weeks before randomization; if subject had been receiving metformin monotherapy at randomization they must have been at least 75% compliant with regiment during Run-in/Stabilization Period; had received no other treatment with antidiabetic agents (other than metformin) within 8 weeks of Screening; had an HbA1c concentration between 7.0% and 10.0% at Screening; had a body mass index between 23 and 45 kg/m^2; had a fasting C-peptide concentration of 0.8 ng/mL (0.26 nmol/L) or greater; and had a fasting plasma glucose concentration less than 275 mg/dL (<15.27 mmol/L) at Screening and at the Week -1 visit. Additional inclusion criteria included, but were not limited to protocol-specified ranges for blood pressure, hemoglobin, alanine aminotransferase, serum creatinine, urine albumin/creatinine ratio, and thyroid stimulating hormone measurements. Subjects were to be willing and able to self-monitor blood glucose concentrations with a home glucose monitor.

Test Product and Mode of Administration/Lot Number:

	Lot Number
SYR-472, 12.5 mg, orally administered tablet	Z6433011
SYR-472, 25 mg, orally administered tablet	Z6434011

Duration of Treatment:

12 weeks

Reference Therapy, Dose and Mode of Administration, Lot Number:

	Lot Number
Placebo for SYR-472, orally administered matching tablet	Z6431011

Criteria for Evaluation:

The primary efficacy endpoint was the change from Baseline (Day 1) in HbA1c at Week 12.

The secondary efficacy variables were assessment of glycemic control (change from Baseline in HbA1c level, change from Baseline in fasting plasma glucose, change from Baseline in 1,5-anhydroglucitol, incidence of marked hyperglycemia, and incidence of rescue); assessment of pancreatic function (change from Baseline in proinsulin, insulin, proinsulin/insulin ratio, C-peptide, homeostasis model assessment of insulin resistance [HOMA-IR], and homeostasis model of beta-cell function [HOMA-BCF]); incidences of HbA1c of ≤6.5% and ≤7.0% at Week 12; and change from Baseline in body weight.

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Safety:

Safety variables were adverse events (AEs), clinical laboratory test results (hematology, serum chemistry, and urinalysis); vital sign measurements (systolic and diastolic blood pressure, pulse rate); physical examination findings (including a clinical examination of skin and digits); 12-lead electrocardiogram tracings; and the incidence of hypoglycemia (blood glucose <60 mg/dL [<3.33 mmol/L] in the presence of symptoms or blood glucose <50 mg/dL [<2.78 mmol/L] regardless of symptoms).

Statistical Methods:

The analysis of the primary efficacy variable was performed for the FAS using analysis of covariance (ANCOVA) with last observation carried forward values. An analysis with observed values was also performed. The primary model included study treatment, geographic region, and antidiabetic medication usage as class effects, and Baseline HbA1c as a continuous covariate. Parameters in the ANCOVA models were estimated using SAS PROC MIXED using only fixed effects options. Least squares mean (LS mean) differences were computed between each active dose and placebo. Corresponding 95% confidence intervals (CIs) and p-values for treatment group comparisons based on the t-distribution were presented. Treatment effect LS means and standard errors were also summarized.

All secondary continuous variables were analyzed at each visit using the primary model as specified for the analysis of HbA1c, but with the corresponding Baseline value modeled as a covariate (in place of Baseline HbA1c). The incidence variables (clinical response variables, hyperglycemia incidence, rescue incidence) were summarized by frequency and percentage for each treatment group, and treatment comparisons were performed using nonparametric, covariance-adjusted, extended Mantel-Haenszel tests. As a supportive analysis, odds ratios and associated 95% confidence intervals obtained from a logistic regression model with effects for treatment, geographic region Baseline antidiabetic medication usage, and Baseline HbA1c were used to compare treatments.

SUMMARY OF RESULTS

Efficacy Results:

Treatment with SYR-472 resulted in mean decreases from Baseline in HbA1c compared with placebo after 12 weeks of treatment in subjects who were experiencing inadequate glycemic control with lifestyle modification or metformin. The LS mean differences from placebo in HbA1c change from Baseline were -0.36%, -0.35%, -0.50 and -0.50% for the 25 mg SYR-472, 50 mg SYR-472, 100 mg SYR-472, and 200 mg SYR-472 groups, respectively ($P<0.001$). Dose-dependent reductions in mean HbA1c from Baseline were apparent for the 2 highest doses of SYR-472 (100 mg and 200 mg) compared with 50 mg and 25 mg at the Week 8 and Week 12 visits. Mean HbA1c values at Baseline were similar for all of the treatment groups. For the subjects who received lifestyle modification at Baseline, the treatment effect differences compared with placebo were statistically significant for the SYR-472 doses of 25 mg, 50 mg, and 100 mg SYR-472 dose groups. For the subjects who were receiving stable metformin at Baseline, the treatment effect differences compared with placebo were statistically significant for all of the SYR-472 dose groups. The placebo-corrected treatment effects observed in the subgroups as analyzed by Baseline antidiabetic medication usage were similar to the primary analysis.

In other parameters of glycemic control, statistically significant ($P<0.025$) decreases in the LS mean changes from Baseline in fasting plasma glucose at Week 12 were observed in the 25, 100, and 200 mg SYR-472 dose groups compared with the placebo group. Significant ($P\leq0.002$) increases from Baseline in 1,5-anhydroglucitol levels were also observed in all active treatment groups when compared with placebo at Week 12.

Clinical response as assessed by the percentage of subjects who achieved HbA1c values ≤6.5% and ≤7.0% was significantly ($P\leq0.007$) higher in the 3 highest SYR-472 dose groups (50, 100, and 200 mg) at Week 12 compared with the placebo group. The increase in the percentage of subjects achieving HbA1c levels at the goal of ≤7% at Week 12 appeared to be dose dependent. A significantly ($P\leq0.029$) higher percentage of subjects in the 50 mg and 100 mg SYR-472 dose groups achieved HbA1c levels of ≤6.5% at Week 12 compared with the placebo group.

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The incidence of marked hyperglycemia (defined as a fasting plasma glucose ≥200 mg/dL) was lower in the 100 mg and 200 mg SYR-472 dose groups but the difference was not statistically significant compared with placebo. Overall, 6 subjects required hyperglycemic rescue. Three of the 6 rescued subjects were in the placebo group, one in the 25 mg SYR-472 group and two in the 50 mg SYR-472 group. The mean and median time to rescue was lower in the placebo group compared with the SYR-472 groups but the difference was not statistically significant.

The mean change in HOMA-BCF from Baseline to Week 12 decreased in the placebo group and increased in the SYR-472 dose groups. The differences between the SYR-472 and placebo groups were statistically significant for the 25 mg, 50 mg, and 200 mg SYR-472 groups. The changes from Baseline in proinsulin/insulin levels at Week 12 were numerically lower in the 50, 100 and 200 mg SYR-472 dose groups compared with the placebo group but the differences were not statistically significant. There were no clinically important differences between the placebo group and the SYR-472 group in other measures of pancreatic function, such as proinsulin and insulin levels or HOMA-IR.

Following 12 weeks of treatment, there were no clinically important differences in the lipid variables analyzed (triglycerides, and total, high-density lipoprotein, and low-density lipoprotein cholesterol) or body weight between the placebo group and the SYR-472 dose groups.

Safety Results:

Overall, 368 subjects were exposed to study drug in this study with 294 subjects receiving SYR-472 at doses of 25, 50, 100, or 200 mg weekly. The proportion of subjects experiencing at least 1 AE in each SYR-472 group was similar to that in the placebo group. Specifically, AEs were experienced by 41.9%, 30.1%, 41.1%, 36.5%, and 39.2% of subjects in the placebo, 25 mg SYR-472, 50 mg SYR-472, 100 mg SYR-472, and 200 mg SYR-472 groups, respectively. Overall, the most common AEs reported in the study were nasopharyngitis and upper respiratory tract infection (3.0% each) and diarrhea (2.4%). All other treatment-emergent AEs occurred in less than 2% of subjects overall. The incidences of common AEs (those occurring in >2% of subjects in any treatment group) was similar across treatment groups.

Among the SYR-472 dose groups, there was no clear dose-response relationship in AEs. Preferred terms that were reported in ≥3% of subjects in a treatment group and occurred in twice the percentage of subjects in any of the active treatment groups than in the placebo group were diarrhea, headache, and bronchitis.

Almost all treatment-emergent AEs were mild or moderate in maximum intensity. Six of 368 subjects (1.6%) experienced a total of 7 treatment-emergent AEs of severe intensity. Overall, 54/368 subjects (14.7%) experienced treatment-emergent AEs that were considered by the investigator to be related (possibly, probably, or definitely) to the blinded study drug.

A total of 5 (1.4%) subjects reported 5 treatment-emergent SAEs during the study; 2 each in the placebo and 50 mg SYR-472 groups and 1 in the 100 mg SYR-472 group. All SAEs were single events; no 2 subjects experienced the same SAE. No subject experienced an SAE that was considered related to blinded study drug.

Four (1.1%) subjects were discontinued because of AEs; 2 in the placebo group and 2 in the 25 mg SYR-472 group. For 2 of these subjects, AEs leading to withdrawal were considered to be related to study drug (event of diarrhea in the placebo group and edema peripheral in the 25 mg SYR-472 group). All AEs leading to discontinuation from the study were single events; no 2 subjects experienced the same AE leading to withdrawal.

The incidence of AEs in the skin and subcutaneous tissue disorders SOC was low and similar across treatment groups.

Overall, only 2 subjects (in the 200 mg SYR-472 group) reported hypoglycemic events. Both these events were mild to moderate in intensity.

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No clinically meaningful changes were observed in clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, ECG findings, or physical examination findings with SYR-472 treatment compared with placebo.

CONCLUSIONS:

- SYR-472 treatment administered once weekly resulted in clinically and statistically significant reductions in mean HbA1c after 12 weeks in subjects with T2DM.
- SYR-472 treatment was not associated with clinically important changes in lipids or body weight.
- The safety and tolerability of SYR-472 was confirmed up to 12 weeks of treatment in subjects with T2DM.

Date of Report:

29 July 2008