The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

**Study No.:** SIR114010 (SRT-2104-011)

**Title:** A Phase IIa, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Assess the Safety, Tolerability, and Activity of Oral SRT2104 Capsules Administered for 28 Days to Subjects with Type 2 Diabetes Mellitus

**Rationale:**

**Phase:** 2a

**Study Period:** 03 Mar 2010 – 25 Dec 2010

**Study Design:** Randomized, Placebo-Controlled, Double-Blind

**Centres:** 1, Germany

**Indication:** Type 2 diabetes mellitus

**Treatment:** SRT2104 2.0 g/day or placebo for 28 days

**Objectives:** To study the safety, tolerability and effects of SRT2104 vs. placebo on insulin sensitivity including hepatic and muscular insulin sensitivity in subjects with type 2 diabetes mellitus (T2DM) in a fed state.

**Primary Outcome/Efficacy Variable:** Oral glucose tolerance test (OGTT), Hyperinsulinemic euglycaemic glucose clamp (HEGC) mean free fatty acid (FFA)

**Secondary Outcome/Efficacy Variable(s):** To determine the pharmacokinetics (PK) of 28 days of dosing with 2.0 g SRT2104 in subjects with type 2 diabetes mellitus in a fed state. To study the effects of SRT2104 vs. placebo on energy expenditure. To study the effects of SRT2104 vs. placebo on muscle histology and biomarkers of oxidative capacity

**Statistical Methods:** For all PK parameters summary statistics were calculated. The analysis of SRT2104 accumulation over the dosing period and time invariance employed an analysis of variance (ANOVA) with a 90% confidence interval. The analysis of pharmacodynamic endpoints, exploratory activity endpoints and lipids (post-hoc analysis) employed an analysis of covariance (ANCOVA) fit by study day, where changes in variables from baseline values were defined as the response variables, treatment as a fixed factor and baseline values as covariates. For between-treatment comparisons of activity variables, the difference between the least square means (LS-means) was determined. Two-sided 95% confidence intervals were calculated, and probabilities were based on a two-sided unpaired t–test. LS-mean estimates of change from baseline within each treatment group and associated 95% confidence intervals from the same ANCOVA model were also determined. The level of significance was set to 5%. There was no adjustment for multiplicity of endpoints. The impact of the subject's diet on the absorption of SRT2104 was analyzed using an ANOVA with $AUC_{0\text{-}24h}$ or Cmax as response variables and diet as fixed effect, and association between PK and PD parameters or lipids were analyzed by Pearson correlation coefficients. All efficacy and exploratory endpoints were also analyzed descriptively. Safety endpoints were analyzed solely by descriptive methods.

**Study Population:** Male and female patients, age 18-65 with T2DM, on stable metformin monotherapy and with HbA1c $\leq$ 8.5%

| | **Placebo** | **SRT2104** |
|---|---|---|
| Number of Subjects: | | |
| Planned, N | 40 | 40 |
| Randomised, | 40 | 40 |
| Completed, n (%) | 37 (92.5) | 39 (97.5) |
| Total Number Subjects Withdrawn, N (%) | 3 (7.5) | 1 (2.5) |
| Withdrawn due to Adverse Events n (%) | 0 | **0** |
| Withdrawn due to Lack of Efficacy n (%) | 0 | **0** |
| Withdrawn for other reasons n (%) | 3 (7.5) | 1 (2.5) |
| **Demographics** | **Placebo** | **SRT2104** |
| N (ITT) | 40 | 40 |
| Females: Males | 4:36 | 5:35 |
| Mean Age, years (SD) | 54 (8.9) | 56 (7.7) |
| White, n (%) | 40 (100) | 40 (100) |
| | | |

**Primary Efficacy Results:**

**ANCOVA Estimates of Between-treatment Comparison of Change from Baseline HEGC-derived Insulin Sensitivity Parameters (Full Analysis Set)**

| Parameter | Study Period | Statistical Comparison | N | Arithmetic LS-mean* | 95% Confidence Interval | P-Value |
|---|---|---|---|---|---|---|
| SI | Day 29 – Day 0 | SRT2104 vs. Placebo | 34/37 | 0.21 | (-0.267; 0.691) | 0.3799 |
| | Day 43 – Day 0 | | 35/36 | 0.25 | (-0.219; 0.720) | 0.2912 |
| | Day 43 – Day 29 | | 32/38 | 0.20 | (-0.300; 0.704) | 0.4239 |
| M1 | Day 29 – Day 0 | SRT2104 vs. Placebo | 36/38 | -0.47 | (-0.997; 0.060) | 0.0814 |
| | Day 43 – Day 0 | | 36/38 | -0.42 | (-1.008; 0.173) | 0.1633 |
| | Day 43 – Day 29 | | 35/39 | 0.42 | (-0.147; 0.978) | 0.1449 |
| M2 | Day 29 – Day 0 | SRT2104 vs. Placebo | 34/38 | -0.73 | (-1.355; -0.115) | **0.0209** |
| | Day 43 – Day 0 | | 36/38 | -0.25 | (-0.995; 0.499) | 0.5103 |
| | Day 43 – Day 29 | | 33/39 | 0.86 | (0.116; 1.609) | **0.0242** |
| MCR1 | Day 29 – Day 0 | SRT2104 vs. Placebo | 36/38 | -0.44 | (-0.970; 0.096) | 0.1068 |
| | Day 43 – Day 0 | | 36/38 | -0.35 | (-0.942; 0.236) | 0.2364 |
| | Day 43 – Day 29 | | 35/39 | 0.43 | (-0.146; 0.999) | 0.1416 |
| MCR2 | Day 29 – Day 0 | SRT2104 vs. Placebo | 34/38 | -0.74 | (-1.371; -0.113) | **0.0214** |
| | Day 43 – Day 0 | | 36/38 | -0.21 | (-0.946; 0.534) | 0.5802 |
| | Day 43 – Day 29 | | 33/39 | 0.90 | (0.146; 1.652) | **0.0199** |
| M/I1 | Day 29 – Day 0 | SRT2104 vs. Placebo | 36/37 | -0.01 | (-0.016; 0.002) | 0.1469 |
| | Day 43 – Day 0 | | 36/38 | -0.00 | (-0.13; 0.011) | 0.8676 |
| | Day 43 – Day 29 | | 35/39 | 0.01 | (-0.003; 0.020) | 0.1491 |
| M/I2 | Day 29 – Day 0 | SRT2104 vs. Placebo | 34/38 | -0.00 | (-0.010; 0.003) | 0.3178 |
| | Day 43 – Day 0 | | 36/38 | -0.00 | (-0.008; 0.008) | 0.9917 |
| | Day 43 – Day 29 | | 33/39 | 0.00 | (-0.003; 0.012) | 0.2138 |
| $M1_{ree}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 36/38 | -0.34 | (-0.715; 0.043) | 0.0818 |
| | Day 43 – Day 0 | | 36/38 | -0.25 | (-0.640; 0.145) | 0.2126 |
| | Day 43 – Day 29 | | 35/39 | 0.36 | (-0.088; 0.800) | 0.1146 |
| $M2_{ree}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 34/38 | -0.50 | (-0.967;-0.029) | **0.0378** |
| | Day 43 – Day 0 | | 36/38 | -0.03 | (-0.635; 0.576) | 0.9233 |
| | Day 43 – Day 29 | | 33/39 | 0.65 | (-0.008; 1.304) | 0.0528 |
| $MCR1_{ree}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 36/38 | -0.31 | (-0.698; 0.070) | 0.1070 |
| | Day 43 – Day 0 | | 36/38 | -0.20 | (-0.593; 0.193) | 0.3137 |
| | Day 43 – Day 29 | | 35/39 | 0.37 | (-0.083; 0.817) | 0.1087 |
| $MCR2_{ree}$ | Day 29 – Day 0 | SRT2104 vs. | 34/38 | -0.50 | (-0.977; -0.030) | **0.0374** |
| | Day 43 – Day 0 | | 36/38 | -0.00 | (-0.600; 0.594) | 0.9918 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Day 43 – Day 29 | Placebo | 33/39 | 0.67 | (0.014; 1.335) | **0.0455** |
| $M/I1_{ree}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 36/38 | -0.00 | (-0.011; 0.002) | 0.1674 |
| | Day 43 – Day 0 | | 36/38 | -0.00 | (-0.008; 0.008) | 0.9926 |
| | Day 43 – Day 29 | | 35/39 | 0.01 | (-0.003; 0.015) | 0.1817 |
| $M/I2_{ree}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 34/38 | -0.00 | (-0.006; 0.002) | 0.3905 |
| | Day 43 – Day 0 | | 36/38 | 0.00 | (-0.006; 0.007) | 0.8957 |
| | Day 43 – Day 29 | | 33/39 | 0.00 | (-0.004; 0.010) | 0.3994 |

* Arithmetic LS-mean difference of treatments

**ANCOVA Estimates of Between-treatment Comparison of Change from Baseline OGTT Parameters (Full Analysis Set)**

| Parameter | Study Period | Statistical comparison | N | Arithmetic LS-mean* | 95% Confidence Interval | P-Value |
|---|---|---|---|---|---|---|
| $AUC_{0-2h}$ (glucose) | Day 28 – Day -1 | SRT2104 vs. Placebo | 37/40 | 0.89 | (-0.812; 2.602) | 0.2997 |
| | Day 42 – Day -1 | | 37/38 | -2.08 | (-3.408; -0.761) | **0.0024** |
| | Day 42 – Day 28 | | 36/38 | -3.05 | (-4.408; -1.697) | **<.0001** |
| $AUC_{0-2h}$ (insulin) | Day 28 – Day -1 | SRT2104 vs. Placebo | 36/39 | -9.83 | (-19.99; 0.332) | 0.0578 |
| | Day 42 – Day -1 | | 37/38 | 2.91 | (-7.304; 13.120) | 0.5720 |
| | Day 42 – Day 28 | | 35/37 | 18.19 | (3.670; 32.711) | **0.0148** |
| ISIcomposite (Matsuda Index) | Day 28 – Day -1 | SRT2104 vs. Placebo | 36/40 | 3.18 | (-6.411; 12.779) | 0.5105 |
| | Day 42 – Day -1 | | 37/38 | 1.68 | (-6.967; 10.336) | 0.6990 |
| | Day 42 – Day 28 | | 35/38 | -3.27 | (-14.02; 7.481) | 0.5461 |
| ISIest (Stumvoll Index) | Day 28 – Day -1 | SRT2104 vs. Placebo | 34/37 | 9.87 | (-33.31; 53.052) | 0.6497 |
| | Day 42 – Day -1 | | 36/37 | 16.50 | (-27.30; 60.291) | 0.4550 |
| | Day 42 – Day 28 | | 33/37 | 27.59 | (-17.53; 72.714) | 0.2266 |
| HIRI | Day 28 – Day -1 | SRT2104 vs. Placebo | 36/40 | -4.86 | (-13.36; 3.631) | 0.2576 |
| | Day 42 – Day -1 | | 37/38 | -2.43 | (-13.67; 8.813) | 0.6683 |
| | Day 42 – Day 28 | | 35/38 | 4.18 | (-8.340; 16.700) | 0.5077 |
| MISI | Day 28 – Day -1 | SRT2104 vs. Placebo | 22/29 | -0.01 | (-0.025; 0.010) | 0.3839 |
| | Day 42 – Day -1 | | 24/28 | 0.00 | (-0.028; 0.029) | 0.9913 |
| | Day 42 – Day 28 | | 25/25 | 0.01 | (-0.012; 0.026) | 0.4567 |
| HOMA-IR | Day 28 – Day -1 | SRT2104 vs. Placebo | 38/40 | 0.02 | (-0.305; 0.350) | 0.8922 |
| | Day 42 – Day -1 | | 37/39 | -0.10 | (-0.452; 0.259) | 0.5889 |
| | Day 42 – Day 28 | | 37/39 | -0.20 | (-0.617; 0.211) | 0.3310 |
| HOMA-%B | Day 28 – Day -1 | SRT2104 vs. Placebo | 38/40 | -10.71 | (-21.29; -0.131) | **0.0473** |
| | Day 42 – Day -1 | | 37/39 | 5.70 | (-6.814; 18.209) | 0.3671 |
| | Day 42 – Day 28 | | 37/39 | 15.19 | (-0.109; 30.497) | 0.0516 |
| QUICKI | Day 28 – Day -1 | SRT2104 vs. | 36/40 | -0.00 | (-0.004; 0.002) | 0.6853 |
| | Day 42 – Day -1 | | 37/38 | 0.00 | (-0.003; 0.003) | 0.9707 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Day 42 – Day 28 | Placebo | 35/38 | 0.00 | (-0.003; 0.004) | 0.8150 |

* Arithmetic LS-mean difference of treatments

**Table 11.4.1.1-1 ANCOVA Estimates of Between-treatment Comparison of Change from Baseline HEGC-derived FFA, Glycerol and C-peptide Concentrations (Full Analysis Set)**

| Parameter | Study Period | Statistical Comparison | N | Arithmetic LS-mean* | 95% Confidence Interval | P-Value |
|---|---|---|---|---|---|---|
| Mean $FFA_{SS1}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 36/38 | -0.01 | (-0.046; 0.021) | 0.4511 |
| | Day 43 – Day 0 | | 36/38 | -0.06 | (-0.108; -0.017) | **0.0074** |
| | Day 43 – Day 29 | | 35/39 | -0.05 | (-0.086; -0.017) | **0.0042** |
| Mean $FFA_{SS2}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 34/38 | 0.02 | (-0.010; 0.056) | 0.1703 |
| | Day 43 – Day 0 | | 36/38 | -0.04 | (-0.086; 0.015) | 0.1627 |
| | Day 43 – Day 29 | | 33/39 | -0.04 | (-0.095; 0.009) | 0.1047 |
| Mean $glycerol_{SS1}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 36/38 | 0.00 | (-0.006; 0.009) | 0.6120 |
| | Day 43 – Day 0 | | 36/38 | -0.01 | (-0.018; -0.002) | **0.0143** |
| | Day 43 – Day 29 | | 35/39 | -0.01 | (-0.018; -0.006) | **0.0001** |
| Mean $glycerol_{SS2}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 34/38 | 0.01 | (-0.002; 0.015) | 0.1113 |
| | Day 43 – Day 0 | | 36/38 | -0.01 | (-0.016; 0.001) | 0.0932 |
| | Day 43 – Day 29 | | 33/39 | -0.01 | (-0.020; -0.004) | **0.0057** |
| Mean $C\text{-peptide}_{SS1}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 36/38 | -0.04 | (-0.085; 0.010) | 0.1193 |
| | Day 43 – Day 0 | | 36/38 | 0.00 | (-0.051; 0.058) | 0.9097 |
| | Day 43 – Day 29 | | 35/39 | 0.05 | (-0.002; 0.099) | 0.0592 |
| Mean $C\text{-peptide}_{SS2}$ | Day 29 – Day 0 | SRT2104 vs. Placebo | 34/38 | -0.07 | (-0.107; -0.023) | **0.0029** |
| | Day 43 – Day 0 | | 36/38 | 0.01 | (-0.050; 0.064) | 0.7992 |
| | Day 43 – Day 29 | | 33/39 | 0.08 | (0.035; 0.127) | **0.0008** |

* Arithmetic LS-mean difference of study days

**Secondary Outcome Variable(s):**

| Parameter | Day 1–2 after Dosing | Day 28–29 after Dosing |
|---|---|---|
| $AUC_{0\text{-}24h}$ [ng*h/mL] | 4042 (56.8) | 5469 (50.1) |
| $AUC_{0\text{-}\infty}$ [ng*h/L] | 5189 (55□3) | 8772 (53□8) |
| $C_{max}$ [ng/mL] | 673 (52.0) | 701 (52.5) |
| $t_{max}$ [h] | 2.9 (0.65) | 3.3 (3.62) |
| $t_{1/2}$ [h] | 11.8 (39.2) | 16.3 (45.4) |
| $\lambda_Z$ [ /h] | 0.06 (121.7) | 0.04 (91.2) |

**On-therapy AEs** and SAEs were defined as an AE with an onset date on or after the first dose of study medication. On-therapy SAEs were recorded up through 30 days after last dose of study drug

| | Placebo | SRT2104 |
|---|---|---|
| **Most Frequent Adverse Events – On-Therapy** | **n (%)** | **n (%)** |
| Subjects with any AE(s), n(%) | 24 (60.0) | 21 (52.5) |

| | | |
|---|---|---|
| Headache | 9 (22.5) | 5 (12.5) |
| Fatigue | 8 (20.0) | 3 (7.5) |
| Nasopharyngitis | 4 (10.0) | 3 (7.5) |
| Hypoglycemia | 4 (10.0) | 3 (7.5) |
| Back pain | 3 (7.5) | 2 (5.0) |
| Diarrhea | 1 (2.5) | 3 (7.5) |
| Nausea | 3 (7.5) | 1 (2.5) |
| Post procedural hematoma | 4 (10.0) | 0 |
| Procedural pain | 3 (7.5) | 1 (2.5) |
| Vertigo | 2 (5.0) | 2 (5.0) |

**Serious Adverse Events - On-Therapy**
**n (%) [n considered by the investigator to be related to study medication**

| | **Placebo** | **SRT2104** |
|---|---|---|
| Subjects with non-fatal SAEs, n (%) | 1 (2.5) [0] | 0 |
| Subjects with fatal SAEs, n (%) | 0 | 0 |

**Conclusion:** SRT2104, given at a daily dose of 2.0 g for 28 consecutive days, did not display consistent effects on insulin sensitivity compared to placebo.

SRT2104 treatment caused statistically significant decreases of C-peptide concentrations at SS2 and HOMA%-B consistent with a slightly reduced beta-cell function and secretory activity.

Following oral administration, maximum SRT2104 plasma concentrations were reached after about 3 hours. Over the treatment period of 28 days, SRT2104 accumulated by about 40%. Consumption of liquid meals was accompanied by lower SRT2104 absorption compared to solid standardized meals. However, when data from 2 subjects were removed from the statistical analysis because of completely flat SRT2104 concentration profiles, and given the large variability and small sample size, no statistical significant difference was observed.

The total number and proportion of subjects with AEs was similar in the SRT2104 and placebo arm. The incidence of hypoglycemic episodes, which were all asymptomatic, was similar in both treatment arms.