Study No.: SIR113160 (SRT-2104-005)

Title: A Phase II, Randomized, Placebo-controlled, Double-blind, Multiple-dose Clinical Study to Assess the Safety and Pharmacokinetics of SRT2104 in Type 2 Diabetic Human Subjects

Rationale: Evaluate safety, tolerability, PK profile and effects on fasting glucose and insulin of SRT2104 when administered to subjects with Type 2 diabetes

Phase: 2

Study Period: 19 Aug 2009 – 18 Sept 2010

Study Design: Randomized, double-blind, placebo-controlled, multiple dose

Centres: 45: Bulgaria (7), Estonia (1), Hungary (4), Poland (4), Romania (6), Russia (13), UK (3), Ukraine (7)

Indication: Type 2 diabetes

Treatment: SRT2104 250 mg, 500 mg, 1,000 mg, 2,000 mg or placebo once daily for 28 days

- **Objectives:**
- To determine the safety and tolerability of SRT2104 (0.25, 0.5, 1.0, and 2.0 g/day) in type 2 diabetic subjects when administered once daily for 28 consecutive days.
- To characterize the pharmacokinetic profile of SRT2104 (0.25, 0.5, 1.0, and 2.0 g/day) after a single dose and multiple administrations in type 2 diabetic subjects.

Primary Outcome/Efficacy Variable: Efficacy was not a primary objective. Primary outcomes variables were:

- Safety evaluations based on the incidence, intensity, relationship, and type of AEs, and clinically significant changes in physical examination findings, vital signs, ECG parameters, and clinical laboratory results.
- Area under plasma concentration curve from time 0 to last measurable time point [AUC(0-t)], Area under plasma concentration curve from time 0 to infinity [AUC(0-∞)], Area under plasma concentration curve from time 0 to steady-state concentration [AUC(0-tau)], Observed maximum plasma concentration (Cmax), Elimination half life ($T_{1/2}$), Time to maximum plasma concentration (Tmax), Total body clearance (CL/F), Volume of distribution (Vd/F).

Secondary Outcome/Efficacy Variable(s): Observed values and change from baseline for fasting plasma glucose (FPG), fasting plasma insulin (FPI), post-prandial glucose (PPG), post-prandial insulin (PPI), and HbA_{1c}.

Statistical Methods:

- Safety evaluations were based on the incidence, intensity, relationship, and type of AEs, and clinically significant changes in the subject's physical examination findings, vital signs, ECG parameters, and clinical laboratory results. Safety variables were tabulated and presented for all subjects who received test material (i.e. the safety sample) using summary statistics only.
- For pharmacokinetics, listings of individual subject and summary statistics for plasma SRT2104 concentrations, actual blood sampling times relative to dose, and pharmacokinetic parameters and graphs of concentration versus time were prepared by dosing cohort. Plasma concentrations and pharmacokinetic parameters were summarized by and compared among dosing cohorts using descriptive statistics.
- For efficacy, observed values and change from baseline for FPG, FPI, PPG, PPI, and HbA_{1c} for each active dose group were compared with placebo using a general linear model with Dunnett's test and post-hoc unadjusted ANOVA for each study day assessed. Percent change for FPG, FPI, PPG, PPI, and HbA_{1c} for each active dose group was compared with placebo using Dunnett's test for Day 28 only.

Study Population: Male or female subjects within the age range of 30 to 70 years with a glycosylated hemoglobin (HbA_{1c}) ≥7.5% and ≤10.5% and a fasting glucose ≥160 and ≤240 mg/dL. All subjects had to be on stable metformin medication for at least 3 months (≥1.0 g/day) prior to Screening.

	Placebo	**SRT2104**
Number of Subjects:		
Planned, N	45	180
Randomised, N	46	181
Completed, n (%)	43 (93.5)	160 (88.4)
Total Number Subjects Withdrawn, N (%)	3 (6.5)	21 (11.6)
Withdrawn due to Adverse Events n (%)	0	8 (4.4)
Withdrawn due to Lack of Efficacy n (%)	N/A	N/A
Withdrawn for other reasons n (%)	3 (6.5)	13 (7.2)
Demographics	**Placebo**	**SRT2104**
N (ITT)	46	181
Females: Males	28:18	98:83

Mean Age, years (SD)	55.8 (8.4)	57.3 (8.73)
White, n (%)	45 (97.8)	180 (99.4)

Primary Efficacy Results: Efficacy was not a primary outcome. PK parameters are below:

Summary of Statistical Analysis of SRT2104 Pharmacokinetic Data: Day 28 vs Day 1 (PK set)

		Geometric LS Means		
SRT2104 Dose Level	**Parameter**	**Day 1**	**Day 28**	**Day 28/Day 1 (90% C.I.)**
0.25 g/day	C_{max} (ng/ml)	84.36	103.01	122.22 (86.94 - 171.80)
	$AUC_{(0-t)}$ (ng.h/ml)	576.85	971.41	168.40 (123.87 - 228.94)
	$AUC_{(0-\infty)}$* (ng.h/ml)	829.52	919.78	110.88 (88.18 - 139.43)
0.5 g/day	C_{max} (ng/ml)	177.66	167.80	94.45 (69.07 - 129.16)
	$AUC_{(0-t)}$ (ng.h/ml)	1172.34	1560.44	133.11 (100.55 - 176.21)
	$AUC_{(0-\infty)}$* (ng.h/ml)	1654.65	1560.40	94.30 (70.31 - 126.48)
1.0 g/day	C_{max} (ng/ml)	163.97	188.22	114.79 (91.54 - 143.95)
	$AUC_{(0-t)}$ (ng.h/ml)	1186.44	1680.41	141.63 (111.20 - 180.39)
	$AUC_{(0-\infty)}$* (ng.h/ml)	1528.84	1749.88	114.46 (85.56 - 153.11)
2.0 g/day	C_{max} (ng/ml)	193.95	233.31	120.30 (88.66 - 163.23)
	$AUC_{(0-t)}$ (ng.h/ml)	1522.80	2544.46	167.09 (120.73 - 231.25)
	$AUC_{(0-\infty)}$* (ng.h/ml)	2103.80	2476.76	117.73 (85.14 - 162.79)

* AUC values included in the analysis are $AUC_{(0-\infty)}$ on Day 1 and $AUC_{(0-t)}$ on Day 28.
Results obtained from a mixed model ANOVA on log-transformed data with a fixed effect of study day and a random effect of subject

Secondary Outcome Variable(s):

		Active Dose (g/day)				
(mean ± SD)	**Placebo (N=46)**	**0.25 (N=45)**	**0.5 (N=46)**	**1.0 (N=45)**	**2.0 (N=45)**	**All Active (N=181)**
Fasting Plasma Glucose [mmol/L] on Day 28						
n	**43**	**36**	**42**	**38**	**38**	**154**
Observed data	9.60 (2.02)	10.21 (2.12)	10.49 (2.22)	10.32 (2.16)	10.05 (2.38)	10.27 (2.21)
n	**43**	**35**	**42**	**36**	**38**	**151**
Change from baseline	-1.17 (2.42)	-1.11 (3.45)	-0.52 (2.60)	-0.97 (2.83)	-0.15 (2.38)	-0.67 (2.82)
Fasting Plasma Insulin [mmol/L] on Day 28						
n	**43**	**37**	**41**	**40**	**39**	**157**
Observed data	82.4 (56.91)	91.7 (118.05)	63.7 (44.87)	63.3 (55.69)	89.2 (134.56)	76.5 (95.40)
n	**41**	**36**	**39**	**38**	**36**	**149**
Change from baseline	1.0 (51.66)	8.9 (95.04)	-6.9 (41.45)	4.1 (57.16)	15.2 (138.79)	5.1 (89.53)
Post-prandial Glucose [mmol/L] at 120 mins after standardized meal on Day 28						
n	**43**	**35**	**41**	**40**	**39**	**155**
Observed data	13.16 (4.26)	13.15 (3.55)	14.74 (3.15)	13.90 (3.60)	13.61 (4.43)	13.88 (3.72)
n	**43**	**35**	**41**	**38**	**38**	**152**
Change from baseline	3.56 (3.37)	2.93 (3.33)	4.23 (2.88)	3.66 (2.54)	3.47 (3.44)	3.60 (3.07)
Post-prandial Insulin [mmol/L] at 120 mins after standardized meal on Day 28						
n	**43**	**37**	**40**	**40**	**39**	**156**
Observed data	224.4 (129.69)	215.0 (309.78)	192.5 (132.93)	183.8 (160.20)	206.4 (202.40)	199.1 (208.28)
n	**43**	**37**	**40**	**40**	**39**	**156**
Change from baseline	142.0 (113.58)	123.3 (253.84)	128.7 (106.87)	120.5 (129.95)	117.3 (127.26)	122.5 (161.48)

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 to 30 days after last dose of study medication.

	Placebo	SRT2104
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	11 (25.6)	60 (34.9)
Hyperglycemia	3 (7.0)	12 (7.0)
Nausea	2 (4.7)	10 (5.8)
Diarrhea	2 (4.7)	8 (4.7)
Blood glucose increased	2 (4.7)	1 (0.6)
Asthenia	1 (2.3)	5 (2.9)
Dizziness	1 (2.3)	5 (2.9)
Tachycardia	0	4 (2.3)
Hypertriglyceridemia	0	4 (2.3)
Abdominal pain	0	4 (2.3)

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 (%)	0	1 (0.6) [0]
Wound infection*	0	1 (0.6) [0]
Interstitial lung disease	0	1 (0.6) [0]
Subjects with fatal SAEs, n (%)	0	1 (0.6)
Sepsis*	0	1 (0.6)
*The same subject experienced both events		

Conclusion:

Pharmacokinetic analysis indicated that exposure to SRT2104 (as assessed by $AUC_{[0\text{-}t]}$) increased in a less than dose-proportional fashion. However, there was a high degree of inter-subject variability in the exposure parameters, which should be considered when interpreting these data. It was observed that although trough levels of SRT2104 decreased slightly with time in most groups, an increase in exposure was observed between Days 1 and 28. Previous studies had indicated that about a 3-fold increase in total exposure could be expected when SRT2104 is dosed in the fed state. The food effect seen in this study was lower than expected, possibly due to differences in the composition of the standard meal provided in this study compared with previous studies.

Mean peak plasma concentrations of SRT2104 increased in an approximately proportional fashion between 0.25 and 0.5 g/day doses, but with little further change in mean C_{max} in subjects who received 1.0 or 2.0 g/day.

A total of 71 (33.0%) subjects experienced AEs during the treatment phase of the study. The number of subjects experiencing AEs in the active treatment groups was 60 compared with 11 subjects in the placebo group. The majority of subjects' AEs were mild (38 subjects) or moderate (30 subjects) in intensity, with only 2 subjects experiencing severe AEs. A minority of AEs were considered by the Investigator to be possibly related (16 subjects) or related (3 subjects) to study medication.

Two subjects experienced 3 serious adverse events (SAEs). One of these 2 subjects died (sepsis). All three SAEs were considered by the Investigator to be not related to study medication.

There appeared to be no impact of SRT2104 on fasting plasma glucose or insulin or on post-prandial glucose or insulin compared to placebo at the doses tested and exposures achieved in this study.