SYNOPSIS

Name of Sponsor:
Laboratoires Fournier S.A. (an Abbott company)

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
SLV337

Name of Active Ingredient:
SLV337

Study Title:
A Double-blind, Randomized, Placebo-controlled, Parallel Group Study to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of SLV337 in Patients with Type 2 Diabetes on Metformin Monotherapy

Investigator(s):
12 Investigators (Dr. Marek Konieczny acted as the Coordinating Investigator)

Study Center(s):
14 Study centers in three countries (Bulgaria, Poland and South Africa) of which only 12 study centers recruited subjects

Publication (Reference):
Not applicable

Study Period:
11 DEC 2009 (first subject first visit) to
02 DEC 2010 (last subject last visit)

Phase of Development:
II

Objectives:
The primary objective of this study was to explore the safety and tolerability of three oral doses of a new anti-diabetic agent, SLV337, in subjects with type 2 diabetes mellitus (T2DM) treated with metformin monotherapy, during four weeks of administration.

The secondary objectives were:

- To investigate the pharmacokinetic (PK) profiles of these three oral doses of SLV337 in subjects with T2DM.
- To explore the effect of SLV337 on metformin plasma levels in subjects on stable treatment doses administered in the morning.
- To explore the exposure-response relationships and preliminary efficacies of these three oral doses of SLV337 in subjects with T2DM.

Methodology:
This was a multi-centre, randomized, double-blind, placebo-controlled, parallel group study investigating the safety, tolerability, PK and pharmacodynamics (PD) of SLV337 in subjects

with T2DM on metformin monotherapy.

The study was conducted in Bulgaria, Poland and South Africa. In total, 14 study centers were initiated of which 12 study centers recruited subjects (four in Bulgaria, five in Poland, and three in South Africa).

Subjects were randomized to one of four possible treatment groups: 400, 800, 1,400 mg SLV337 or placebo. The study consisted of an up to four-week screening period, a four-week treatment period and a one-week follow-up period. Subjects were to receive seven capsules of study drug (200 mg SLV337 and/or matching placebo) orally once per day to achieve daily doses of 400, 800 and 1,400 mg SLV337 or placebo, in the morning with breakfast. Dosing was to continue once daily from Days 1 to 28.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Planned: 56 subjects: (14 subjects in each of the four treatment groups).
Consented: 123 subjects.
Randomized: 61 subjects:
400 mg/day SLV337: 17 subjects.
800 mg/day SLV337: 15 subjects.
1,400 mg/day SLV337: 15 subjects.
placebo: 14 subjects.
Analyzed Safety Full Analysis/Pharmacodynamic (FA/PD) subject sample: 61 subjects:
400 mg/day SLV337: 17 subjects.
800 mg/day SLV337: 15 subjects.
1,400 mg/day SLV337: 15 subjects.
placebo: 14 subjects.
Analyzed Per-protocol (PP) subject sample: 49 subjects:
400 mg/day SLV337: 11 subjects.
800 mg/day SLV337: 13 subjects.
1,400 mg/day SLV337: 11 subjects.
placebo: 14 subjects.
Analyzed SLV337/SLV337 acyl-glucuronide PK subject sample: 46 subjects:
400 mg/day SLV337: 17 subjects.
800 mg/day SLV337: 14 subjects.
1,400 mg/day SLV337: 15 subjects.
placebo: 0 subjects.
Analyzed Metformin PK subject sample: 40 subjects:
400 mg/day SLV337: 13 subjects.
800 mg/day SLV337: 14 subjects.
1,400 mg/day SLV337: 13 subjects.
placebo: 0 subjects.

Diagnosis and Main Criteria for Inclusion:
Eligible subjects were aged 18 to 75 years inclusive, males and females of non-childbearing potential, diagnosed with T2DM defined by the American Diabetes Association criteria (fasting plasma glucose [FPG] ≥ 7.0 mmol/L [126 mg/dL]; or two hours postprandial glucose ≥ 11.1 mmol/L [200 mg/dL]); treated with diet and exercise and on a stable dose of metformin monotherapy (≥ 850 mg daily dose) for at least three months. Subjects had a FPG < 15 mmol/L

(270 mg/dL) and had inadequate glycemic control, defined by hemoglobin A1c (HbA1c) ≥ 7%, but < 9% (the threshold of HbA1c was increased from < 9% to < 10% in protocol amendment 1).

Test Product, Dose and Mode of Administration, Batch Number:

Capsules of 200 mg SLV337 were orally administered once per day, in the morning with breakfast, to achieve daily doses of 400, 800 or 1,400 mg.

Batch numbers: 1060105-610339 and 1060105-610340.

Duration of Treatment:

28 days

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

Capsules of matching placebo were orally administered once per day, in the morning with breakfast.

Batch number: 1060106-610335.

Criteria for Evaluation

Pharmacokinetics:

- Whole blood samples were collected for the determination of SLV337 and its acyl-glucuronide metabolite plasma concentrations at predose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and 24 hours after administration of SLV337 on Day 28. Predose samples were also collected at ambulant visits (Days 7, 14 and 21).
- Whole blood samples were collected for the determination of metformin plasma concentrations at predose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and 24 hours after administration of metformin on Days -1 and 28.
- Noncompartmental methods were used to determine the following PK parameters for SLV337 and its acyl-glucuronide metabolite: observed maximum plasma concentration (C_{max}), observed predose (trough) plasma concentration (C_{trough}), time to reach maximum plasma concentration after drug administration (t_{max}), area under the plasma concentration-time curve from zero to the last measurable timepoint (AUC_{0-t}), area under the plasma concentration-time curve over a dosing interval ($AUC_{0-\tau}$), and apparent clearance (CL/F) (SLV337 only), and for metformin: C_{max}, t_{max}, $AUC_{0-\tau}$, terminal elimination rate constant (λ_z), elimination half-life ($t_{1/2}$), and CL/F.

Pharmacodynamics:

- Fasting blood samples were collected for determination of FPG, adiponectin, high molecular weight (HMW) adiponectin, triglyceride (TG), free fatty acid (FFA), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) predose on Days 1, 7, 14, 21 and 28. A fasting blood sample was collected for the determination of FPG, HbA1c and C-peptide at Screening.
- Fasting blood samples were collected for determination of insulin, pro-insulin, fructosamine, HbA1c, apolipoprotein A1 (apoA1), apolipoprotein B (apoB), apolipoprotein C-III (apoCIII) levels and high sensitivity C-reactive protein (hsCRP) predose on Days 1

and 28.

- Seven finger prick blood glucose tests using a glucometer were performed on Days -1 and 28: immediately before and one to two hours after each standard meal (one hour post breakfast and two hours post lunch and dinner) and at bedtime. The mean value of the three postprandial measures (one hour post breakfast, two hours post lunch and dinner) were also calculated.
- HMW/total adiponectin ratio, homeostasis model assessment of insulin resistance (HOMA_IR), and apoB/apoA1 ratio were calculated.

Safety:

The safety and tolerability data collected during this study included those from physical examination, vital signs measurements (semi-recumbent blood pressure, pulse rate and weight), 12-lead electrocardiograms (ECGs), clinical laboratory assessments (hematology, biochemistry, urinalysis, bone markers and serum biobank), ankle foot volume (AFV) and ankle circumferences (ACs), adverse events (AEs) and concomitant medication.

Genotyping:

Separate informed consent was to be signed for subjects participating in the genotyping research. Refusal to participate in the genotyping research did not prevent study participation. Thirty subjects gave additional informed consent and were analyzed for genotyping.

The genes listed in the protocol to be analyzed were cytochrome P450 (CYP) isozymes 2D6, 2C8, 2C19 and 2C9. Some genes were subsequently added to be analyzed: CYP3A4 and urinidine diphosphate-glucuronosyltransferases (UGTs) 1A1, 1A3 and 2B7.

Assay procedures and results were described in a separate study plan and report.

Statistical Methods:

Pharmacokinetics:

The PK analysis was performed on the SLV337 PK and the Metformin PK samples. Plasma concentration time courses of SLV337 and its acyl-glucuronide metabolite were to be tabulated and graphically displayed per subject and by treatment. Trough plasma levels were to be similarly presented. Plots of geometric mean time courses were to be provided by treatment. Similar presentations were to be provided for metformin dose-normalized plasma concentration data (although this was planned, the actual statistical analysis was not dose-normalized).

Pharmacokinetic parameters of SLV337, its acyl-glucuronide metabolite and metformin were to be tabulated per subject by treatment, including summary statistics by treatment. Metformin exposure parameters were to be dose-normalized for summaries as well as presented per category of administered morning dose (actual statistical analysis was not dose-normalized). For SLV337 and its acyl-glucuronide metabolite, AUC_{0-t}, $AUC_{0-\tau}$ and C_{max} scatter plots by treatment were to be presented. For metformin, dose-normalized $AUC_{0-\tau}$ and C_{max} scatter plots by treatment day and treatment were to be presented (actual statistical analysis was not dose-normalized).

Dose proportionality of SLV337 and its acyl-glucuronide metabolite were to be explored using a power model (value $=\alpha \times dose^{\beta}$). This was to be done by applying a linear regression model on the log-transformed PK parameters AUC_{0-t}, $AUC_{0-\tau}$ and C_{max}, with the log-transformed dose

as the regression variable. Dose proportionality was to be established if the 90% CI for β was fully contained within the interval (0.82 to 1.18). In addition, an alternative statistical model based on fitting an analysis of variance (ANOVA) was to be performed. This model would use the log-transformed PK parameters (AUC_{0-t}, $AUC_{0-\tau}$ and C_{max}) with dose group fitted as a factor. Dose proportionality for adjacent doses was to be concluded if the 90% CI entirely lay within the limits (0.8 to 1.25). The results from the power model were to be used as primary basis for discussion. If there appeared to be a significant departure from linearity, the results from the ANOVA were to be the primary basis for discussion.

To explore the effect of SLV337 on metformin exposure, log-transformed dose-normalized metformin PK parameters ($AUC_{0-\tau}$ and C_{max}) were to be compared between Day 28 and Day -1 using a paired t-test (actual statistical analysis was not dose-normalized). Point estimates and 90% CI of the geometric mean ratios for Day 28 versus Day -1 were to be determined.

Pharmacodynamics:

The PD analysis was to be performed on the PD sample. Descriptive statistics for PD endpoints (observed, change from baseline and percentage change from baseline) were to be provided, including placebo-adjusted values. Baseline was to be defined as the last assessment before study drug intake. An exploratory analysis of covariance (ANCOVA) was to be performed to compare the effect of various SLV337 doses and placebo on the PD endpoints with treatment as fixed effect and the baseline PD value as covariate, no multiplicity correction was performed. The relationship between SLV337 plasma parameters and change from baseline PD measurements on Day 28 was to be graphically presented for relevant PD endpoints.

Safety:

The safety sample was used for the analysis of the safety and tolerability data. Only treatment-emergent AEs (TEAEs) were summarized by unique treatment. Severity and drug-event relationship of TEAEs were summarized separately.

Ankle foot volume (right/left), ankle circumferences (AC) (right and left) and body weight including changes from baseline, percentage change, mean and placebo-adjusted mean were summarized. Laboratory variables, including changes from baseline, percentage change, mean and placebo-adjusted mean were summarized. A frequency table was presented for markedly abnormal values. Shift tables were presented according to the reference ranges (low, normal or high). Vital signs including changes from baseline, percentage change, mean and placebo-adjusted mean were summarized. A frequency table was presented for markedly abnormal values. Safety ECG variables, including changes from baseline, were summarized. All safety data were listed.

Summary – Conclusions

The study population was 59 years old on average, with 57% male and overall obese (31 kg/m^2 body mass index [BMI]). The baseline HbA1c level was 7.9% (± 0.70), LDL-C was 2.9 mmol/L (± 1.1) and TG was 2.1 mmol/L (± 1.3). All subjects completed the study.

Pharmacokinetic Results:

SLV337, SLV337 Acyl-glucuronide, and Metformin

Steady-state SLV337 and SLV337 acyl-glucuronide concentrations were achieved by Day 7 and appeared to be maintained between Day 7 and Day 28 for all dosing groups.

The SLV337 PK parameters following administration of 400, 800, and 1,400 mg SLV337 on Day 28 are summarized in Table 1. Corresponding PK parameters for SLV337 acyl-glucuronide are presented in Table 2. The metformin mean PK parameters following administration of stable metformin doses on Days -1 and 28 are summarized in Table 3.

Table 1. Summary of Arithmetic Mean (SD) and Geometric Mean Plasma SLV337 Pharmacokinetic Parameters for All SLV337 Dosing Groups

Parameters	SLV337 Dosing Group		
	400 mg (N = 17)	800 mg (N = 13)	1400 mg (N = 15)
$AUC_{0-\tau}$ (µg.h/mL)	33.6 (10.1)	51.5 (22.2)	73.7 (30.6)
	32.2	47.2	66.2
AUC_{0-t} (µg.h/mL)	33.6 (10.1)	51.5 (22.2)	73.7 (30.6)
	32.2	47.2	66.2
C_{max} (µg/mL)	4.34 (1.32)	6.34 (2.45)	8.63 (3.22)
	4.16	5.85	7.90
t_{max}[a] (h)	3.00 (1.00 – 6.00)	2.50 (1.50 – 4.17)	3.00 (1.00 – 6.00)
CL/F (L/h)	13.0 (4.00)	18.6 (8.24)	24.5 (16.0)
	12.4	17.0	21.2

[a] t_{max} is presented as median (minimum - maximum); SD = standard deviation.
Source: Table 10.1.2.3.1

Table 2. Summary of Arithmetic Mean (SD) and Geometric Mean Plasma SLV337 Acyl-glucuronide Pharmacokinetic Parameters for All SLV337 Dosing Groups

Parameters	SLV337 Dosing Group		
	400 mg (N = 17)	800 mg (N = 13)	1400 mg (N = 15)
$AUC_{0-\tau}$ (µg.h/mL)	34.3 (11.5)	50.7 (21.4)	71.4 (29.2)
	32.3	46.4	65.2
AUC_{0-t} (µg.h/mL)	34.3 (11.5)	50.7 (21.4)	71.4 (29.2)
	32.3	46.4	65.2
C_{max} (µg/mL)	4.80 (2.14)	6.85 (2.91)	8.24 (3.32)
	4.39	6.20	7.54
t_{max}[a] (h)	3.00 (1.00 – 6.00)	2.50 (1.50 – 4.17)	3.00 (0.00 – 6.00)
M/P_$AUC_{0-\tau}$	1.04 (0.268)	1.04 (0.323)	1.03 (0.321)
	1.00	0.984	0.986
M/P_C_{max}	1.10 (0.337)	1.10 (0.275)	1.01 (0.330)
	1.06	1.06	0.955

[a] t_{max} is presented as median (minimum - maximum); SD = standard deviation.
Source: Table 10.1.2.3.2

Across the studied dose range of 400 mg to 1,400 mg, exposure parameters ($AUC_{0-\tau}$ and C_{max}) increased in a less than dose-proportional manner for both SLV337 and SLV337 acyl-glucuronide on Day 28 with increasing doses. Median t_{max} for SLV337 and SLV337 acyl-glucuronide was independent of the administered SLV337 dose.

SLV337 acyl-glucuronide exposure was comparable to SLV337 exposure across the doses.

Table 3. Summary of Arithmetic Mean (SD) and Geometric Mean Plasma Metformin Pharmacokinetic Parameters

Parameters	Metformin	
	Day -1	Day 28
All Subjects	**n = 37**	**n = 39**
AUC_{0-t} (ng.h/mL)	23800 (10300)	24900 (13300)
	21500	21100
C_{max} (ng/mL)	1800 (698)	1850 (718)
	1660	1670
t_{max}[a] (h)	4.00 (0.00 - 24.00)	4.00 (0.00 - 24.13)
Low Metformin Dose[b]	**n = 10**	**n = 11**
AUC_{0-t} (ng.h/mL)	13000 (4800)	16900 (12200)
	12300	14100
C_{max} (ng/mL)	1170 (438)	1450 (647)
	1110	1320
t_{max}[a] (h)	3.75 (0.00 - 12.00)	3.47 (0.00 - 24.00)
Medium Metformin Dose[b]	**n = 18**	**n = 18**
AUC_{0-t} (ng.h/mL)	25900 (8590)	27000 (14100)
	24600	22800
C_{max} (ng/mL)	1960 (695)	1930 (795)
	1850	1710
t_{max}[a] (h)	3.50 (1.00 - 24.00)	5.00 (0.00 - 24.13)
High Metformin Dose[b]	**n = 9**	**n = 10**
AUC_{0-t} (ng.h/mL)	31800 (8380)	29900 (9370)
	30800	28400
C_{max} (ng/mL)	2170 (502)	2130 (465)
	2110	2090
t_{max}[a] (h)	8.00 (0.00 - 12.02)	6.00 (1.48 - 12.00)

[a] t_{max} is presented as median (minimum - maximum); SD = standard deviation.

[b] low metformin dose: ≤ 1,000 mg; medium metformin dose: > 1,000 and ≤ 2,000 mg; high metformin dose: > 2,000 mg.

Source: Table 10.1.2.3.3 and 10.1.2.3.3.b

Concomitant administration of SLV337 with stable doses of metformin did not significantly alter metformin exposure.

Pharmacodynamic Results:

For the FA/PD subject sample, after 400 to 1400 mg SLV337, dose-related improvement (decrease) of FPG was reported in the 800 and 1400 mg doses groups: -8% and -9% at Day 21, -11% and -15% at Day 28, respectively. The SLV337 400 mg dose had only a small lowering effect on FPG (≤ 5%) and placebo group modestly improved FPG on the first three weeks but decreased it up to 11% on Day 28. The placebo-adjusted LS mean differences of percentage change from baseline of FPG were -5% at Day 21 with the 800 and 1,400 mg doses of SLV337 but only -2% and 3%, respectively at Day 28 (Table 4).

Similarly average blood glucose and average postprandial blood glucose did not change in the 400 and 800 mg dose groups but decreased about 13% in the 1,400 mg dose group. The placebo-adjusted LS mean differences of percentage change from baseline for average blood glucose and average postprandial blood glucose were -5% and -7%, respectively at Day 28 with the 1,400 mg dose of SLV337 (Table 4).

Insulin and pro-insulin decreased after SLV337 doses. The HOMA_IR was decreased with increasing SLV337 dose.

Table 4. FA/PD: LS Mean Difference* (SE) Percentage Change From Baseline Values of Glucose-related Pharmacodynamic Variables

Parameter/Day	Statistics	400 mg N = 17	800 mg N = 15	1,400 mg N = 15
FPG	n	17	15	15
Day 21	LSM Diff (SE)	0.303 (6.09)	-5.48 (6.23)	-4.53 (6.25)
Day 28	LSM Diff (SE)	8.16 (6.02)	-2.03 (6.21)	-3.23 (6.19)
Mean 7 Glucose	n	17	15	15
Day 28	LSM Diff (SE)	2.05 (4.97)	0.519 (5.13)	-4.79 (5.11)
Mean 3 PP Glucose	n	17	15	15
Day 28	LSM Diff (SE)	2.17 (6.24)	-1.84 (6.42)	-7.43 (6.42)
Insulin	n	17	14	15
Day 28	LSM Diff (SE)	-12.8 (17.4)	-1.17 (18.5)	-33.1 (18.0)
Pro-insulin	n	17	14	15
Day 28	LSM Diff (SE)	-22.2 (14.2)	-18.0 (14.8)	-33.0 (14.6)

* placebo-corrected
Note: significant difference ($p < 0.05$) was reported for pro-insulin at dose SLV337 1400 mg
LSM Diff = least square mean difference; FPG = fasting plasma glucose; SE = standard error; mean 7 glucose = average blood glucose; mean 3 PP glucose = average postprandial blood glucose.
Source: Table 10.1.2.4.1.1

The mean levels of fructosamine, HbA1c, and pro-insulin/insulin ratio were comparable between SLV337 dose groups and placebo.

The TG levels were significantly lower in the 800 and 1400 mg dose groups on Day 28 than those in placebo ($p < 0.05$). There was a trend toward decreasing TG level with increasing SLV337 dose, the decrease reached a plateau after two weeks with SLV337. The placebo-adjusted LS mean differences of percentage change from baseline ranged from -18% to -27% with SLV337 doses at Day 28 (Table 5).

The HDL-C levels were significantly higher in the 800 and 1,400 mg dose groups on Day 28 than those in placebo ($p < 0.05$). The HDL-C was increased in all doses but the 1,400 mg group increased the largest. HDL-C increase was gradual and did not reach plateau during the study.

The placebo-adjusted LS mean differences of percentage change from baseline of HDL-C were +9%, +15%, and +25% at Day 28 with increasing doses of SLV337 (Table 5).

The LDL-C levels overall increased on Day 28 (9% to 25%) but similar increases from baseline were reported in the 400 mg, 1,400 mg, and placebo group whereas no increase was found in the 800 mg group. The placebo-adjusted LS mean differences of percentage change from baseline for LDL-C varied from -9% to +8% with the doses of SLV337 at Day 28 (Table 5), without any dose-related relationship. At Baseline the observed mean levels of LDL-C were markedly different within the four groups. Subgroup analyses by baseline LDL-C values < or ≥ median LDL-C (2.8 mmol/L), reported no change in LDL-C in the ≥ median LDL-C subgroup. The overall LDL-C increase effect of SLV337 could be related to marked LDL-C rises in few subjects with very low LDL-C levels at Baseline (from 1.2 to 2.2 mmol/L), most of them included in the 1,400 mg group. In these few subjects LDL-C rising was progressive with time.

The FFA was decreased compared to the placebo in which the FFA did not change.

The effect of increasing doses of SLV337 on TC, non-HDL-C, apoA1, apoB and apo CIII levels over Day 7 though Day 28 interval following multiple doses was minimal and not different from placebo Table 5).

Table 5. FA/PD: LS Mean Difference* (SE) Percentage Change From Baseline Values of Lipid-related Pharmacodynamic Variables

Parameter/Day	Statistics	400 mg N = 17	800 mg N = 15	1,400 mg N = 15
TG	n	16	14	14
Day 28	LSM Diff (SE)	-17.7 (9.84)	-22.4 (10.3)	-26.5 (10.1)
TC	n	16	14	14
Day 28	LSM Diff (SE)	0.410 (8.53)	3.42 (9.40)	0.946 (9.08)
HDL-C	n	16	14	14
Day 28	LSM Diff (SE)	9.40 (6.06)	15.0 (6.25)	24.5 (6.24)
LDL-C	n	16	14	14
Day 28	LSM Diff (SE)	3.23 (12.6)	-8.75 (13.6)	7.59 (13.5)
Non-HDL-C	n	16	14	14
Day 28	LSM Diff (SE)	-3.71 (13.3)	0.789 (14.8)	-8.32 (14.2)
FFA	n	17	15	14
Day 21	LSM Diff (SE)	-32.0 (14.8)	-16.5 (14.9)	-28.9 (14.9)
apo B	n	16	15	14
Day 28	LSM Diff (SE)	0.159 (8.28)	-6.38 (8.88)	-3.12 (8.94)
apoAI	n	16	15	14
Day 28	LSM Diff (SE)	7.08 (4.67)	3.16 (4.74)	8.41 (4.82)
apo B/ apoAI	n	16	15	14
Day 28	LSM Diff (SE)	-6.43 (8.06)	-6.80 (8.62)	-9.24 (8.66)
apoCIII	n	17	15	15
Day 28	LSM Diff (SE)	-0.223 (10.6)	6.23 (10.9)	10.5 (10.9)

* placebo-corrected
Note: significant differences ($p < 0.05$) were reported for TG and HDL-C at doses SLV337 800 and 1400 mg
LSM Diff = least square mean difference; TG = triglyceride; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; FFA = free fatty acid; apoA1 = apolipoprotein A1; SE = standard error.
Source: Table 10.1.2.4.4.1

Dose-dependent increases of total adiponectin were seen. The levels of total adiponectin and HMW adiponectin in the 800 and 1,400 mg dose groups on Day 28 were significantly higher than those in the placebo group ($p < 0.05$). The increases of total and HMW adiponectin were progressive over the time. The 1,400 mg dose showed greater increases in the levels of HMW adiponectin/total adiponectin ratio than the other dose groups. HsCRP level decreased in the SLV337 800 mg group but did not change in the other dose groups.

The analyses of PD variables for PP subject sample and subgroups gave similar results as that in FA/PD.

Pharmacokinetic/Pharmacodynamic Relationship:

At exposure lower than $AUC_{0-\tau} < 40$ µ·h/mL, no clear trend in change for FPG was seen. At $AUC_{0-\tau}$ between 40 and 80 µ.h/mL, a trend to FPG decrease, up to about -15%, was seen. No clear PK/PD relationship was identified for FPG with C_{max}. Overall TG decreased with increasing SLV337 exposure ($AUC_{0-\tau}$ and C_{max}). Up to 40% TG lowering was reported at exposure of about 50 µg·h/mL for $AUC_{0-\tau}$ and about 10 µg/mL for C_{max}. With higher exposure of SLV337, there was no additional TG-lowering effect. Overall HDL-C increased with increasing SLV337 exposure. At least 15% HDL-C rising effect was observed at $AUC_{0-\tau}$ of 55 µg·h/mL and at C_{max} of about 7 µg/mL. Up to 40% increasing was reported at $AUC_{0-\tau}$ of about 80 µg·h/mL and C_{max} of about 10 µg/mL. Overall total adiponectin, HMW-adiponectin, and HMW-adiponectin/total adiponectin increased with increasing SLV337 exposure. Exposures of about 50 µg.h/mL for $AUC_{0-\tau}$ and about 7 µg/mL for C_{max} resulted in more than 200% increase for the percentage change from baseline total adiponectin.

Safety Results:

There were no deaths, serious adverse events (SAEs), treatment-emergent serious adverse events (TESAEs), or subjects who withdrew from the study or discontinued study drug due to a TEAE. No incidences of TEAEs of special interest were reported.

One subject reported one severe TEAE (headache) in the SLV337 800 mg group. The event was considered to have a causal relationship to the study drug by the investigator. The majority of TEAEs reported in all the treatment groups were considered to be mild in severity and resolved by the end of the study. The five TEAEs considered to have a causal relationship to the study drug were hypochromic anemia (one event reported by one subject), constipation (one event reported by one subject), urinary tract infection (one event reported by one subject) and headache (two events reported by one subject).

No subjects had post-baseline hypoglycemic episodes, diagnosis of muscle events, diagnosis of pedal edema or diagnosis of cardiovascular events requiring adjudication by the independent cardiovascular committee.

No subjects had increased values of aspartate aminotransferase, alanine aminotransferase (ALT) or total bilirubin, and no subjects had creatine kinase values > 3 x upper limit if normal.

Small changes were noted in the mean and median values over time for the hematology, biochemistry, and urinalysis variables, but no clinically relevant effects were noticed and no trends could be identified for hematology, albumin, creatinine, cystatin C, creatine kinase, osteocalcin, and urinalysis variables. Compared to placebo, trends were noted for SLV337 to

decrease ALT and alkaline phosphatase, and to increase serum homocysteine and B-Crosslaps. Markedly abnormal post-baseline hematocrit values (decreases in five subjects) and white blood cell values (increases in two subjects and decrease from Day 1 before study drug administration in one subject) were reported. No clinically relevant effects or trends were noted for the other parameters.

Small changes from baseline at post-baseline visits were observed but no trends could be noted for the vital signs measurements. The number of subjects with weight gain > 3% was small (11 subjects) and similar numbers of subjects were reported in the four treatment groups. The number of subjects with quick weight gain (> 3% at Day 7 or Day 14) was also small and similar in the four treatment groups.

Markedly abnormal post-baseline values for weight (8% increase in one subject), systolic blood pressure (increase to 180 mmHg in one subject), and pulse rate (increase to 124 bpm in one subject) were reported with SLV337.

For the Safety/FA/PD subject sample as well as the PP subject sample, variation in the AFV and left and right AC measurements were observed for the mean change from baseline at the post-baseline visits, but no trends could be identified.

Although changes were noted in the heart rate, PR interval, QRS interval, QT interval, QTcB, QTcF, and RR interval over time, no trends could be identified. Abnormal clinically significant ECG assessments were reported for a number of subjects in all the treatment groups including the placebo group at all time points. In total, 31 subjects (50.8%) reported a treatment-emergent ECG diagnosis. The most frequently reported treatment-emergent ECG diagnoses were non-specific T wave abnormality. None of these diagnoses were identified to belong to cardiovascular diagnoses requiring adjudication by the independent cardiovascular committee.

Conclusion:

Safety

- There were no deaths, SAEs or subjects who withdrew from the study or discontinued study drug. No TEAEs of special interest were reported (edema-related events and cardiovascular diagnoses).
- No subjects had hypoglycemic episodes, diagnosis of muscle events or diagnosis of pedal edema.
- No trends could be identified for hematology, albumin, creatinine, cystatin C, creatine kinase, osteocalcin, and urinalysis variables. Compared to placebo, trends were noted for SLV337 to decrease ALT and alkaline phosphatase, and to increase serum homocysteine and B-Crosslaps.
- No trends could be noted for the vital signs measurements and in the ECG assessments.
- Overall, SLV337 was safe and well tolerated when administered as 400, 800 and 1,400 mg oral doses once daily for four weeks to males and females with T2DM on metformin monotherapy

Pharmacokinetic

- Exposure parameters ($AUC_{0-\tau}$ and C_{max}) of SLV337 and SLV337 acyl-glucuronide

increased in a less than dose-proportional manner following once-daily oral dose of 400 mg, 800 mg, and 1,400 mg SLV337 on Day 28 in patients with T2DM on metformin monotherapy.

- Steady-state SLV337 and SLV337 acyl-glucuronide concentrations were achieved by Day 7 and were maintained between Day 7 and Day 28 for all dosing groups.
- SLV337 acyl-glucuronide exposure was comparable to SLV337. The metabolite/parent ratio for $AUC_{0-\tau}$ and C_{max} on Day 28 was close to one.
- SLV337 concomitantly administered with stable doses of metformin did not significantly alter the metformin exposure.

Pharmacodynamic – Glucose-related Parameters

- SLV337 400 mg had only small decrease effect on FPG and no time-related improvement, whereas SLV337 800 and 1,400 mg improved FPG in a time and dose related manner. However, in FPG also improved in the fourth week of treatment. Therefore, the effect of increasing doses of SLV337 on FPG resulted in no difference between SLV337 and placebo at Day 28.
- Compared to placebo average blood glucose and average postprandial blood glucose did not change in the 400 and 800 mg dose groups but decreased in the 1,400 mg dose group.
- SLV337 decreased insulin and pro-insulin across SLV337 doses and dose-related decrease in HOMA_IR.
- SLV337 and placebo had minor effect on fructosamine and HbA1c.

Pharmacodynamic – Lipids and Apolipoproteins

- Dose-related TG decreasing effect was seen, up to about 32% in the 1,400 mg group. The TG mean values reached a plateau after about two weeks of treatment.
- Dose-related HDL-C increasing effect was seen, up to 28% in the 1,400 mg group. There was a gradual, increase of HDL-C with time for the doses of SLV337, which did not reach plateau during the study.
- Overall SLV337 increased LDL-C on Day 28, but similar increases were reported in the SLV337 400 mg and 1,400 mg groups and in placebo whereas no increase was found in the 800 mg group. The overall LDL-C increase effect of SLV337 was likely to be related to marked LDL-C rises in few subjects with very low LDL-C levels at Baseline. In these few subjects LDL-C rising was progressive with time.
- SLV337 decreased FFA but no dose effect was evident.
- The effect of increasing doses of SLV337 on TC, non-HDL-C, apoA1, apoB and apo CIII was not different from placebo.

Pharmacodynamic – Other Parameters

- SLV337 had a dose-related increasing effect on total adiponectin and HMW-adiponectin. The increases were progressive over the time. The 1,400 mg SLV337 dose group increased

HMW-adiponectin/total adiponectin ratio.

- SLV337 had no consistent effect on hsCRP.

Pharmacokinetic-Pharmacodynamic Relationship

- The PK/PD relationship was difficult to interpret for FPG. A trend to FPG decrease was possibly documented when exposure increased over $AUC_{0-\tau}$ of about 40 µg·h/mL.
- Overall change from baseline and percentage change from baseline TG decreased when SLV337 exposure ($AUC_{0-\tau}$ and C_{max}) increased. With higher exposure of SLV337, there was no additional TG-lowering effect. Up to 40% TG lowering was reported at $AUC_{0-\tau}$ exposure of about 50 µg·h/mL.
- Overall, change from baseline and percentage change from baseline HDL-C increased when SLV337 exposure increased. At least 15% HDL-C rising effect was observed at $AUC_{0-\tau}$ of 55 µg·h/mL.
- Overall, change from baseline and percentage change from baseline total adiponectin, HMW-adiponectin, and HMW-adiponectin/total adiponectin increased with increasing SLV337 exposure. Exposures of about 50 µg·h/mL for $AUC_{0-\tau}$ resulted in more than 200% increase for the percentage change from baseline total adiponectin.

Overall, SLV337 showed effects on glucose-related parameters and improved TG and HDL-C in the range of dose from 400 to 1,400 mg/day.