SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP1941 L-proline		
Title of Study: A Phase 2a, Randomized, Double-Blind, Placebo Controlled, Multiple Dose Study to Assess the Safety and Tolerability of ASP1941 in Adult Patients with Type 2 Diabetes Mellitus (ISN/Protocol 1941-CL-0016)		
Responsible Medical Officer/Investigators: [redacted], MD, MBA		
Study Center(s): The study consisted of one site [redacted]		
Publication (reference): None		
Study Period: **Date of First Enrollment:** 23 October 2008 (1st randomization) **Date of Last Evaluation:** 06 March 2009	**Phase of Development:** 2a	
Objectives: The primary objective of this study was to assess the safety and tolerability of 28 days of dosing with ASP1941 compared with placebo in adult patients with type 2 diabetes mellitus (T2DM). Secondary objectives of this study were to assess the pharmacodynamic effects of ASP1941 compared with placebo, and to assess the pharmacokinetics of ASP1941 in patients with T2DM.		
Methodology: This was a 4-week, single-center, double-blind, randomized, parallel-group, placebo-controlled, multiple-dose study in patients with T2DM. Patients were randomized to double-blind treatment in 1 of 5 treatment groups, of which each treatment group contained 12 patients: Group 1: ASP1941 50 mg once daily Group 2: ASP1941 100 mg once daily Group 3: ASP1941 200 mg once daily Group 4: ASP1941 300 mg once daily Group 5: Placebo Patients who took oral antidiabetic medication underwent a 2-week washout period followed by a 4-week treatment		

period. Patients who were naïve to antidiabetic medication entered directly into the 4-week treatment period. Patients were confined for the duration of the treatment period, beginning confinement on Day -1 and ending on Day 30. During confinement, patients were fed a standardized, weight maintenance diet, which was adjusted based on caloric needs. All patients were followed for 2 weeks after study treatment was discontinued.

Number of Patients (enrolled and analyzed): A total of 61 patients were enrolled in the study and included in the SAF (safety analysis set) and the PKAS (pharmacokinetic analysis set). Sixty patients were analyzed in the PDAS (pharmacodynamic set).

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Patient was ≥ 18 years and ≤ 75 years of age.
2. Patient was diagnosed with type 2 diabetes mellitus for at least 3 months.
3. Patient had an HbA1c value between 7.0 and 10.0%, inclusive, at Day -14.
4. Patient was naïve to antidiabetic medication (diet-controlled), or was willing and able to safely discontinue antidiabetic therapy at Screening (for at least 2 weeks prior to the first dose of study medication) and for the duration of the study (8 weeks total).
5. Patient had a body mass index (BMI) 20 to 45 kg/m^2 on Day -14.

Exclusion Criteria

1. Patient had any known complication of T2DM indicating a late disease state macro- and/or microvascular disorder.
2. Patient had type 1 diabetes mellitus.
3. Patient received insulin within 3 months prior to Day -14.
4. Patient received high doses of dual oral combination therapy (> 50% of maximum doses of each component).
5. Patient had a serum creatinine higher than upper limit of normal range at Day -14.
6. Patient had an alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) value higher than 3 times upper limit of normal range at Day -14.
7. Patient had a positive urine dipstick for protein or a urinary microalbumin/urinary creatinine ratio > 300 mg/g at Day -14.
8. Patient had a urinary tract infection within 4 weeks prior to Day -14.
9. Patient had persistent, uncontrolled severe hypertension as indicated by a systolic blood pressure > 170 mmHg or a diastolic blood pressure of > 95 mmHg taken in a sitting position after 5 minutes of rest on at least 2 measurements.
10. Patient had clinical evidence of renal disease (including renovascular occlusive disease, nephrectomy and/or renal transplant).
11. Patient had a significant cardiovascular disease, such as myocardial infarction or a vascular intervention (e.g., angioplasty or stent) within 6 months prior to Day -14, history of heart failure (NYHA Class II-IV) or any other concurrent illness which, in the opinion of the investigator, may have interfered with treatment or evaluation of safety.
12. Patient was known to have hepatitis or be a carrier of hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody (ELISA plus confirmatory test), or was known positive for HIV-1 and/or HIV-2.
13. Patient had a history of drug or alcohol abuse/dependency within 12 months prior to screening as defined in the Diagnostic and Statistical Manual-IV (DSM-IV) and/or had a positive urine drug screen at Day -14 or Day -1.

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

ASP1941 was administered orally (6 tablets in total) as described below:

Group 1: ASP1941 50 mg once daily before breakfast
Group 2: ASP1941 100 mg once daily before breakfast
Group 3: ASP1941 200 mg once daily before breakfast
Group 4: ASP1941 300 mg once daily before breakfast

The batch number for the active lot of ASP1941 was [redacted].

Duration of Treatment (or Duration of Study, if applicable): 28 days.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Group 5: Placebo to match (PTM) was administered orally (6 tablets in total).

The batch number for the placebo lot of ASP1941 was [redacted].

Placebo was chosen as the reference product to assist the medical assessment whether or not any abnormalities were due to ASP1941 or to study procedures.

Criteria for Evaluation:

Primary Variables:

Safety:

- Nature, frequency and severity of AEs
- Vital sign measurements (blood pressure, heart rate, respiration, and body temperature) including assessment of postural changes on blood pressure and heart rate
- Electrocardiogram measurements
- Physical examination
- Routine clinical safety laboratory evaluations (chemistry, hematology, urinalysis) including serum creatinine and bedside fingerstick glucose measurement
- Incidence of hypoglycemia defined as a blood glucose of < 70 mg/dL or 3.9 mmol/L

Secondary Variables

Pharmacokinetic parameters

- Plasma: Area under the curve over a 24-hour period (AUC_{24}), maximum observed concentration (C_{max}), time to reach C_{max} (t_{max})
- Plasma: Observed trough concentration obtained just prior to dosing (C_{trough})
- Plasma: Amount of drug or glucose excreted in plasma over the time interval between consecutive dosing (AUC_{tau}), C_{max}, t_{max}
- Urine: Fraction of drug or glucose excreted into urine (Ae) in a 24-hour period (Ae_{24}).
- Urine: Amount of drug or glucose excreted in urine over the time interval between consecutive dosing (Ae_{tau}), Ae_{tau}%, renal clearance calculated as AE/AUC (CL_R)

Pharmacodynamic parameters

- Hemoglobin A_{1c} (HbA_{1c})
- Fasting Plasma Glucose (FPG)
- Urinary glucose profiles; rate of glucose excretion (Ae_{24})
- Blood glucose; mean amplitude glucose excursion (MAGE), C_{max}, and AUC_{24}
- Fructosamine
- Insulin

Exploratory:

[redacted]

Statistical Methods:

All statistical comparisons were made using 2-sided tests at the alpha=0.05 significance level unless specifically stated otherwise. All null hypotheses were of no treatment difference. All alternative hypotheses were 2-sided.

Pharmacokinetic parameters were calculated using non-compartmental analysis. For continuous PK/PD parameters, descriptive statistics were calculated by the number of patients (n), mean, standard deviation (SD), coefficient of variation, geometric mean, minimum, median and maximum.

Plots of mean change from baseline±SD of urinary [redacted] over time by treatment group were displayed for patients in the SAF set.

Summary

Demographics:

Overall, the number of male versus female patients were relatively equally distributed; 35 male patients versus 26 female patients, and most patients were white (93%) and Hispanic or Latino (77%). The total mean age of patients was 57 years; however the mean age in the placebo group was lower (53 years) than all ASP1941 treatment groups. The duration of disease in most (66%) patients was greater than 5 years, and mean weight, height, and BMI were similar among treatment groups [Table 1].

Drug Administration:

The mean cumulative dose for the ASP1941 treatment groups ranged from 1400 mg in the ASP1941 50 mg treatment group to 8100 mg in the ASP1941 300 mg treatment group, and the mean daily dose ranged from 0.60 mg/kg in the ASP1941 50 mg group to 3.53 mg/kg in the ASP1941 300 mg group.

Pharmacokinetic/Pharmacodynamic Results:

Pharmacokinetic results

The AUC and C_{max} of ASP1941 at steady state showed dose linearity in diabetic patients at the tested dose range of 50 mg to 300 mg.

The t_{max} of ASP1941 was approximately 1 hour and similar on Day 1 and Day 28, and C_{max} was slightly higher on Day 28 after repeated doses compared to Day 1 [Table 2 and Table 3].

At steady state, ASP1941 pharmacokinetic parameters including $t_{½}$, clearance, volume of distribution, peak trough ratio (degree of fluctuation) were consistent among different dosing groups (Table 3). Steady state was reached by Day 7. Steady state for trough concentrations prior to dosing was similar among the ASP1941 treatment groups, and occurred on approximately Day 7.

The percentage of cumulative amount of ASP1941 excreted into urine at steady state (Ae_{tau}%) were similar across all dose levels. The renal clearance (CL_R) only accounted for approximately 2% of the total oral clearance.

Urinary ASP1941 concentrations over 24 hours (Ae_{24}) slightly increased on Day 14 compared with Day 1 [Table 4], and the cumulative amount of ASP1941 excreted into urine over time intervals between consecutive doses (Ae_{tau}) on Day 28 was dose proportional among ASP1941 treatment groups. The Ae_{tau}% and renal clearance (CL_R) were similar across treatment groups [Table 5].

Pharmacodynamic results

There were statistically significant decreases in the change from baseline on Day 28 in HbA_{1c}, FPG, and MAGE in all ASP1941 dose groups compared with placebo [Table 6]. Significant decreases in the change from baseline were observed in fasting serum fructosamine in most ASP1941 dose groups at end of treatment compared with placebo. Additionally, significant decreases were observed in the change from baseline for insulin in the ASP1941 300 mg treatment group at end of treatment compared with placebo.

Results for the urinary glucose pharmacodynamic parameter, Ae_{24}, indicated increases compared with baseline on Day 1, 14 and 28 in all ASP1941 treatment groups; mean values in the placebo group decreased compared with baseline through Day 28 [Table 7]. Urinary glucose excretion (when adjusted for baseline) showed a clear dose response up to 100 mg, and reached a plateau above doses of 100 mg. Additional results in urinary glucose assessments, including GER,

revealed increases compared with baseline in all the ASP1941 treatment groups; mean values in the placebo group remained consistent compared with baseline through Day 28.

The volume of urine voided did not change in all treatment groups.

Efficacy Results: Not applicable.

Safety Results:

A total of 43 (90%) patients experienced 214 TEAEs in the ASP1941 treatment groups (ASP1941 50 mg, 9/12 patients; ASP1941 100 mg, 12/12 patients; ASP1941 200 mg, 12/12 patients, ASP1941 300 mg, 10/12 patients), and 68 TEAEs occurred in 85% (11/13 patients) of patients in the placebo group [Table 8].

A total of 20 (41.7%) patients experienced 40 TEAEs in the ASP1941 treatment groups that were considered to be drug-related (ASP1941 50 mg, 5 events; ASP1941 100 mg, 13 events; ASP1941 200 mg, 14 events, ASP1941 300 mg, 8 events), and a greater number occurred in the placebo group (20 events) compared with the individual ASP1941 treatment groups.

The most common TEAE that occurred in at least 3 patients per treatment group was constipation; placebo, 4 patients (30.8%); ASP1941 50 mg, 8 patients (66.7%); ASP1941 100 mg, 4 patients (33.3%); ASP1941 200 mg, 7 patients (58.3%); and ASP1941 300 mg, 7 patients (58.3%).

No deaths occurred during the study.

Two patients experienced an SAE [Table 8]; 1 SAE of atrial fibrillation occurred in the placebo group and was considered to be possibly related to study drug, and 1 SAE of GERD occurred in the ASP1941 100 mg group, and was considered to be not related to study drug.

Substantial decreases in systolic BP and diastolic BP were noted for all dose groups, including placebo with no clear dose relationship among all treatment groups or compared with placebo. All changes in orthostatic blood pressure were asymptomatic, and overall, there were more cases of asymptomatic orthostatic hypotension in ASP1941 treatment groups than in the placebo group.

A decrease in the mean change from baseline in weight was observed in all treatment groups compared with baseline, and was greater in the ASP1941 treatment groups than placebo from Day 2 through Day 28; however, all dose groups experienced a rapid gain in weight after study drug was discontinued following Day 28 through the end of the study.

One patient in the placebo group experienced hyperglycemia that was considered not related to study drug and one patient in the ASP1941 200 mg group experienced hypoglycemia that was considered as possibly related to study drug. A greater number of patients in the placebo group (38.5%) had skin-related TEAEs compared with most individual ASP1941 treatment groups, with the exception of the ASP1941 200 mg treatment group (66.7%).

Most laboratory assessments remained within normal range during the study in all ASP1941 and placebo treatment groups. BUN levels increased in most ASP1941 treatment groups but returned to Baseline levels 2 weeks after end of treatment.

See section 9.2.2.1.1 of the report for results of exploratory urinary assessments.

CONCLUSIONS:

ASP1941 was safe and well tolerated compared with placebo at all doses with no dose-limiting safety findings or pharmacokinetic/pharmacodynamic findings in adult patients with type 2 diabetes mellitus.

Date of Report: 06 Nov 2009

Table 1 Demographic and Baseline Characteristics; SAF

Parameter	Placebo n=13†	ASP1941 50 mg n=12	ASP1941 100 mg n=12	ASP1941 200 mg n=12	ASP1941 300 mg n=12	Total N=61
Sex						
Male	9 (69.2%)	5 (41.7%)	7 (58.3%)	8 (66.7%)	6 (50.0%)	35 (57.4%)
Female	4 (30.8%)	7 (58.3%)	5 (41.7%)	4 (33.3%)	6 (50.0%)	26 (42.6%)
Race, n (%)						
White	13 (100.0%)	12 (100.0%)	11 (91.7%)	10 (83.3%)	11 (91.7%)	57 (93.4%)
Black or African American	0 (0.0)	0 (0.0)	1 (8.3%)	1 (8.3%)	0 (0.0)	2 (3.3%)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3%)	1 (1.6%)
Native Hawaiian-Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3%)	0 (0.0)	1 (1.6%)
Ethnicity, n (%)						
Hispanic or Latino	11 (84.6%)	7 (58.3%)	10 (83.3%)	9 (75.0%)	10 (83.3%)	47 (77.0%)
Non-Hispanic or Latino	2 (15.4%)	5 (41.7%)	2 (16.7%)	3 (25.0%)	2 (16.7%)	14 (23.0%)
Duration of Disease, n (%)						
3 months-< 1 yr	1 (7.7%)	0 (0.0)	1 (8.3%)	0 (0.0)	0 (0.0%)	2 (3.3%)
1 yr-< 3 yrs	1 (7.7%)	1 (8.3%)	2 (16.7%)	1 (8.3%)	1 (8.3%)	6 (9.8%)
3 yr-< 5 yrs	5 (38.5%)	2 (16.7%)	2 (16.7%)	2 (16.7%)	2 (16.7%)	13 (21.3%)
> 5 yrs	6 (46.2%)	9 (75.0%)	7 (58.3%)	9 (75.0%)	9 (75.0%)	40 (65.6%)
Age (years)						
Mean±SD	53.3±11.91	57.7±9.08	57.3±9.53	59.8±6.36	56.8±9.70	56.9±9.45
Median	58.0	59.5	59.5	61.0	57.0	60.0
Range	26, 65	41, 71	39, 69	49, 70	42, 72	26, 72
Weight (kg)						
Mean±SD	89.3±13.48	85.1±12.73	93.8±13.09	87.7±16.68	87.7±18.59	88.7 ±14.83
Median	87.4	86.8	93.6	82.3	83.7	86.4
Range	70.3, 122.9	57.1, 99.3	75.6, 122.6	65.5 122.5	68.9, 140.1	57.1, 140.1
Height (cm)						
Mean±SD	167.3±11.35	167.0±11.29	167.1±11.24	165.1±9.52	163.5±10.25	166.0±10.51
Median	167.0	170.8	170.0	165.3	160.0	167.0
Range	152.0, 196.6	145.8, 178.5	150.5, 181.0	146.9, 181.3	151.3, 182.0	145.8, 196.6
BMI (kg/m^2)						
Mean±SD	32.4±4.32	30.6±4.62	34.1±5.28	32.5±5.49	32.9±4.55	32.5±4.83
Median	31.8	30.7	34.4	32.5	32.8	32.2
Range	25.2, 38.6	23.4, 39.7	26.1, 41.1	23.8, 42.0	24.4, 42.1	23.4, 42.1

All patients who received at least one dose of study drug (Safety Analysis Set)
† Patient [redacted] was included in the Pharmacokinetic and Safety Analysis Sets
BMI: body mass index; SAF: safety analysis set.

Table 2 Day 1 Mean Values for Plasma Pharmacokinetic Parameters; PKAS

Parameter		ASP1941 50 mg n=12	ASP1941 100 mg n=12	ASP1941 200 mg n=12	ASP1941 300 mg n=12
AUC_{24} hr*ng/mL	Mean±SD	4410.03±918.62	8722.58±2345.91	18750.98±5581.98	26998.53±7342.71
	Median	4329.52	7842.76	17712.10	25962.82
	Range	3117.55, 5749.13	5584.48, 12886.78	12564.66, 31085.57	15624.95, 43224.52
	Geometric mean	4320.90	8444.62	18055.26	26109.31
C_{max} ng/mL	Mean±SD	896.90±202.50	1664.86±270.10	3767.71±1157.79	5811.85±1435.79
	Median	869.41	1653.62	3890.92	5481.70
	Range	675.80, 1258.21	1314.53, 2163.65	1887.36, 5447.58	3489.55, 8697.55
	Geometric mean	877.56	1645.29	3589.60	5656.91
t_{max} hr	Mean±SD	1.00±0.00	1.08±0.19	1.13±0.93	1.00±0.21
	Median	1.00	1.00	1.00	1.00
	Range	1.00, 1.00	1.00, 1.50	0.50, 4.00	0.50, 1.50
	Geometric mean	1.00	1.07	0.95	0.98

All patients who provided adequate pharmacokinetic samples (PKAS)

PKAS: pharmacokinetic analysis set.

Table 3 Day 28 Mean Plasma ASP1941 Pharmacokinetic Parameters by Treatment Group; PKAS

Parameter		ASP1941 50 mg n=12	ASP1941 100 mg n=12	ASP1941 200 mg n=11	ASP1941 300 mg n=10
AUC_{tau} hr*ng/mL	Mean±SD	5431.23±1290.74	10740.33±2728.43	23143.22±7713.19	33632.24±12033.34
	Median	5258.10	11116.01	20365.60	28316.82
	Range	3846.04, 8129.81	6861.97, 14425.46	15404.72, 41173.02	18684.30, 55136.00
	Geometric mean	5294.46	10405.81	22169.09	31859.18
AUC_{last} hr*ng/mL	Mean±SD	6787.73±1858.33	12958.36±3626.68	29476.80±13746.13	42070.43±17857.46
	Median	6926.09	13247.69	23784.84	35294.22
	Range	4580.79, 11372.84	7709.58, 18696.18	17273.31, 64496.32	21731.66, 74410.07
	Geometric mean	6576.62	12465.51	27338.09	39028.45
AUC_{inf} hr*ng/mL	Mean±SD	7017.60±2009.08	13361.35±3998.75	31065.64±16518.31	44166.88±20573.43
	Median	7156.24	13528.88	24258.62	36270.32
	Range	4631.29, 12013.64	7725.58, 20427.00	17310.41, 73959.31	21935.95, 81362.97
	Geometric mean	6781.90	12789.51	28284.63	40399.91
C_{max} ng/mL	Mean±SD	957.22±247.73	2047.29±856.10	3998.02±745.80	6081.79±2021.23
	Median	940.70	1870.43	3717.51	5566.84
	Range	546.10, 1432.78	1159.47, 4275.35	3236.49, 5012.41	3413.95, 9577.09
	Geometric mean	926.99	1915.67	3936.91	5782.51
t_{max} hr	Mean±SD	1.09±0.42	1.04±0.26	1.00±0.32	1.06±0.16
	Median	1.00	1.00	1.00	1.00
	Range	0.48, 1.55	0.50, 1.50	0.50, 1.50	1.00, 1.50
	Geometric mean	1.00	1.01	0.95	1.05
$t_{½}$ hr	Mean±SD	14.91±4.87	15.16±7.39	15.54±6.13	16.28±7.15
	Median	13.46	12.24	14.87	12.55
	Range	9.88, 23.83	8.66, 30.59	8.63, 28.12	10.23, 30.56
	Geometric mean	14.24	13.87	14.55	15.09
Vz/F L	Mean±SD	210.69±94.14	206.18±79.45	193.01±40.27	211.18±55.65
	Median	170.01	205.07	197.07	187.59
	Range	116.40, 412.08	105.37, 368.68	134.28, 283.57	141.38, 292.46
	Geometric mean	194.00	192.28	189.41	204.98
CL/F L/hr	Mean±SD	7.61±1.95	8.19±2.66	7.58±2.57	8.04±3.15
	Median	7.02	7.50	8.25	8.28
	Range	4.16, 10.80	4.9, 12.94	2.70, 11.55	3.69, 13.68
	Geometric mean	7.37	7.82	7.07	7.43
PTR	Mean±SD	16.28±7.39	17.03±6.98	14.58±5.31	17.44±13.18
	Median	15.68	14.16	14.80	14.13
	Range	6.50, 30.48	8.27, 30.38	5.34, 22.67	8.54, 54.05
	Geometric mean	14.74	15.76	13.56	15.03

All patients who provided adequate pharmacokinetic samples (PKAS)

PTR: peak trough ratio (degree of fluctuation) at steady-state; PKAS: pharmacokinetic analysis set.

Table 4 Day 1 and Day 14 Mean Values Over 24 Hours for Urinary ASP1941 Pharmacokinetic Parameters; PKAS

Parameter		ASP1941 50 mg n=12	ASP1941 100 mg n=12	ASP1941 200 mg n=12	ASP1941 300 mg n=12
Day 1 Ae_{24} (mg)	Mean±SD	0.65±0.16	1.30 ±0.33	2.74±0.77	4.40±1.07
	Median	0.64	1.29	2.62	4.14
	Range	0.31, 0.91	0.82, 2.03	1.93, 4.51	2.94, 5.95
	Geometric mean	0.62	1.26	2.66	4.27
Day 14 Ae_{24} (mg)	Mean±SD	0.75±0.21	1.59±0.44	3.07±0.76	4.89±1.17
	Median	0.72	1.51	3.02	5.26
	Range	0.35, 1.19	0.93, 2.54	2.07, 4.36	2.99, 6.23
	Geometric mean	0.72	1.53	2.99	4.75

All patients who provided adequate pharmacokinetic samples (PKAS)

PKAS: pharmacokinetic analysis set.

Table 5 Day 28 Mean Values for Urinary ASP1941 Pharmacokinetic Parameters; PKAS

Parameter		ASP1941 50 mg n=12	ASP1941 100 mg n=12	ASP1941 200 mg n=11	ASP1941 300 mg n=10
Day 28 Ae_{tau} (mg)	Mean±SD	0.85±0.38	1.54±0.46	3.12±0.55	4.95±1.34
	Median	0.79	1.56	3.18	4.93
	Range	0.35, 1.90	0.78, 2.57	2.11, 3.94	2.79, 6.86
	Geometric mean	0.79	1.47	3.08	4.77
Day 28 Ae_{tau} %	Mean±SD	1.69±0.76	1.54±0.46	1.56±0.27	1.65±0.45
	Median	1.58	1.56	1.59	1.64
	Range	0.70, 3.80	0.78, 2.57	1.06, 1.97	0.93, 2.29
	Geometric mean	1.57	1.47	1.54	1.59
Day 28 CL_R	Mean±SD	0.17±0.11	0.15±0.04	0.15±0.04	0.16±0.07
	Median	0.12	0.15	0.16	0.15
	Range	0.09, 0.49	0.05, 0.20	0.08, 0.20	0.08, 0.28
	Geometric mean	0.15	0.14	0.14	0.15

All patients who provided adequate pharmacokinetic samples (PKAS)

PKAS: pharmacokinetic analysis set.

Table 6 Change from Baseline at the End of Treatment for Plasma Pharmacodynamic Parameters in All ASP1941 Treatment Groups Compared to Placebo (SI Units); PDAS

Parameter	Placebo n=12 †	ASP1941 50 mg n=12	ASP1941 100 mg n=12	ASP1941 200 mg n=12	ASP1941 300 mg n=12
HbA_{1c} (%)					
LS Mean (SE)	-0.10 (0.14)	-0.73 (0.14)	-0.61 (0.14)	-0.84 (0.15)	-0.73 (0.14)
Treatment Difference (ASP1941 - placebo)	--	-0.63	-0.51	-0.74	-0.63
95% CI for Difference	--	(-1.03,-0.22)	(-0.91,-0.10)	(-1.16,-0.32)	(-1.03,-0.23)
P value	--	0.003	0.015	< 0.001	0.003
FPG (mmol/L)†					
LS Mean (SE)	-0.58 (0.50)	-3.35 (0.48)	-2.72 (0.49)	-3.92 (0.54)	-3.61 (0.49)
Treatment Difference (ASP1941 - placebo)	--	-2.78	-2.14	-3.34	-3.03
95% CI for Difference	--	(-4.18,-1.37)	(-3.56,-0.73)	(-4.83,-1.86)	(-4.43,-1.63)
P value	--	< 0.001	0.004	< 0.001	< 0.001
MAGE (mmol/L)					
LS Mean (SE)	-0.39 (0.63)	-3.00 (0.61)	-2.60 (0.61)	-3.74 (0.67)	-3.23 (0.61)
Treatment Difference (ASP1941 - placebo)	--	-2.61	-2.21	-3.36	-2.84
95% CI for Difference	--	(-4.38,-0.85)	(-3.98,-0.44)	(-5.21,-1.50)	(-4.61,-1.08)
P value	--	0.005	0.015	< 0.001	0.002
Fructosamine (mmol/L)					
LS Mean (SE)	0.001 (0.016)	-0.040 (0.015)	-0.053 (0.016)	-0.063 (0.017)	-0.056 (0.016)
Treatment Difference (ASP1941 - placebo)	--	-0.042	-0.054	-0.065	-0.058
95% CI for Difference	--	(-0.087,0.003)	(-0.099,-0.009)	(-0.112,-0.017)	(-0.103,-0.013)
P Value	--	0.067	0.019	0.008	0.013
Insulin (pmol/L)					
LS Mean (SE)	-32.72 (6.06)	-48.35(5.79)	-34.36(6.07)	-39.11(6.33)	-51.10(5.84)
Treatment Difference (ASP1941 - placebo)	--	-15.62	-1.64	-6.38	-18.38
95% CI for Difference	--	(-32.51,1.27)	(-19.11,15.83)	(-24.01,11.25)	(-35.21,-1.55)
P value	--	0.069	0.851	0.470	0.033

† Patient [redacted] was excluded from PDAS because he did not have adequate PD data to be included in the PD analysis and was therefore replaced

Note: End of treatment is Day 28 unless a patient in the PDAS discontinued earlier in which the patient's last value during treatment was used for the analysis.

Pairwise comparisons between each ASP1941 dose and placebo were performed within an ANCOVA to compare the mean change from baseline at the end of treatment in each PD parameter. The model consisted of treatment, sex and treatment*sex as fixed effects and baseline response and baseline creatinine clearance (MDRD) as covariates. The baseline CLcr was included in the model because Study 0052 showed the potential relationship between urine glucose excretion and baseline CLcr.

-- : Not calculated; PDAS: pharmacodynamic analysis set; CI: confidence interval; HbA_{1c}: hemoglobin A_{1c}; FPG: fasting plasma glucose; MAGE: mean amplitude glucose excursion.

Table 7 Mean Values in Ae_{24} [mmol] (Amount of Glucose Excreted into Urine Over 24 Hours) From Day -1 Through Day 28); PDAS

Day of Assessment	Placebo n=12†	ASP1941 50 mg n=12	ASP1941 100 mg n=12	ASP1941 200 mg n=12‡	ASP1941 300 mg n=12§
Day -1					
Mean (SD)	180.20 (236.30)	109.21 (186.85)	160.18 (176.42)	112.24 (117.26)	115.99 (202.20)
Median	87.77	23.11	96.40	64.90	45.68
Min, Max	0.93, 755.56	1.86, 625.51	2.57, 479.29	4.42, 394.33	2.85, 719.51
Geometric Mean	51.23	21.29	53.45	55.95	37.67
Day 1					
Mean (SD)	171.41 (215.37)	543.04 (247.19)	720.75 (277.26)	757.77 (332.86)	778.33 (207.34)
Median	131.94	496.52	690.36	726.85	792.62
Min, Max	3.12, 783.83	223.53, 1040.97	398.15, 1208.50	359.64, 1340.88	455.95, 1123.65
Geometric Mean	72.92	493.87	673.00	691.95	751.52
Day 14					
Mean (SD)	126.79 (196.11)	473.46 (216.77)	620.18 (228.23)	557.50 (174.27)	578.97 (176.28)
Median	64.04	433.16	592.81	525.17	557.43
Min, Max	0.86, 666.82	199.60, 877.99	264.55, 1023.55	331.81, 812.18	366.79, 1053.13
Geometric Mean	38.99	430.20	580.67	532.59	558.49
Day 28					
Mean (SD)	127.81 (194.26)	451.52 (159.31)	606.05 (229.46)	576.04 (211.59)	613.27 (204.94)
Median	60.63	426.46	593.57	516.90	549.13
Min, Max	0.76, 667.54	186.65, 681.44	233.33, 873.48	318.55, 927.61	431.13, 1157.65
Geometric Mean	37.56	423.30	560.34	541.94	590.37

† Patient [redacted] was excluded from PDAS because he did not have adequate PD data to be included in the PD analysis and was therefore replaced

PDAS: pharmacodynamic analysis set.

‡ASP1941 200 mg treatment group consisted of 11 patients on Day 28.

§ ASP1941 300 mg treatment group consisted of 10 patients on Day 28.

Table 8 Overview of Treatment-Emergent Adverse Events; SAF

	Placebo n=13†	ASP1941 50 mg n=12	ASP1941 100 mg n=12	ASP1941 200 mg n=12	ASP1941 300 mg n=12	ASP1941 Total N=48
Incidence of Adverse Events	11 (84.6%)	9 (75.0%)	12 (100%)	12 (100%)	10 (83.3%)	43 (89.6%)
Number of Adverse Events	68	55	53	56	50	214
Incidence of Drug-Related‡ Adverse Events	5 (38.5%)	3 (25.0%)	5 (41.7%)	6 (50.0%)	6 (50.0%)	20 (41.7%)
Number of Drug-Related‡ Adverse Events	20	5	13	14	8	40
Incidence of Deaths	0	0	0	0	0	0
Incidence of Serious Adverse Events	1 (7.7%)	0	1 (8.3%)	0	0	1 (2.1%)
Number of Serious Adverse Events	1	0	1	0	0	1
Incidence of Drug-Related Serious Adverse Events	1 (7.7%)	0	0	0	0	0
Number of Drug-Related Serious Adverse Events	1	0	0	0	0	0
Incidence of Adverse Events Leading to Permanent Discontinuation of Study Drug	1 (7.7%)	0	0	0	0	0
Number of Adverse Events Leading to Permanent Discontinuation of Study Drug	1	0	0	0	0	0
Incidence of Drug-Related Adverse Events Leading to Permanent Discontinuation of Study Drug	0	0	0	0	0	0
Number of Drug-Related Adverse Events Leading to Permanent Discontinuation of Study Drug	0	0	0	0	0	0

All patients who received at least one dose of study drug (Safety Analysis Set)
† Patient [redacted] was included in the Pharmacokinetic and Safety Analysis Sets
‡Possible or probable, as assessed by the investigator.

SAF: safety analysis set.