ISN 1941-CL-0072

Sponsor: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: Ipragliflozin (ASP1941)		

CLINICAL STUDY REPORT SYNOPSIS

Title of Study: Long-term Study of ASP1941 — Long-term Study in Patients with Type 2 Diabetes Mellitus with Decreased Renal Function (Japanese) — (Study Protocol Number: 1941-CL-0072)

Investigators/Coordinating Investigator: [redacted] at [redacted] and others

Study Centers: 67 centers in Japan

Publication: Not published

Duration of Study: About 1.9 years

Study Initiation Date (date of first informed consent): 18 January, 2011

Study Completion Date (date of last evaluation): 28 November, 2012

Phase of Development: Phase III

Objective: To examine the efficacy and safety of ASP1941 administered at a dose of 50 mg (a dose increase to 100 mg was allowed after Week 24 according to the dose increase criteria) once daily for 24 or 52 weeks in patients with type 2 diabetes mellitus (T2DM) with mild to moderate renal impairment whose blood glucose was poorly controlled with diet/exercise therapy alone or with pharmacotherapy using 1 oral antidiabetic drug (limited to an α-Glucosidase inhibitor, sulfonylureas, or pioglitazone), and examine the effect of renal function on the efficacy and safety of the drug.

Methodology: This study was performed as a long-term study to examine the efficacy and safety of ASP1941 and effect of renal function on them in T2DM patients with renal impairment. The subjects of the study were T2DM patients with mild to moderate renal impairment and whose blood glucose was poorly controlled with diet/exercise therapy alone or pharmacotherapy using 1 oral antidiabetic drug (limited to an α-Glucosidase inhibitor, sulfonylureas, or pioglitazone) for at least 12 weeks before Visit 1. The severity of renal impairment was evaluated based on the estimated glomerular filtration rate (eGFR) value at Visit 2 as calculated using the GFR estimation formula for Japanese people (using the age at Visit 2): a subject with

an eGFR of 60 mL/min/1.73 m^2 or higher and less than 90 mL/min/1.73 m^2 was considered to have mild renal impairment and a subject with an eGFR of 30 mL/min/1.73 m^2 or higher and less than 60 mL/min/1.73 m^2 was considered to have moderate renal impairment.

This study consisted of the observation period, treatment period I, treatment period II, and the follow-up period.

The observation period consisted of a 4-week screening period and 2-week placebo run-in period. In the placebo run-in period, 1 placebo tablet for the ASP1941 Tablet 50 mg for the observation period was administered in a single-blind manner once daily for 2 weeks. Subjects confirmed eligible, based on the inclusion and exclusion criteria, test results at Visits 1 and 2, and demographic characteristics, etc. were randomized either to the ASP1941 50 mg or placebo groups at a ratio of 2:1 between Visits 2 and 3. They were stratified by severity of renal impairment (mild vs. moderate) at randomization.

In treatment period I, 1 ASP1941 Tablet 50 mg or 1 placebo tablet was administered in a double-blind manner once daily for 24 weeks. Subjects who provided a written consent to continue the study by Visit 10 (Week 24) and were confirmed to have no safety concerns proceeded to treatment period II. Upon proceeding to treatment period II, it was allowed to increase the dose to 2 tablets (100 mg) of ASP1941 Tablet 50 mg once daily in subjects who met the dose increase criteria and who wished to increase the dose. Subjects who were unwilling to continue the study or considered to have safety concerns that prevented study continuation at Visit 10 discontinued the treatment with the study drug and proceeded to the follow-up period.

In treatment period II, 1 or 2 ASP1941 Tablet(s) 50 mg (50 or 100 mg) were administered in an open-label manner once daily for 28 weeks. It was allowed to reduce the dose to 1 ASP1941 Tablet 50 mg once daily (50 mg) after the dose was increased to 2 tablets once daily (100 mg) for subjects who were judged to have safety concerns. However, it was not allowed to re-increase the dose after the dose reduction.

A 4-week follow-up period was set after the end of the treatment with the study drug.

Number of Subjects (Target, Enrolled, and Analyzed Number of Subjects)

Target number of subjects: 150 (100 for the ASP1941 50 mg group and 50 for the placebo group in treatment period I). They were stratified by severity of renal impairment (mild vs. moderate) to 75 subjects each (50 in the ASP1941 50 mg group and 25 in the placebo group in treatment period I)

Number of subjects who provided informed consent to participate in the study: 312 (including 7 re-enrolled subjects)

Number of randomized subjects: 165

Number of subjects who received the study drug for treatment period I: 165 in total (84 with mild renal impairment and 81 with moderate renal impairment), including 46 in the placebo group (23 with mild renal impairment and 23 with moderate renal impairment) and 119 in the ASP1941 50 mg group (61 with mild renal impairment and 58 with moderate renal impairment).

Number of subjects who received the study drug for treatment period II: 143 in total (75 with mild renal impairment and 68 with moderate renal impairment), including 15 in the placebo/ASP1941 50 mg group (8 with mild renal impairment and 7 with moderate renal impairment), 26 in the placebo/ASP1941 100 mg group (14 with mild renal impairment and 12 with moderate renal impairment), 68 in the ASP1941

50/50 mg group (41 with mild renal impairment and 27 with moderate renal impairment), and 34 in the ASP1941 50/100 mg group (12 with mild renal impairment and 22 with moderate renal impairment).

(Analysis Sets [Week 24])

- Full Analysis Set (FAS): 46 subjects in the placebo group (23 with mild renal impairment and 23 with moderate renal impairment) and 118 subjects in the ASP1941 50 mg group (60 with mild renal impairment and 58 with moderate renal impairment).
- Per Protocol Set (PPS): 43 subjects in the placebo group (22 with mild renal impairment and 21 with moderate renal impairment) and 111 subjects in the ASP1941 50 mg group (58 with mild renal impairment and 53 with moderate renal impairment).
- Pharmacokinetic Analysis Set (PKAS): 46 subjects in the placebo group (23 with mild renal impairment and 23 with moderate renal impairment) and 119 subjects in the ASP1941 50 mg group (61 with mild renal impairment and 58 with moderate renal impairment).
- Safety Analysis Set (SAF): 46 subjects in the placebo group (23 with mild renal impairment and 23 with moderate renal impairment) and 119 subjects in the ASP1941 50 mg group (61 with mild renal impairment and 58 with moderate renal impairment).

(Analysis Sets [Week 52])

- Full Analysis Set (FAS): 41 subjects in the placebo randomization group (22 with mild renal impairment and 19 with moderate renal impairment) and 118 subjects in the ASP1941 50 mg randomization group (60 with mild renal impairment and 58 with moderate renal impairment).
- Pharmacokinetic Analysis Set (PKAS): 41 subjects in the placebo randomization group (22 with mild renal impairment and 19 with moderate renal impairment) and 119 subjects in the ASP1941 50 mg randomization group (61 with mild renal impairment and 58 with moderate renal impairment).
- Safety Analysis Set (SAF): 41 subjects in the placebo randomization group (22 with mild renal impairment and 19 with moderate renal impairment) and 119 subjects in the ASP1941 50 mg randomization group (61 with mild renal impairment and 58 with moderate renal impairment).

All the subjects who received ASP1941 in treatment period II including 15 in the placebo/ASP1941 50 mg group (8 with mild renal impairment and 7 with moderate renal impairment), 26 in the placebo/ASP1941 100 mg group (14 with mild renal impairment and 12 with moderate renal impairment), 68 in the ASP1941 50/50 mg group (41 with mild renal impairment and 27 with moderate renal impairment), and 34 in the ASP1941 50/100 mg group (12 with mild renal impairment and 22 with moderate renal impairment) were included in the FAS, PKAS, and SAF.

Diagnostic and Primary Enrollment Criteria:

Main inclusion criteria: Provided a written informed consent to participate in the study before the tests at Visit 1; outpatients of 20 years old or older and less than 75 years old at the time of providing informed consent; at least 12 weeks after the diagnosis of T2DM at the time of providing informed consent; treated with diet/exercise therapy alone or 1 oral antidiabetic drug according to the approved constant dosage and administration (limited to an α-Glucosidase inhibitor, sulfonylureas, or pioglitazone) for at least 12 weeks

at Visit 1; eGFR at Visit 2 of 30 mL/min/1.73 m^2 or higher and less than 90 mL/min/1.73 m^2 (using the age at Visit 2), HbA1c level at Visit 2 of 6.5% or higher and 8.5% or lower; and the change in HbA1c level between Visits 1 and 2 of within ±1.0%. Additional inclusion criteria for those who used a sulfonylureas: fasting plasma glucose at Visit 2 of 126 mg/dL or higher; and Body Mass Index (BMI) at Visit 2 of 20.0 kg/m^2 or higher and 45.0 kg/m^2 or lower.

Criteria for continued administration: Subjects who provided a written consent to continue the study by Visit 10 (Week 24) and were confirmed to have no safety concerns by the investigator or subinvestigator proceeded to treatment period II.

Tested Drug, Dosage and Administration Method, and Lot Number: ASP1941 Tablet 50 mg was developed as a light purple film-coated tablet containing 64.3 mg of ASP1941 L-proline (50 mg of ASP1941) (package lot number: [redacted] and [redacted] in treatment period I, and [redacted], [redacted], [redacted], and [redacted] in treatment period II). One tablet of ASP1941 Tablet 50 mg was orally administered once daily before breakfast for 24 weeks in treatment period I. One or two tablets of ASP1941 Tablet 50 mg were orally administered once daily before breakfast for 28 weeks in treatment period II. It was allowed to increase the dose to 2 tablets once daily (100 mg) for subjects who provided a written consent to continue the study by Visit 10 (Week 24), met the dose increase criterion (HbA1c level at Visit 9 [Week 20] of 7.0% or higher for subjects with a level at Visit 3 [Week 0] of 7.0 % or higher, and HbA1C level at Visit 9 [Week 20] of 6.5% or higher for subjects with a level at Visit 3 [Week 0] less than 7.0%), were considered to have no safety concerns by the investigator or subinvestigator, and wished to increase the dose.

Treatment Period (Study Period, as Appropriate):

Screening period: 4 weeks
Placebo run-in period: 2 weeks
Treatment period I: 24 weeks
Treatment period II: 28 weeks
Follow-up period: 4 weeks

Control Drug, Dosage and Administration Method, and Lot Number: The placebo of the ASP1941 Tablet 50 mg was developed as a tablet that could not be distinguished from ASP1941 Tablet 50 mg by appearance (package lot number: [redacted]). One placebo tablet of the ASP1941 Tablet 50 mg was orally administered once daily before breakfast for 24 weeks in treatment period I.

Evaluation Criteria:

Efficacy variables: HbA1c level (JDS value), fasting plasma glucose, fasting insulin, leptin, adiponectin, body weight, and waist circumference
Pharmacokinetic endpoint: Plasma concentration of the unchanged drug
Safety endpoints: Adverse event (AE), vital signs, clinical laboratory values, 12-Lead electrocardiogram (ECG), and eGFR

Statistical Methods: The study data were analyzed twice at the end of the treatment period I and at the end of the treatment period II (at the end of the study). The analyses were performed for the whole subject population and by the severity of renal impairment.
Efficacy variables: For the analysis of data from 24 weeks of administration, the change in HbA1c level from baseline to the end of the treatment period I was compared between the groups with a two-sided significance level of 0.05 according to the analysis of covariance (ANCOVA) with the baseline HbA1c level as a covariate, severity of renal impairment as a factor (which was not included as a factor in the analysis by the severity of renal impairment), and treatment group as a fixed effect (ANCOVA 1) and another ANCOVA with the baseline HbA1c level and eGFR of the placebo run-in period as covariates and treatment group as a fixed effect (ANCOVA 2). For the analysis of data from 52 weeks of administration, the summary statistics of the measured values of HbA1c level and its change from baseline were calculated by treatment group at each evaluation time point and at the end of the administration of ASP1941. The start of the treatment period was considered as the baseline for the analysis of the data from 24 weeks of administration. The start of the treatment period was considered as the baseline in the ASP1941 50 mg group, and Week 24 in the treatment period as the baseline in the placebo group for the analysis of the data from 52 weeks of administration.
Pharmacokinetic endpoint: Summary statistics of the plasma concentration of the unchanged drug were calculated by the evaluation time points.
Safety endpoints: The number and percentage of subjects who experienced AE or AE for which the causal relationship to the study drug could not be denied (adverse reaction) were calculated by treatment group. The number and percentage of subjects who experienced serious adverse event (SAE), AE leading to the discontinuation of the drug administration, or notable AE (AE related to hypoglycemia, urinary tract infection, genital infection, or polyuria or pollakiuria) were calculated by treatment group. AE that developed after the start of administration of the study drug for treatment period I were analyzed in the analysis of data from 24 weeks of administration. Those that developed after the start of ASP1941 were analyzed in the analysis of data from 52 weeks of administration. For laboratory values, the summary statistics of measured values at each evaluation time point were calculated by treatment group for quantitative variables. For count variables, a cross table of the baseline × each evaluation time point was prepared by treatment group.

Summary of Results/Conclusions

Study Population:

[Disposition of Subjects]

A total of 312 subjects (including 7 re-enrolled subjects) provided the informed consent to participate in the study. Of them, 277 received the study drug for the observation period and 165 were randomized either to the placebo or ASP1941 50 mg groups.

All the 165 subjects, including 46 subjects randomized to the placebo group (23 with mild renal impairment and 23 with moderate renal impairment) and 119 subjects randomized to the ASP1941 50 mg group (61 with mild renal impairment and 58 with moderate renal impairment), received the study drug for treatment period I. Of the 165 subjects, 42 in the placebo group (22 with mild renal impairment and 20 with moderate renal impairment) and 107 in the ASP1941 50 mg group (55 with mild renal impairment and 52

with moderate renal impairment) completed treatment period I. The remainder of the subjects in the placebo group (1 with mild renal impairment and 3 with moderate renal impairment) and 12 in the ASP1941 50 mg group (6 with mild renal impairment and 6 with moderate renal impairment) discontinued the treatment. The most common reasons for discontinuation were AEs in both groups (3 in the placebo group [1 with mild renal impairment and 2 with moderate renal impairment] and 9 in the ASP1941 50 mg group [5 with mild renal impairment and 4 with moderate renal impairment]).

Of the subjects who completed treatment period I, 41 in the placebo group (22 with mild renal impairment and 19 with moderate renal impairment) and 102 in the ASP1941 50 mg group (53 with mild renal impairment and 49 with moderate renal impairment) proceeded to treatment period II. The remainder of the subjects, including 1 in the placebo group (with moderate renal impairment) and 5 in the ASP1941 50 mg group (2 with mild renal impairment and 3 with moderate renal impairment), did not proceed to treatment period II. The most common reasons for not proceeding to treatment period II were AEs (1 in the placebo group [with moderate renal impairment] and 3 in the ASP1941 50 mg group [1 with mild renal impairment and 2 with moderate renal impairment]) and unwillingness to continue the study (2 in the ASP1941 50 mg group [1 with mild renal impairment and 1 with moderate renal impairment]).

All 143 subjects who proceeded to treatment period II (75 with mild renal impairment and 68 with moderate renal impairment) received the study drug for treatment period II. Of the 41 subjects who received the placebo during treatment period I (22 with mild renal impairment and 19 with moderate renal impairment), 15 subjects (8 with mild renal impairment and 7 with moderate renal impairment) received ASP1941 50 mg (placebo/ASP1941 50 mg group) and 26 subjects (14 with mild renal impairment and 12 with moderate renal impairment) received ASP1941 100 mg (placebo/ASP1941 100 mg group). Of the 102 subjects who received ASP1941 50 mg during treatment period I (53 with mild renal impairment and 49 with moderate renal impairment), 68 subjects (41 with mild renal impairment and 27 with moderate renal impairment) continued to receive ASP1941 50 mg (ASP1941 50/50 mg group); in 34 subjects (12 with mild renal impairment and 22 with moderate renal impairment), the dose was increased to 100 mg (ASP1941 50/100 mg group). In addition, the placebo/ASP1941 100 mg group included 1 subject (with moderate renal impairment) in whom the dose was increased to 100 mg and then reduced to 50 mg due to an AE (hunger).

Eventually, a total of 130 subjects (71 with mild renal impairment and 59 with moderate renal impairment) completed treatment period II and 13 (4 with mild renal impairment and 9 with moderate renal impairment) discontinued the treatment during treatment period II. When the subjects who completed treatment period II were analyzed by treatment group, they included 15 in the placebo/ASP1941 50 mg group (8 with mild renal impairment and 7 with moderate renal impairment), 25 in the placebo/ASP1941 100 mg group (14 with mild renal impairment and 11 with moderate renal impairment), 59 in the ASP1941 50/50 mg group (38 with mild renal impairment and 21 with moderate renal impairment), and 31 in the ASP1941 50/100 mg group (11 with mild renal impairment and 20 with moderate renal impairment). Similarly, subjects who discontinued treatment during treatment period II included 1 in the placebo/ASP1941 100 mg group (with moderate renal impairment), 9 in the ASP1941 50/50 mg group (3 with mild renal impairment and 6 with moderate renal impairment), and 3 in the ASP1941 50/100 mg group (1 with mild renal impairment and 2 with moderate renal impairment). The most common reason for discontinuation was AE in 9 subjects (3 with mild renal impairment and 6 with moderate renal impairment).

When analyzed by treatment group, they included 1 in the placebo/ASP1941 100 mg group (with moderate renal impairment), 6 in the ASP1941 50/50 mg group (2 with mild renal impairment and 4 with moderate renal impairment), and 2 in the ASP1941 50/100 mg group (1 each with mild and moderate renal impairment).

[Demographic and Other Baseline Characteristics]

Administration for 24 weeks

Overall Analysis

Male subjects accounted for 78.3% of the placebo group and 78.0% of the ASP1941 50 mg group in the FAS. The mean age of subjects in the placebo and ASP1941 50 mg groups was 65.7 years old and 63.9 years old, respectively. The percentage of subjects younger than 65 years old was 39.1% and 53.4% in the placebo and ASP1941 50 mg groups, respectively. The mean BMI in the placebo and ASP1941 50 mg groups was 24.96 kg/m^2 and 25.84 kg/m^2, respectively. The percentage of subjects with a BMI less than 25 kg/m^2 was 63.0% and 45.8% in the placebo and ASP1941 50 mg groups, respectively. The mean duration of T2DM was 113.0 months and 114.3 months in the placebo and ASP1941 50 mg groups, respectively.

At the start of the treatment period, HbA1c level (mean value) was 7.12% in both groups, and fasting plasma glucose (mean value) was 143.8 and 144.3 mg/dL in the placebo and ASP1941 50 mg groups, respectively. The percentage of subjects who received any oral antidiabetic drug during the screening period was 78.3% and 69.5% in the placebo and ASP1941 50 mg groups, respectively. Sulfonylureas were most frequently used concomitantly in both groups.

The demographic and disease baseline characteristics were examined for any imbalance between the treatment groups. The result showed no statistically significant difference for any of the characteristics in the FAS.

Analysis of Subjects by Severity of Renal Impairment

In the FAS, the percentage of male subjects with mild renal impairment was 87.0% and 75.0% and that of male subjects with moderate renal impairment was 69.6% and 81.0% in the placebo and ASP1941 50 mg groups, respectively. The percentage of male subjects with mild renal impairment was higher in the placebo group, while the percentage of male subjects with moderate renal impairment was higher in the ASP1941 50 mg group. The mean age of subjects with mild renal impairment was 63.0 years old and 63.2 years old and that of subjects with moderate renal impairment was 68.5 and 64.6 years in the placebo and ASP1941 50 mg groups, respectively. The percentage of subjects younger than 65 years old with mild renal impairment was comparable between the placebo and ASP1941 50 mg groups at 56.5% and 61.7%, respectively. In contrast, the percentage of subjects younger than 65 years old with moderate renal impairment in the ASP1941 50 mg group was more than 2 times as high as that in the placebo group (44.8% vs. 21.7%). The mean BMI in subjects with mild renal impairment was 24.47 kg/m^2 and 25.88 kg/m^2 in the placebo and ASP1941 50 mg groups, respectively, and that in subjects with moderate renal impairment was 25.45 kg/m^2 and 25.80 kg/m^2 in the placebo and ASP1941 50 mg groups, respectively. These results indicate that the mean BMI was comparable between the treatment groups, irrespective of the severity of renal impairment. The percentage of subjects with a BMI less than 25 kg/m^2 in subjects with

mild renal impairment was 65.2% and 46.7% in the placebo and ASP1941 50 mg groups, respectively, and that in subjects with moderate renal impairment was 60.9% and 44.8% in the placebo and ASP1941 50 mg groups, respectively. These results indicate that the percentage of subjects with a BMI less than 25 kg/m^2 was higher in the placebo than ASP1941 50 mg groups, irrespective of the severity of renal impairment. The mean duration of T2DM in subjects with mild renal impairment was 90.6 months and 100.0 months and that in subjects with moderate renal impairment was 133.5 months and 129.6 months in the placebo and ASP1941 50 mg groups, respectively. The mean duration was longer in subjects with moderate renal impairment in both groups.

HbA1c level (mean value) at the start of the treatment period in subjects with mild renal impairment was 7.17% and 7.05% and that in subjects with moderate renal impairment was 7.07% and 7.19% in the placebo and ASP1941 50 mg groups, respectively. Fasting plasma glucose (mean value) at the start of the treatment period in subjects with mild renal impairment was 146.3 mg/dL and 143.1 mg/dL and that in subjects with moderate renal impairment was 141.3 mg/dL and 145.6 mg/dL in the placebo and ASP1941 50 mg groups, respectively. The percentage of subjects who used any oral antidiabetic drug during the screening period in subjects with mild renal impairment was 73.9% and 66.7% and that in subjects with moderate renal impairment was 82.6% and 72.4% in the placebo and ASP1941 50 mg groups, respectively. Sulfonylureas were most frequently used concomitantly in both groups, irrespective of the severity of renal impairment.

Demographic and disease baseline characteristics were examined for any imbalance between the treatment groups. The results showed no statistically significant difference in any of the characteristics in the FAS, except the mean age in subjects with moderate renal impairment (P=0.011).

Efficacy Results:

Although the present report (synopsis) mentions statistical significance, the present study was designed as an exploratory study and is not intended to confirm statistical significance.

Administration for 24 weeks

When ASP1941 50 mg or placebo was administered once daily for 24 weeks in T2DM patients with mild to moderate renal impairment and whose blood glucose was poorly controlled with diet/exercise therapy alone or pharmacotherapy using 1 oral antidiabetic drug (limited to an α-Glucosidase inhibitor, sulfonylureas, or pioglitazone), ASP1941 reduced HbA1c level, fasting plasma glucose, leptin, and body weight significantly more than the placebo. Analyzing the results by the severity of renal impairment showed that ASP1941 reduced HbA1c level, fasting plasma glucose, and body weight in subjects with mild renal impairment and body weight in subjects with moderate renal impairment significantly more than the placebo.

Main efficacy results are shown below.

Overall Analysis

- The mean change in HbA1c level (JDS value) from baseline to the end of the treatment period I was −0.17% and −0.42% in the placebo and ASP1941 50 mg groups, respectively. The difference in the change (adjusted mean) in the ASP1941 50 mg group as compared with the placebo group was −0.25% in ANCOVA 1 (ANCOVA with the baseline HbA1c level as a covariate, severity of renal impairment as a factor, and treatment group as a fixed effect, the same applies hereinafter) and −0.28% in ANCOVA 2 (ANCOVA with the baseline HbA1c level and eGFR of the placebo run-in

period as covariates and treatment group as a fixed effect; the same applies hereinafter). Both differences were statistically significant (P=0.004 and P=0.001, respectively).

- The percentage of subjects with HbA1c level less than 7.0% or 6.5% at the end of the treatment period I was higher in the ASP1941 50 mg than the placebo group.
- The mean change in fasting plasma glucose from baseline to the end of the treatment period I was −4.2 mg/dL and −12.4 mg/dL in the placebo and ASP1941 50 mg groups, respectively. The difference in the change (adjusted mean) in the ASP1941 50 mg group as compared with the placebo group was −8.0 mg/dL in ANCOVA 1 and −8.8 mg/dL in ANCOVA 2. Both differences were statistically significant (P=0.021 and P=0.010, respectively).
- The mean change in leptin from baseline to the end of the treatment period I was 0.37 ng/mL and −0.86 ng/mL in the placebo and ASP1941 50 mg groups, respectively. The difference in the change (adjusted mean) in the ASP1941 50 mg group as compared with the placebo group was −1.22 ng/mL in ANCOVA 1 and −1.26 ng/mL in ANCOVA 2. Both differences were statistically significant (P=0.037 and P=0.032, respectively).
- The mean change in body weight from baseline to the end of the treatment period I was −0.06 kg and −1.87 kg in the placebo and ASP1941 50 mg groups, respectively. The difference in the change (adjusted mean) in the ASP1941 50 mg group as compared with the placebo group was −1.77 kg in ANCOVA 1 and −1.77 kg in ANCOVA 2. Both differences were statistically significant (P<0.001 for both differences).
- The difference in the change (adjusted mean) in the ASP1941 50 mg group as compared with the placebo group was not statistically significant for fasting insulin, adiponectin, and waist circumference.

Analysis of Subjects by Severity of Renal Impairment

- The mean change in HbA1c level from baseline to the end of the treatment period I in subjects with mild renal impairment was −0.26% and −0.56% and that in subjects with moderate renal impairment was −0.09% and −0.28% in the placebo and ASP1941 50 mg groups, respectively. The difference in the change (adjusted mean) in the ASP1941 50 mg group as compared with the placebo group was −0.35% in subjects with mild renal impairment and −0.17% in those with moderate renal impairment in ANCOVA 1 (ANCOVA with the baseline value as a covariate and treatment group as a fixed effect; the same applies hereinafter) and −0.36% in subjects with mild renal impairment and −0.16% in those with moderate renal impairment in ANCOVA 2 (ANCOVA with the baseline value and eGFR of the placebo run-in period as covariates and treatment group as a fixed effect; the same applies hereinafter). The difference observed in subjects with mild renal impairment was statistically significant in both ANCOVA 1 and 2 (P<0.001 for both analyses): HbA1c level was lower in the ASP1941 50 mg group than in the placebo group. Although the difference observed in subjects with moderate renal impairment was not statistically significant (P=0.207 and P=0.258, respectively), HbA1c level was lower in the ASP1941 50 mg group than in the placebo group.
- The percentage of subjects with HbA1c level less than 7.0% at the end of the treatment period I was higher in the ASP1941 50 mg than the placebo group, irrespective of the severity of renal impairment. The percentage of subjects with HbA1c level less than 6.5% at the end of the treatment period I was

higher in the ASP1941 50 mg than in the placebo group of subjects with mild renal impairment, but was comparable between the groups of subjects with moderate renal impairment.

- The mean change in fasting plasma glucose from baseline to the end of the treatment period I in subjects with mild renal impairment was −3.2 mg/dL and −16.2 mg/dL and that in subjects with moderate renal impairment was −5.2 mg/dL and −8.6 mg/dL in the placebo and ASP1941 50 mg groups, respectively. The difference in the change (adjusted mean) in the ASP1941 50 mg group as compared with the placebo group was −14.8 mg/dL in subjects with mild renal impairment and −1.8 mg/dL in those with moderate renal impairment in ANCOVA 1 and −15.5 mg/dL in subjects with mild renal impairment and −3.2 mg/dL in those with moderate renal impairment in ANCOVA 2. The difference was statistically significant in subjects with mild renal impairment for both ANCOVA 1 and 2 ($P<0.001$ for both analyses): fasting plasma glucose was lower in the ASP1941 50 mg group than the placebo group. Although the difference was not statistically significant in subjects with moderate renal impairment ($P=0.733$ and 0.559, respectively), fasting plasma glucose was lower in the ASP1941 50 mg group than in the placebo group.
- The mean change in body weight from baseline to the end of the treatment period I in subjects with mild renal impairment was −0.19 kg and −1.88 kg and that in subjects with moderate renal impairment was 0.07 kg and −1.85 kg in the placebo and ASP1941 50 mg groups, respectively. The difference in the change (adjusted mean) in the ASP1941 50 mg group as compared with the placebo group was −1.61 kg in subjects with mild renal impairment and −1.92 kg in those with moderate renal impairment in ANCOVA 1 and −1.66 kg in subjects with mild renal impairment and −1.80 kg in those with moderate renal impairment in ANCOVA 2. The difference was statistically significant in subjects with mild and moderate renal impairment for both ANCOVA 1 and 2 ($P<0.001$ for both differences).
- The difference in the change (adjusted mean) for the ASP1941 50 mg group as compared with the placebo group was not statistically significant for fasting insulin, leptin, adiponectin, and waist circumference in subjects with mild or moderate renal impairment.

Administration for 52 weeks

When ASP1941 was administered once daily for 52 weeks in T2DM patients with mild to moderate renal impairment and whose blood glucose was poorly controlled with diet/exercise therapy alone or pharmacotherapy using 1 oral antidiabetic drug (limited to an α-Glucosidase inhibitor, sulfonylureas, or pioglitazone), the effect of ASP1941 to reduce HbA1c level, fasting plasma glucose, leptin, and body weight continued until Week 52 after the start of administration. When the ASP1941 dose was increased to 100 mg from Week 24 according to the dose increase criteria in subjects whose blood glucose was poorly controlled after 24 weeks of treatment with ASP1941 50 mg, HbA1c level and fasting plasma glucose were further improved. Analyzing the results by the severity of renal impairment showed that the effects of the dose increase became more evident in subjects with moderate renal impairment than those with mild renal impairment.

Main results of HbA1c level, fasting plasma glucose, leptin, and body weight for which the data from 24 weeks of administration showed significant improvements in the ASP1941 50 mg group as compared with the placebo group are shown below.

Overall Analysis

- The mean change in HbA1c level from baseline in the ASP1941 50 mg randomization group was −0.42% at the end of the treatment period I and −0.44% at the end of the administration of ASP1941. The mean change in HbA1c level from the end of the treatment period I to the end of the administration of ASP1941 in the ASP1941 50/100 mg group was −0.15%.
- The mean change in fasting plasma glucose from baseline in the ASP1941 50 mg randomization group was −12.4 mg/dL at the end of the treatment period I and −13.0 mg/dL at the end of the administration of ASP1941. The mean change in fasting plasma glucose from the end of the treatment period I to the end of administration of ASP1941 in the ASP1941 50/100 mg group was −4.6 mg/dL.
- The mean change in leptin from baseline in the ASP1941 50 mg randomization group was −0.86 ng/mL at the end of the treatment period I and −0.95 ng/mL at the end of the administration of ASP1941.
- The mean change in body weight from baseline in the ASP1941 50 mg randomization group was −1.87 kg at the end of the treatment period I and −2.16 kg at the end of the administration of ASP1941. The mean change in body weight from the end of the treatment period I to the end of administration of ASP1941 in the ASP1941 50/100 mg group was −0.63 kg.

Analysis of Subjects by Severity of Renal Impairment

- The mean change in HbA1c level from baseline in the ASP1941 50 mg randomization group was −0.56% at the end of the treatment period I and −0.54% at the end of the administration of ASP1941 in subjects with mild renal impairment, and −0.28% and −0.33% in subjects with moderate renal impairment, respectively. The mean change in HbA1c level from the end of the treatment period I to the end of the administration of ASP1941 in the ASP1941 50/100 mg group was −0.02% in subjects with mild renal impairment and −0.22% in those with moderate renal impairment.
- The mean change in fasting plasma glucose from baseline in the ASP1941 50 mg randomization group was −16.2 mg/dL at the end of the treatment period I and −16.8 mg/dL at the end of the administration of ASP1941 in subjects with mild renal impairment, and −8.6 mg/dL and −9.1 mg/dL in subjects with moderate renal impairment, respectively. The mean change in fasting plasma glucose from the end of the treatment period I to the end of the administration of ASP1941 in the ASP1941 50/100 mg group was −0.5 mg/dL in subjects with mild renal impairment and −6.9 mg/dL in those with moderate renal impairment.
- The mean change in leptin from baseline in the ASP1941 50 mg randomization group was −0.88 ng/mL at the end of the treatment period I and −1.22 ng/mL at the end of the administration of ASP1941 in subjects with mild renal impairment, and −0.83 ng/mL and −0.67 ng/mL in subjects with moderate renal impairment, respectively.
- The mean change in body weight from baseline in the ASP1941 50 mg randomization group was −1.88 kg at the end of the treatment period I and −2.13 kg at the end of administration of ASP1941 in subjects with mild renal impairment, and −1.85 kg and −2.18 kg in subjects with moderate renal impairment, respectively.

Pharmacokinetic Results

Administration for 24 weeks

There was no notable change in the plasma concentration of the unchanged drug (median value) through evaluation time points in the ASP1941 50 mg group. When analyzed by the severity of renal impairment, the plasma concentration of the unchanged drug (median value) showed no notable change through evaluation time points in either subject with mild or moderate renal impairment. The plasma concentration of the unchanged drug (median value) changed in a comparable manner between subjects with mild and moderate renal impairment.

Administration for 52 weeks

There was no notable change in the plasma concentration of the unchanged drug (median value) through evaluation time points in 52 weeks in the ASP1941 50/50 mg group. In the ASP1941 50/100 mg group, the plasma concentration of the unchanged drug (median value) showed no notable change through evaluation time points in either of the treatment durations of ASP1941 50 mg and ASP1941 100 mg. The plasma concentration of the unchanged drug (median value) during the treatment duration of ASP1941 100 mg was approximately twice as high as that during the treatment duration of ASP1941 50 mg. These tendencies were similarly observed in the analysis by the severity of renal impairment.

Analyzing the change in the plasma concentration of the unchanged drug (median value) by the severity of renal impairment showed that the concentration remained higher in subjects with moderate than mild renal impairment in the ASP1941 50/50 mg group, but it was comparable in subjects with mild and moderate renal impairment in the ASP1941 50/100 mg group.

Safety Results:

Administration for 24 weeks

No clinically important safety concerns were observed when ASP1941 50 mg was administered once daily for 24 weeks in T2DM patients with mild to moderate renal impairment. There was no difference in the safety profile of the drug by the severity of renal impairment.

- The incidence of AEs in treatment period I was 73.9% (34/46 subjects) in the placebo group and 81.5% (97/119 subjects) in the ASP1941 50 mg group. The analysis by the severity of renal impairment showed that the incidence was 78.3% (18/23 subjects) in the placebo group and 80.3% (49/61 subjects) in the ASP1941 50 mg group for subjects with mild renal impairment and 69.6% (16/23 subjects) and 82.8% (48/58 subjects) for those with moderate renal impairment, respectively. The incidence of AEs for which the causal relationship to the study drug was not denied (adverse reactions) was 17.4% (8/46 subjects) in the placebo group and 27.7% (33/119 subjects) in the ASP1941 50 mg group. The analysis by the severity of renal impairment showed that the incidence was 13.0% (3/23 subjects) in the placebo group and 34.4% (21/61 subjects) in the ASP1941 50 mg group for subjects with mild renal impairment and 21.7% (5/23 subjects) and 20.7% (12/58 subjects) for those with moderate renal impairment, respectively. There was no statistically significant difference in the incidence of AEs or adverse reactions in the overall analysis or analysis by the severity of renal impairment (P=0.289 and P=0.228 in the overall analysis, P=1.000 and P=0.062 for

subjects with mild renal impairment, and P=0.230 and P=1.000 for subjects with moderate renal impairment; Fisher's exact test).

- Most AEs were mild in severity. No severe AE was observed.
- Adverse events observed in 5% or more of subjects in the placebo group were nasopharyngitis (34.8%, 16/46 subjects), back pain (8.7%, 4/46 subjects), and insomnia (6.5%, 3/46 subjects) and those in the ASP1941 50 mg group were nasopharyngitis (21.0%, 25/119 subjects), pollakiuria (8.4%, 10/119 subjects), and constipation (7.6%, 9/119 subjects). The analysis by the severity of renal impairment showed that AEs observed in 5% or more of subjects with mild renal impairment were nasopharyngitis (21.3%, 13/61 subjects), pollakiuria and constipation (8.2%, 5/61 subjects each) in the ASP1941 50 mg group, and nasopharyngitis (21.7%, 5/23 subjects), back pain, myalgia, and pollakiuria (8.7%, 2/23 subjects each) in the placebo group. Adverse events observed in 5% or more of subjects with moderate renal impairment were nasopharyngitis (20.7%, 12/58 subjects), pollakiuria (8.6%, 5/58 subjects), constipation, diabetes mellitus, and dizziness (6.9%, 4/58 subjects each), anaemia, dental caries, and dermatitis contact (5.2%, 3/58 subjects) in the ASP1941 50 mg group, and nasopharyngitis (47.8%, 11/23 subjects), asymptomatic bacteriuria, back pain, insomnia, and pruritus (8.7%, 2/23 subjects each) in the placebo group.
- The incidence of SAEs was 4.3% (2/46 subjects) in the placebo group and 6.7% (8/119 subjects) in the ASP1941 50 mg group. The analysis by the severity of renal impairment showed that the incidence was 4.3% (1/23 subjects) in the placebo group and 8.2% (5/61 subjects) in the ASP1941 50 mg group for subjects with mild renal impairment and 4.3% (1/23 subjects) and 5.2% (3/58 subjects) for those with moderate renal impairment, respectively. SAEs for which the causal relationship to the study drug could not be denied were atrioventricular block complete in a subject with moderate renal impairment in the placebo group and upper gastrointestinal haemorrhage in a subject with moderate renal impairment in the ASP1941 50 mg group.
- The incidence of AEs leading to the discontinuation of the drug administration was 8.7% (4/46 subjects) in the placebo group and 10.1% (12/119 subjects) in the ASP1941 50 mg group. The analysis by the severity of renal impairment showed that the incidence was 4.3% (1/23 subjects) in the placebo group and 9.8% (6/61 subjects) in the ASP1941 50 mg group for subjects with mild renal impairment, and 13.0% (3/23 subjects) and 10.3% (6/58 subjects) for those with moderate renal impairment, respectively. The causal relationship to the study drug could not be denied for the following AEs leading to the discontinuation of the drug administration: atrioventricular block complete and malaise (1 subject each) in the placebo group and pruritus (2 subjects), gastroenteritis, and upper gastrointestinal haemorrhage (1 subject each) in the ASP1941 50 mg group.
- For notable AEs, AEs related to hypoglycemia were observed at an incidence of 0% (0/46 subjects) in the placebo group and 0.8% (1/119 subjects) in the ASP1941 50 mg group, those related to urinary tract infection at 4.3% (2/46 subjects) and 0.8% (1/119 subjects), those related to genital infection at 0% (0/46 subjects) and 0.8% (1/119 subjects), and those related to polyuria or pollakiuria at 4.3% (2/46 subjects) and 8.4% (10/119 subjects), respectively. The analysis of notable AEs by the severity of renal impairment showed that AEs related to hypoglycemia occurred at an incidence of 0% each (0/23 and 0/61 subjects) in both groups for subjects with mild renal impairment and 0% (0/23 subjects) in the placebo group and 1.7% (1/58 subjects) in the ASP1941 50 mg group for subjects with

moderate renal impairment. AEs related to urinary tract infection occurred at an incidence of 0% each (0/23 and 0/61 subjects) in both groups for subjects with mild renal impairment and 8.7% (2/23 subjects) in the placebo group and 1.7% (1/58 subjects) in the ASP1941 50 mg group for subjects with moderate renal impairment. AEs related to genital infection occurred at an incidence of 0% (0/23 subjects) in the placebo group and 1.6% (1/61 subjects) in the ASP1941 50 mg group for subjects with mild renal impairment and 0% (0/23 and 0/58 subjects) in both groups for subjects with moderate renal impairment. Finally, AEs related to polyuria or pollakiuria occurred in 8.7% (2/23 subjects) of subjects in the placebo group and in 8.2% (5/61 subjects) in the ASP1941 50 mg group for subjects with mild renal impairment and in 0% (0/23 subjects) of subjects in the placebo group and in 8.6% (5/58 subjects) of subjects in the ASP1941 50 mg group with moderate renal impairment.

- None of laboratory values showed a notable difference between the placebo and ASP1941 50 mg groups at the start of the treatment period or at the end of the treatment period I. The analysis by the severity of renal impairment showed that none of laboratory values showed a notable difference between the groups at the start of the treatment period or at the end of the treatment period I, irrespective of the severity of renal impairment.
- For the mean change in vital signs from baseline to the end of the treatment period I, systolic blood pressure changed by −2.7 mmHg and −4.6 mmHg, diastolic blood pressure by −1.2 mmHg and −2.5 mmHg, and pulse rate by −0.5 bpm and −0.1 bpm in the placebo and ASP1941 50 mg groups, respectively. The analysis by the severity of renal impairment showed that systolic blood pressure changed by −2.5 mmHg in the placebo group and −3.8 mmHg in the ASP1941 50 mg group for subjects with mild renal impairment and −2.8 mmHg and −5.4 mmHg for subjects with moderate renal impairment, respectively; diastolic blood pressure changed by −1.1 mmHg in the placebo group and −3.4 mmHg in the ASP1941 50 mg group for subjects with mild renal impairment and −1.4 mmHg and −1.6 mmHg for subjects with moderate renal impairment, respectively; and pulse rate changed by −1.2 bpm in the placebo group and −1.8 bpm in the ASP1941 50 mg group for subjects with mild renal impairment and 0.1 bpm and 1.8 bpm for subjects with moderate renal impairment, respectively.
- The examination of 12-lead ECG findings showed a clinically important abnormality in 1 subject in the placebo group (with mild renal impairment) and 2 subjects in the ASP1941 50 mg group (both with moderate renal impairment) after the administration of the study drug for treatment period I. All the findings were reported as AEs. These AEs were considered as not related to the study drug.

Administration for 52 weeks

No clinically important safety concerns were observed when ASP1941 was administered once daily for 52 weeks in T2DM patients with mild to moderate renal impairment. There was no difference in the safety profile of ASP1941 by the severity of renal impairment.

Main safety results from the ASP1941 50 mg group are shown below. Death, SAEs, AEs leading to the discontinuation of the drug administration, and severe AEs observed in subjects in the placebo randomization groups (placebo/ASP1941 50 mg and placebo/ASP1941 100 mg groups) were also included in the results.

- The incidence of AEs and adverse reactions was 93.3% (111/119 subjects) and 39.5% (47/119 subjects), respectively. The analysis by the severity of renal impairment showed that the incidence of

AEs was 93.4% (57/61 subjects) in subjects with mild renal impairment and 93.1% (54/58 subjects) in subjects with moderate renal impairment, and that the incidence of adverse reactions was 49.2% (30/61 subjects) in subjects with mild renal impairment and 29.3% (17/58 subjects) in subjects with moderate renal impairment.

- Most AEs were mild in severity. Severe AEs were observed in 1 subject in the placebo/ASP1941 100 mg group (with moderate renal impairment) and 2 subjects in the ASP1941 50/50 mg groups (both with mild renal impairment). The 3 severe AEs were death, cerebral infarction, and angina unstable. The causal relationship to the study drug was not denied for death and angina unstable.
- AEs observed in 5% or more of subjects in the ASP1941 50 mg randomization group were nasopharyngitis (35.3%, 42/119), constipation (11.8%, 14/119), pollakiuria (10.1%, 12/119 subjects), dizziness (5.9%, 7/119 subjects), dental caries, gastritis, thirst, weight loss, back pain, and dermatitis contact (5.0%, 6/119 subjects each). AEs observed in 5% or more of subjects with mild renal impairment in the ASP1941 50 mg randomization group were nasopharyngitis (39.3%, 24/61 subjects), constipation (11.5%, 7/61 subjects), pollakiuria (9.8%, 6/61 subjects), thirst, and back pain (6.6%, 4/61 subjects each). AEs observed in 5% or more of subjects with moderate renal impairment in the ASP1941 50 mg randomization group were nasopharyngitis (31.0%, 18/58 subjects), constipation (12.1%, 7/58 subjects), pollakiuria (10.3%, 6/58 subjects), dental caries, bronchitis, diabetes mellitus, and dizziness (8.6%, 5/58 subjects each), anaemia, gastritis, reflux oesophagitis, contusion, and weight loss (6.9%, 4/58 subjects each), abdominal pain upper, gastroenteritis, scratch, hyperuricaemia, musculoskeletal stiffness, renal impairment, dermatitis contact, and rash (5.2%, 3/58 subjects each).
- One death was reported in the placebo/ASP1941 100 mg group during treatment period II. The subinvestigator could not identify the cause of the death and considered it as possibly related to the study drug. Another physician recorded the cause of death as [redacted] in the postmortem certificate. The sponsor ruled out the causal relationship between the study drug and death because patient predispositions including complications ([redacted], [redacted], and [redacted]) might have a great effect on the onset of the event.
- The incidence of SAEs was 16.0% (19/119 subjects). In treatment period II, SAEs occurred in 2 subjects in the placebo/ASP1941 100 mg group (1 each with mild and moderate renal impairment), 9 in the ASP1941 50/50 mg group (3 with mild renal impairment and 6 with moderate renal impairment), and 2 in the ASP1941 50/100 mg group (1 each with mild and moderate renal impairment). The causal relationship to the study drug could not be denied for the following SAEs: death in the placebo/ASP1941 100 mg group (in a subject with moderate renal impairment) and angina unstable (in a subject with mild renal impairment), haemolytic anaemia, uterine cancer, and large intestine carcinoma (in subjects with moderate renal impairment) in the ASP1941 50/50 mg group.
- The incidence of AEs leading to the discontinuation of the drug administration was 17.6% (21/119 subjects). In treatment period II, AEs leading to the discontinuation of the drug administration occurred in 1 subject in the placebo/ASP1941 100 mg group (with moderate renal impairment), 6 in the ASP1941 50/50 mg group (2 with mild renal impairment and 4 with moderate renal impairment), and 3 in the ASP1941 50/100 mg group (1 with mild renal impairment and 2 with moderate renal impairment). The causal relationship to the study drug could not be denied for the AEs observed in 1

subject in the placebo/ASP1941 100 mg group (with moderate renal impairment), 3 in the ASP1941 50/50 mg group (1 with mild renal impairment and 2 with moderate renal impairment), and 1 in the ASP1941 50/100 mg group (1 with mild renal impairment). Adverse reactions leading to the discontinuation of the drug administration were death in the placebo/ASP1941 100 mg group, angina unstable, haemolytic anaemia, and uterine cancer in the ASP1941 50/50 mg, and vulvitis in the ASP1941 50/100 mg group.

- The examination of notable AEs showed that AEs related to hypoglycemia occurred at an incidence of 5.9% (7/119 subjects, 4 with mild renal impairment and 3 with moderate renal impairment), those related to urinary tract infection at 2.5% (3/119 subjects, 3 with moderate renal impairment), those related to genital infection at 0.8% (1/119 subjects, with mild renal impairment), and those related to polyuria or pollakiuria at 10.9% (13/119 subjects, 7 with mild renal impairment and 6 with moderate renal impairment).
- The analysis by the time of onset showed that the incidence rate of all AEs, SAEs, or AEs leading to the discontinuation of the drug administration did not increase over time until Week 52 of administration. Adverse events with an incidence of 5% or higher did not show an increase in incidence over time. These tendencies were similarly found in the analysis by the severity of renal impairment.
- None of the laboratory values showed a clinically important change from baseline to the end of the treatment period I or to the end of the administration of ASP1941. The analysis by the severity of renal impairment showed that none of the laboratory values had a clinically important change from baseline to the end of the treatment period I or to the end of the administration of ASP1941.
- For vital signs, the mean change from baseline to the end of the administration of ASP1941 was −4.1 mmHg for systolic blood pressure, −1.5 mmHg for diastolic blood pressure, and 0.5 bpm for pulse rate. The analysis by severity of renal impairment showed that the mean change in systolic blood pressure from baseline to the end of the administration of ASP1941 was −4.0 mmHg in subjects with mild renal impairment and −4.2 mmHg in subjects with moderate renal impairment, and that the mean change in diastolic blood pressure was −2.5 mmHg and −0.4 mmHg, respectively, and that the mean change in pulse rate was −0.6 bpm and 1.6 bpm for pulse rate, respectively.
- The examination of 12-lead ECG findings showed that 1 subject in the ASP1941 50/100 mg group (with mild renal impairment) had a clinically important abnormality after the administration of the study drug for treatment period II. It was reported as an AE (mild arrhythmia). The causal relationship between the event and study drug was not denied.

Conclusions:

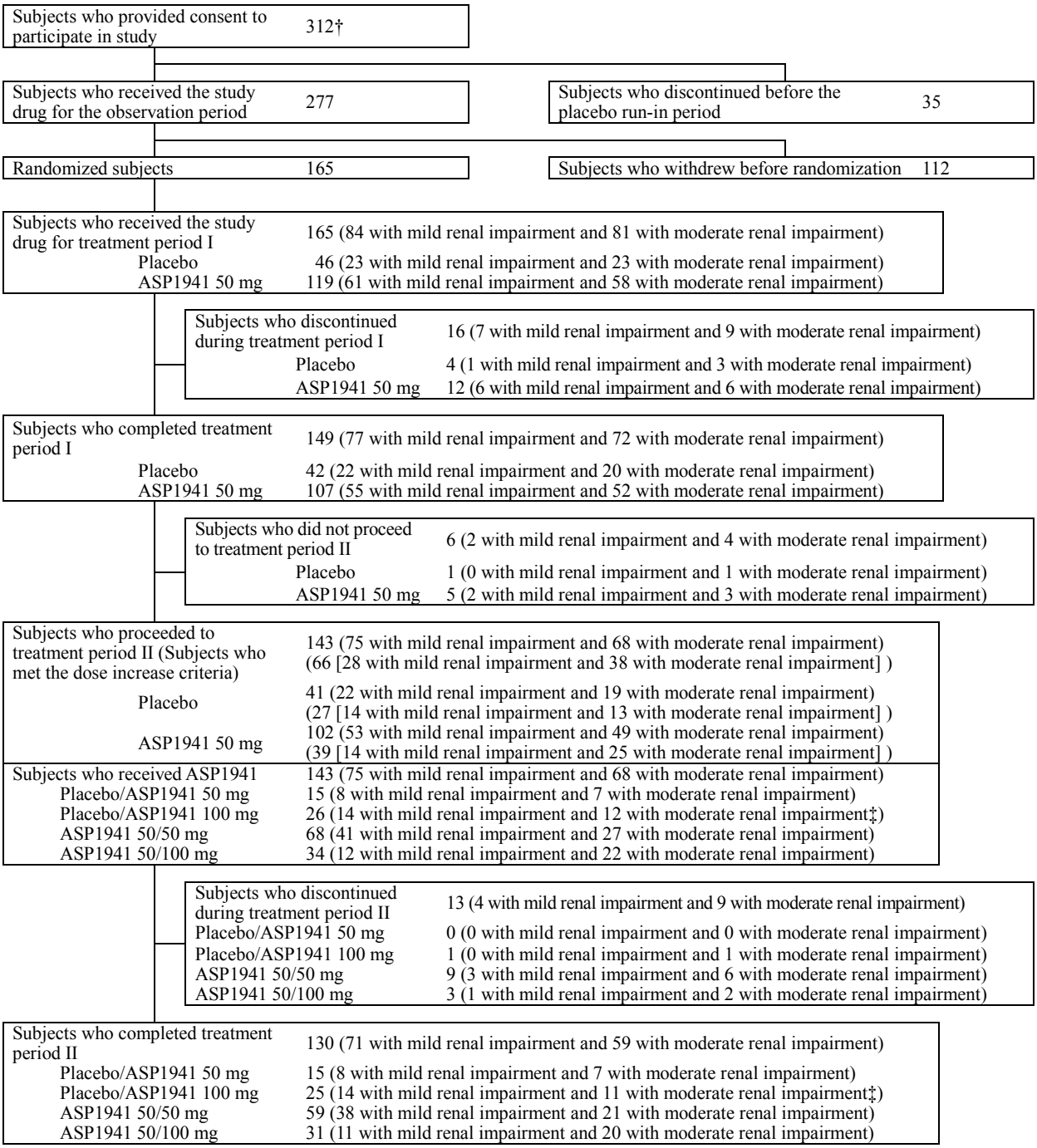
- When ASP1941 50 mg or placebo was administered once daily for 24 weeks in T2DM patients with mild to moderate renal impairment and whose blood glucose was poorly controlled with diet/exercise therapy alone or pharmacotherapy using 1 oral antidiabetic drug (limited to an α-Glucosidase inhibitor, sulfonylureas, or pioglitazone), ASP1941 reduced HbA1c level, fasting plasma glucose, leptin, and body weight significantly more than the placebo.
- The hypoglycemic effect of ASP1941 was confirmed even in patients with renal impairment.
  The hypoglycemic effect was lower in subjects with moderate than mild renal impairment, which

suggests the effect of renal impairment on thehypoglycemic effect of the drug. The effect of ASP1941 to reduce body weight was not influenced by the severity of renal impairment.

- No clinically important safety concerns were observed when ASP1941 50 mg was administered once daily for 24 weeks. There was no difference in the safety profile of the drug by the severity of renal impairment.
- When ASP1941 50 mg was administered once daily for 52 weeks, the effect of the drug to reduce HbA1c level, fasting plasma glucose, leptin, and body weight continued until Week 52 of administration. When the ASP1941 dose was increased to 100 mg at Week 24 according to the dose increase criteria in subjects whose blood glucose was poorly controlled after 24 weeks of treatment with ASP1941 50 mg, HbA1c level and fasting plasma glucose were further reduced. The analysis by the severity of renal impairment showed that the dose increase effect was more evident in subjects with moderate than mild renal impairment.
- When ASP1941 was administered once daily for 52 weeks in T2DM patients with mild or moderate renal impairment, no important safety concerns were observed in all the patients including those in whom the dose was increased from 50 to 100 mg at Week 24.

Date of the report: 5 March, 2013

Figure 1 Disposition of Subjects



†: Seven re-enrolled subjects are included. [redacted]

‡: One subject in whom the dose of ASP1941 was increased to 100 mg and then reduced to 50 mg is included.

The severity of renal impairment is categorized by eGFR at Visit 2 into mild ($60 \leq eGFR < 90$ mL/min/1.73 m^2) or moderate ($30 \leq eGFR < 60$ mL/min/1.73 m^2).

Source: Tables 12.1A.1.1, 12.1A.1.3, 12.1A.1.4, 12.1A.1.6.1, 12.1A.1.6.2, 12.1A.1.7.1, 12.1A.1.7.2, 12.1A.1.11.1, 12.1A.1.11.2, 12.1A.1.13.1, 12.1A.1.13.2, 12.1B.1.2.2, 12.1B.1.2.3, 12.1B.1.2.5, and 12.1B.1.2.6

Table 1 Demographic and Other Baseline Characteristics: FAS (24 Weeks)

		Placebo (n=46)	ASP1941 50 mg (n=118)	P-value
Sex	Male	36 (78.3%)	92 (78.0%)	1.000†
	Female	10 (21.7%)	26 (22.0%)	
Age (at the time of informed consent) (year)	Mean (SD)	65.7 (6.93)	63.9 (6.59)	0.117‡
	Minimum value, maximum value	45, 74	44, 74	
	<65	18 (39.1%)	63 (53.4%)	0.119†
	≥65	28 (60.9%)	55 (46.6%)	
Body height (at screening) (cm)	Mean (SD)	163.30 (7.861)	163.33 (7.736)	0.982‡
	Minimum value, maximum value	143.2, 178.5	144.0, 179.8	
Body weight (at screening) (kg)	Mean (SD)	66.70 (10.940)	69.16 (11.571)	0.215‡
	Minimum value, maximum value	49.0, 94.2	41.5, 101.5	
BMI (at screening) (kg/m^2)	Mean (SD)	24.96 (3.362)	25.84 (3.450)	0.140‡
	Minimum value, maximum value	20.0, 35.9	20.0, 35.6	
	<25	29 (63.0%)	54 (45.8%)	0.056†
	≥25	17 (37.0%)	64 (54.2%)	
Duration of disease (at screening) (month)	n	42	114	
	Mean (SD)	113.0 (99.77)	114.3 (92.26)	0.941‡
	Median	98.5	90.5	
	Minimum value, maximum value	3, 547	3, 465	
	<60	14 (33.3%)	34 (29.8%)	0.698†
	≥60	28 (66.7%)	80 (70.2%)	
Complications	No	0	0	-
	Yes	46 (100.0%)	118 (100.0%)	
Smoking history	No smoking history	14 (30.4%)	43 (36.4%)	0.778†
	Previous smoker	24 (52.2%)	55 (46.6%)	
	Current smoker	8 (17.4%)	20 (16.9%)	
Alcohol habits	No drinking history	13 (28.3%)	29 (24.6%)	0.701†
	Previous drinker	6 (13.0%)	12 (10.2%)	
	Current drinker	27 (58.7%)	77 (65.3%)	
Alcohol consumption§	Non-drinker	19 (41.3%)	41 (34.7%)	0.739†
	LEVEL 1	20 (43.5%)	55 (46.6%)	
	LEVEL 2	7 (15.2%)	22 (18.6%)	
	LEVEL 3	0	0	
Concomitant oral antidiabetic drug (1) (at screening)	No	10 (21.7%)	36 (30.5%)	0.334†
	Yes	36 (78.3%)	82 (69.5%)	
Concomitant oral antidiabetic drug (2) (at screening)	No	10 (21.7%)	36 (30.5%)	0.531†
	α-Glucosidase inhibitor	9 (19.6%)	15 (12.7%)	
	Sulfonylureas	20 (43.5%)	52 (44.1%)	
	Pioglitazone	7 (15.2%)	15 (12.7%)	
Severity of renal impairment (placebo run-in period)¶	Mild	23 (50.0%)	60 (50.8%)	1.000†
	Moderate	23 (50.0%)	58 (49.2%)	
HbA1c level (at the start of the treatment period) (%, JDS)	Mean (SD)	7.12 (0.536)	7.12 (0.550)	0.986‡
	Minimum value, maximum value	6.5, 8.6	5.9, 8.5	
Fasting plasma glucose (at the start of the treatment period) (mg/dL)	Mean (SD)	143.8 (23.89)	144.3 (22.63)	0.903‡
	Minimum value, maximum value	73, 207	89, 204	
eGFR (at the start of the treatment period) ($mL/min/1.73\ m^2$)	Mean (SD)	62.7 (13.13)	60.2 (13.08)	0.278‡
	Minimum value, maximum value	37, 97	29, 88	
	<60	22 (47.8%)	57 (48.3%)	1.000†
	≥60	24 (52.2%)	61 (51.7%)	

The classification variable represents the number of subjects (%).

BMI: body mass index, eGFR: estimated glomerular filtration rate, FAS: full analysis set, HbA1c: hemoglobin A1c, JDS: Japan Diabetes Society

†: Fisher's exact test, ‡: t test

§: Alcohol consumption was classified into 3 levels based on daily consumption: LEVEL 1 (Middle bottle of beer - Less than 1 bottle, Sake - Less than 1 cup, Whiskey/brandy - Less than 60 mL, Shochu [35 degrees] - Less than 90 mL, Wine - Less than 240 mL), LEVEL 2 (Middle bottle of beer - 1 bottle or more and less than 3 bottles, Sake - 1cup or more and less than 3 cups, Whiskey/brandy - 60 mL or more and less than 180 mL, Shochu [35 degrees] - 90 mL or more and less than 270 mL, Wine - 240 mL or more and less than 720 mL), LEVEL 3 (Middle

bottle of beer - 3 bottles or more, Sake - 3 cups or more, Whiskey/brandy - 180 mL or more, Shochu [35 degrees] - 270 mL or more, and Wine 720 mL or more).

¶: The severity of renal impairment is categorized by eGFR at Visit 2 into mild ($60 \leq eGFR < 90$ mL/min/1.73 m^2) or moderate ($30 \leq eGFR < 60$ mL/min/1.73 m^2).

Source: Tables 12.1A.2.1.1.1, 12.1A.2.2.1.1, 12.1A.2.3.1.1, 12.1A.2.4.1.1, and 12.1A.2.5.1.1

Table 2 Demographic and Other Baseline Characteristics (by Severity of Renal Impairment): FAS (24 Weeks)

		Subjects with mild renal impairment			Subjects with moderate renal impairment		
		Placebo (n=23)	ASP1941 50 mg (n=60)	P-value	Placebo (n=23)	ASP1941 50 mg (n=58)	P-value
Sex	Male Female	20 (87.0%) 3 (13.0%)	45 (75.0%) 15 (25.0%)	0.373†	16 (69.6%) 7 (30.4%)	47 (81.0%) 11 (19.0%)	0.374†
Age (at the time of informed consent) (year)	Mean (SD) Minimum value, maximum value	63.0 (7.95) 45, 74	63.2 (6.53) 44, 73	0.871‡	68.5 (4.35) 59, 74	64.6 (6.62) 44, 74	0.011‡
	<65 ≥65	13 (56.5%) 10 (43.5%)	37 (61.7%) 23 (38.3%)	0.803†	5 (21.7%) 18 (78.3%)	26 (44.8%) 32 (55.2%)	0.076†
Body height (at screening) (cm)	Mean (SD) Minimum value, maximum value	165.43 (7.477) 150.3, 178.5	163.33 (6.947) 144.3, 174.8	0.230‡	161.18 (7.813) 143.2, 173.0	163.34 (8.537) 144.0, 179.8	0.295‡
Body weight (at screening) (kg)	Mean (SD) Minimum value, maximum value	67.40 (11.213) 49.0, 91.4	69.10 (10.015) 51.5, 99.0	0.505‡	65.99 (10.863) 54.2, 94.2	69.23 (13.077) 41.5, 101.5	0.297‡
BMI (at screening) (kg/m^2)	Mean (SD) Minimum value, maximum value	24.47 (2.509) 21.1, 29.7	25.88 (3.131) 20.0, 34.5	0.057‡	25.45 (4.040) 20.0, 35.9	25.80 (3.780) 20.0, 35.6	0.708‡
	<25 ≥25	15 (65.2%) 8 (34.8%)	28 (46.7%) 32 (53.3%)	0.148†	14 (60.9%) 9 (39.1%)	26 (44.8%) 32 (55.2%)	0.225†
Duration of disease (at screening) (month)	n	20	59		22	55	
	Mean (SD) Median Minimum value, maximum value	90.6 (73.19) 59.0 7, 233	100.0 (73.37) 79.0 3, 280	0.619‡	133.5 (116.92) 106.0 3, 547	129.6 (107.56) 99.0 4, 465	0.890‡
	<60 ≥60	10 (50.0%) 10 (50.0%)	21 (35.6%) 38 (64.4%)	0.296†	4 (18.2%) 18 (81.8%)	13 (23.6%) 42 (76.4%)	0.764†
Complications	No Yes	0 23 (100.0%)	0 60 (100.0%)	-	0 23 (100.0%)	0 58 (100.0%)	-
Smoking history	No smoking history Previous smoker Current smoker	5 (21.7%) 13 (56.5%) 5 (21.7%)	26 (43.3%) 25 (41.7%) 9 (15.0%)	0.199†	9 (39.1%) 11 (47.8%) 3 (13.0%)	17 (29.3%) 30 (51.7%) 11 (19.0%)	0.678†
Alcohol habits	No drinking history Previous drinker Current drinker	3 (13.0%) 2 (8.7%) 18 (78.3%)	15 (25.0%) 5 (8.3%) 40 (66.7%)	0.520†	10 (43.5%) 4 (17.4%) 9 (39.1%)	14 (24.1%) 7 (12.1%) 37 (63.8%)	0.122†
Alcohol consumption §	Non-drinker LEVEL 1 LEVEL 2 LEVEL 3	5 (21.7%) 12 (52.2%) 6 (26.1%) 0	20 (33.3%) 27 (45.0%) 13 (21.7%) 0	0.629†	14 (60.9%) 8 (34.8%) 1 (4.3%) 0	21 (36.2%) 28 (48.3%) 9 (15.5%) 0	0.118†
Concomitant oral antidiabetic drug (1) (at screening)	No Yes	6 (26.1%) 17 (73.9%)	20 (33.3%) 40 (66.7%)	0.604†	4 (17.4%) 19 (82.6%)	16 (27.6%) 42 (72.4%)	0.404†
Concomitant oral antidiabetic drug (2) (at screening)	No α-Glucosidase inhibitor Sulfonylureas Pioglitazone	6 (26.1%) 4 (17.4%) 9 (39.1%) 4 (17.4%)	20 (33.3%) 6 (10.0%) 24 (40.0%) 10 (16.7%)	0.741†	4 (17.4%) 5 (21.7%) 11 (47.8%) 3 (13.0%)	16 (27.6%) 9 (15.5%) 28 (48.3%) 5 (8.6%)	0.669†
HbA1c level (at the start of the treatment period) (%, JDS)	Mean (SD) Minimum value, maximum value	7.17 (0.523) 6.6, 8.3	7.05 (0.485) 6.3, 8.1	0.318‡	7.07 (0.554) 6.5, 8.6	7.19 (0.605) 5.9, 8.5	0.383‡
Fasting plasma glucose (at the start of the treatment period) (mg/dL)	Mean (SD) Minimum value, maximum value	146.3 (21.53) 117, 199	143.1 (20.73) 89, 194	0.525‡	141.3 (26.27) 73, 207	145.6 (24.55) 92, 204	0.488‡
eGFR (at the start of the treatment period) (mL/min/1.73 m^2)	Mean (SD) Minimum value, maximum value	72.1 (10.79) 57, 97	69.5 (8.81) 55, 88	0.263‡	53.2 (7.01) 37, 67	50.5 (9.16) 29, 70	0.210‡
	<60 ≥60	3 (13.0%) 20 (87.0%)	8 (13.3%) 52 (86.7%)	1.000†	19 (82.6%) 4 (17.4%)	49 (84.5%) 9 (15.5%)	1.000†

The classification variable represents the number of subjects (%).

The severity of renal impairment is categorized by eGFR at Visit 2 into mild (60≤eGFR<90 mL/min/1.73 m^2) or moderate (30≤eGFR<60 mL/min/1.73 m^2).

BMI: body mass index, eGFR: estimated glomerular filtration rate, FAS: full analysis set, HbA1c: hemoglobin A1c, JDS: Japan Diabetes Society

†: Fisher's exact test, ‡: t test

§: Alcohol consumption was classified into 3 levels based on daily consumption: LEVEL 1 (Middle bottle of beer - Less than 1 bottle, Sake - Less than 1 cup, Whiskey/brandy - Less than 60 mL, Shochu [35 degrees] - Less than 90 mL, Wine - Less than 240 mL), LEVEL 2 (Middle bottle of beer - 1 bottle or more and less than 3 bottles, Sake - 1cup or more and less than 3 cups, Whiskey/brandy - 60 mL or more and less than 180 mL, Shochu [35 degrees] - 90 mL or more and less than 270 mL, Wine - 240 mL or more and less than 720 mL), LEVEL 3 (Middle bottle of beer - 3 bottles or more, Sake - 3 cups or more, Whiskey/brandy - 180 mL or more, Shochu [35 degrees] - 270 mL or more, and Wine 720 mL or more).

Source: Tables 12.1A.2.1.1.2, 12.1A.2.2.1.2, 12.1A.2.3.1.2, 12.1A.2.4.1.2, and 12.1A.2.5.1.2

Table 3 Change in HbA1c Level (%) from Baseline to the End of Treatment Period I: FAS (24 Weeks)

	Placebo (n=46)	ASP1941 50 mg (n=118)
Baseline mean (SD)	7.12 (0.536)	7.12 (0.550)
Mean at the end of treatment period I (SD)	6.95 (0.671)	6.70 (0.659)
Mean change from baseline to the end of treatment period I (SD)	−0.17 (0.516)	−0.42 (0.510)
ANCOVA 1†		
Adjusted mean difference in the change from the placebo group (95% CI)	-	−0.25 (−0.414, −0.082)
P-value	-	0.004
ANCOVA 2‡		
Adjusted mean difference in the change from the placebo group (95% CI)	-	−0.28 (−0.445, −0.110)
P-value	-	0.001

CI: confidence interval, FAS: full analysis set, HbA1c: hemoglobin A1c

†: Analysis of covariance with the baseline HbA1c level as a covariate, severity of renal impairment as a factor, and treatment group as a fixed effect.

‡: Analysis of covariance with the baseline HbA1c level and eGFR of the placebo run-in period as covariates and treatment group as a fixed effect.

Source: Tables 12.3A.1.1.1.1, 12.3A.1.1.2.1, 12.3A.1.1.6.1.1, and 12.3A.1.1.6.2.1

Table 4 Change in HbA1c Level (%) from Baseline to the End of Treatment Period I by Severity of Renal Impairment: FAS (24 Weeks)

	Subjects with mild renal impairment		Subjects with moderate renal impairment	
	Placebo (n=23)	ASP1941 50 mg (n=60)	Placebo (n=23)	ASP1941 50 mg (n=58)
Baseline mean (SD)	7.17 (0.523)	7.05 (0.485)	7.07 (0.554)	7.19 (0.605)
Mean at the end of treatment period I (SD)	6.92 (0.618)	6.49 (0.462)	6.97 (0.732)	6.91 (0.762)
Mean change from baseline to the end of treatment period I (SD)	−0.26 (0.522)	−0.56 (0.397)	−0.09 (0.507)	−0.28 (0.575)
ANCOVA 1†				
Adjusted mean difference in the change from the placebo group (95% CI)	-	−0.35 (−0.545, −0.153)	-	−0.17 (−0.448, 0.099)
P-value	-	< 0.001	-	0.207
ANCOVA 2‡				
Adjusted mean difference in the change from the placebo group (95% CI)	-	−0.36 (−0.556, −0.166)	-	−0.16 (−0.444, 0.121)
P-value	-	< 0.001	-	0.258

The severity of renal impairment is categorized by eGFR at Visit 2in to mild (60 ≤eGFR<90mL/min/1.73 m^2) or moderate (30≤eGFR<60 mL/min/1.73 m^2).

CI: confidence interval, FAS: full analysis set, HbA1c: hemoglobin A1c

†: Analysis of covariance with the baseline HbA1c level as a covariate and treatment group as a fixed effect.

‡: Analysis of covariance with the baseline HbA1c level and eGFR of the placebo run-in period as covariates and treatment group as a fixed effect.

Source: Tables 12.3A.1.1.1.2, 12.3A.1.1.2.2, 12.3A.1.1.6.1.2, and 12.3A.1.1.6.2.2

Table 5 Change in Fasting Plasma Glucose (mg/dL) from Baseline to the End of Treatment Period I: FAS (24 Weeks)

	Placebo (n=46)	ASP1941 50 mg (n=118)
Baseline mean (SD)	143.8 (23.89)	144.3 (22.63)
Mean at the end of treatment period I (SD)	139.6 (22.23)	131.9 (24.17)
Mean change from baseline to the end of treatment period I (SD)	−4.2 (20.17)	−12.4 (22.66)
ANCOVA 1†		
Adjusted mean difference in the change from the placebo group (95% CI)	-	−8.0 (−14.71, −1.24)
P-value	-	0.021
ANCOVA 2‡		
Adjusted mean difference in the change from the placebo group (95% CI)	-	−8.8 (−15.52, −2.12)
P-value	-	0.010

†: Analysis of covariance with the baseline fasting plasma glucose as a covariate, severity of renal impairment as a factor, and treatment group as a fixed effect

‡: Analysis of covariance with the baseline fasting plasma glucose and eGFR of the placebo run-in period as covariates and treatment group as a fixed effect

CI: confidence interval, FAS: full analysis set

Source: Tables 12.3A.2.1.1.1.1, 12.3A.2.1.2.1.1, 12.3A.2.1.4.1.1, and 12.3A.2.1.4.2.1

Table 6 Changes in Fasting Plasma Glucose (mg/dL) from Baseline to the End of Treatment Period I by Severity of Renal Impairment: FAS (24 Weeks)

	Subjects with mild renal impairment		Subjects with moderate renal impairment	
	Placebo (n=23)	ASP1941 50 mg (n=60)	Placebo (n=23)	ASP1941 50 mg (n=58)
Baseline mean (SD)	146.3 (21.53)	143.1 (20.73)	141.3 (26.27)	145.6 (24.55)
Mean at the end of treatment period I (SD)	143.2 (17.21)	126.9 (19.84)	136.1 (26.25)	137.0 (27.19)
Mean change from baseline to the end of treatment period I (SD)	−3.2 (21.06)	−16.2 (20.24)	−5.2 (19.66)	−8.6 (24.51)
ANCOVA 1†				
Adjusted mean difference in the change from the placebo group (95% CI)	-	−14.8 (−23.08, −6.55)	-	−1.8 (−12.49, 8.82)
P-value	-	<0.001	-	0.733
ANCOVA 2‡				
Adjusted mean difference in the change from the placebo group (95% CI)	-	−15.5 (−23.69, −7.25)	-	−3.2 (−14.26, 7.77)
P-value	-	<0.001	-	0.559

The severity of renal impairment is categorized by eGFR at Visit 2 into mild (60 ≤eGFR<90mL/min/1.73 m^2) or moderate (30≤eGFR<60 mL/min/1.73 m^2).

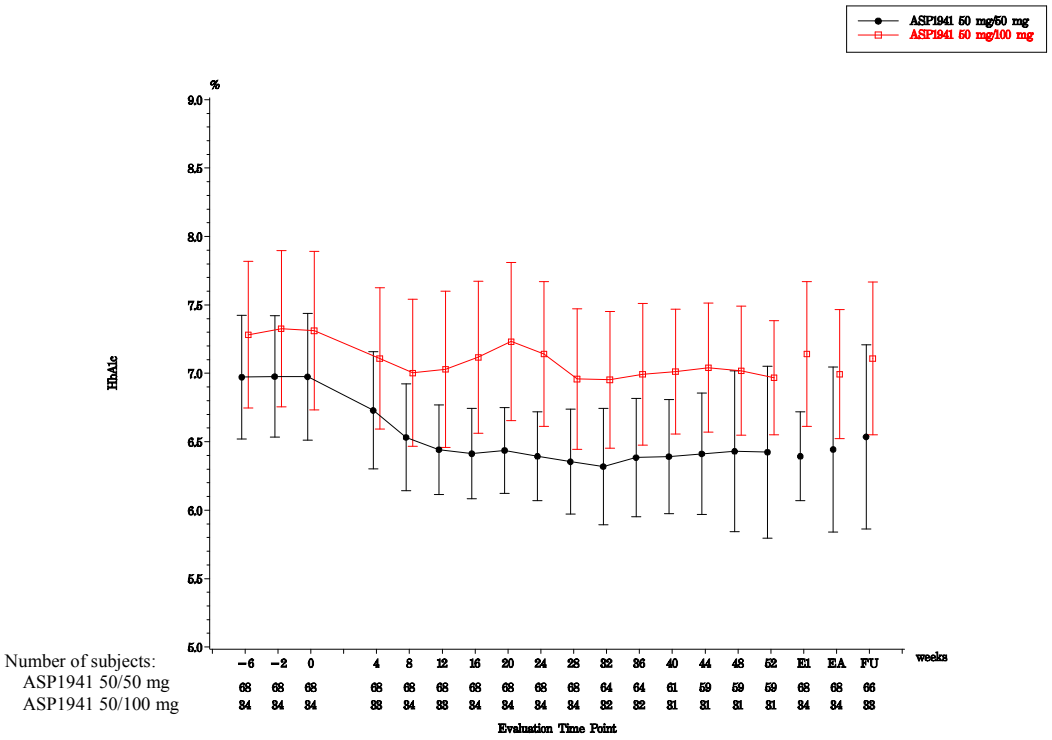
†: Analysis of covariance with the baseline fasting plasma glucose as a covariate and treatment group as a fixed effect

‡: Analysis of covariance with the baseline fasting plasma glucose and eGFR of the placebo run-in period as covariates and treatment group as a fixed effect

CI: confidence interval, FAS: full analysis set

Source: Tables 12.3A.2.1.1.1.2, 12.3A.2.1.2.1.2, 12.3A.2.1.4.1.2, and 12.3A.2.1.4.2.2

Figure 2 Changes over Time in HbA1c Level (%) (Mean and SD): FAS (52 Weeks)



E1: end of treatment period I, EA: end of administration of ASP1941, FAS: full analysis set, FU: follow-up, HbA1c: hemoglobin A1c
Source: Figure 12.3B.1.1.3

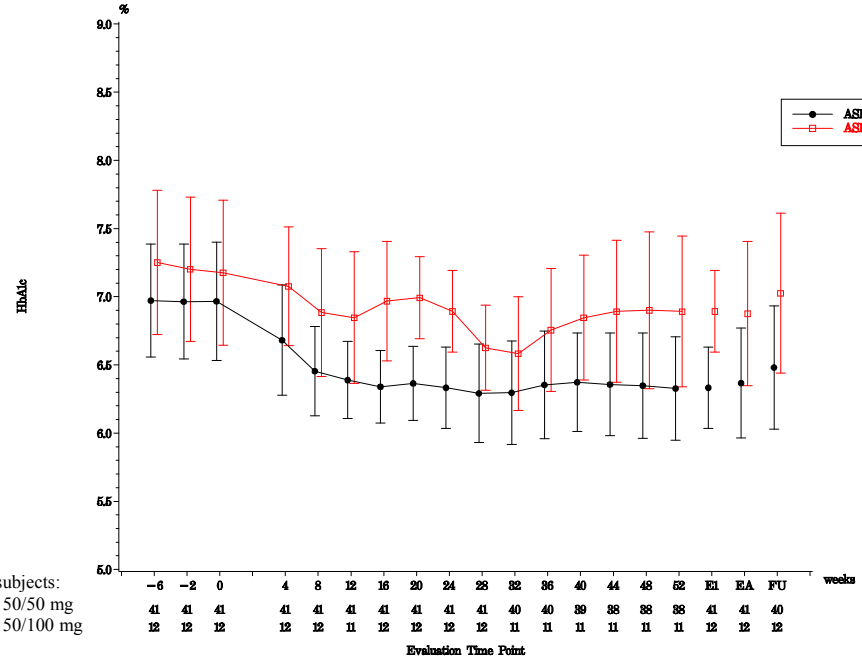
Table 7 Changes over Time in HbA1c Level (%) from the End of Treatment Period I: FAS (52 Weeks)

	Study drug in treatment period I/treatment period II			
	ASP1941 50/50 mg		ASP1941 50/100 mg	
	n	Mean (SD)	n	Mean (SD)
Week 28	68	−0.04 (0.208)	34	−0.18 (0.210)
Week 32	64	−0.06 (0.235)	32	−0.21 (0.332)
Week 36	64	0.00 (0.242)	32	−0.17 (0.449)
Week 40	61	0.02 (0.248)	31	−0.10 (0.457)
Week 44	59	0.04 (0.266)	31	−0.07 (0.460)
Week 48	59	0.06 (0.448)	31	−0.09 (0.495)
Week 52	59	0.06 (0.482)	31	−0.15 (0.452)
End of administration of ASP1941	68	0.05 (0.472)	34	−0.15 (0.435)
Follow-up period	66	0.15 (0.534)	33	−0.05 (0.522)

FAS: full analysis set, HbA1c: hemoglobin A1c
Source: Table 12.3B.1.3.1

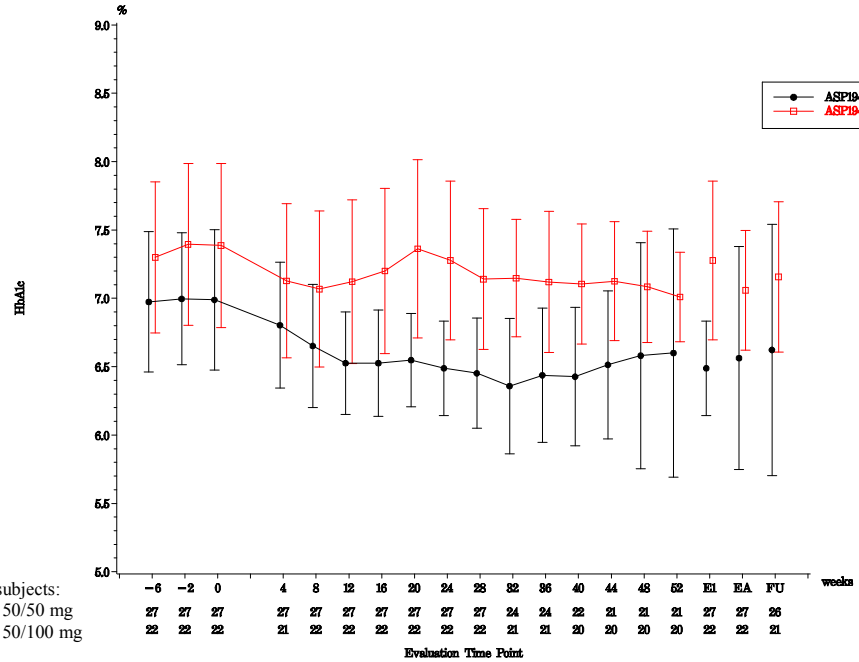
Figure 3 Changes over Time in HbA1c Level (%) by Severity of Renal Impairment (Mean and SD): FAS (52 Weeks)

A. ASP1941 50/50 mg Group, ASP1941 50/100 mg Group: Subjects with Mild Renal Impairment



Number of subjects:	−6	−2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	E1	EA	FU
ASP1941 50/50 mg	41	41	41	41	41	41	41	41	41	41	40	40	39	38	38	38	41	41	40
ASP1941 50/100 mg	12	12	12	12	12	11	12	12	12	12	11	11	11	11	11	11	12	12	12

B. ASP1941 50/50 mg Group, ASP1941 50/100 mg Group: Subjects with Moderate Renal Impairment



Number of subjects:	−6	−2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	E1	EA	FU
ASP1941 50/50 mg	27	27	27	27	27	27	27	27	27	27	24	24	22	21	21	21	27	27	26
ASP1941 50/100 mg	22	22	22	21	22	22	22	22	22	22	21	21	20	20	20	20	22	22	21

The severity of renal impairment is categorized by eGFR at Visit 2 into mild (60≤eGFR<90 mL/min/1.73 m^2) or moderate (30≤eGFR<60 mL/min/1.73 m^2).

E1: end of treatment period I, EA: end of administration of ASP1941, FAS: full analysis set, FU: follow-up, HbA1c: hemoglobin A1c

Source: Figure 12.3B.1.1.7

Table 8 Changes over Time in HbA1c Level (%) from the End of Treatment Period I by Severity of Renal Impairment: FAS (52 Weeks)

	Subjects with mild renal impairment				Subjects with moderate renal impairment			
	Study drug in treatment period I/ treatment period II				Study drug in treatment period I/ treatment period II			
	ASP1941 50/50 mg		ASP1941 50/100 mg		ASP1941 50/50 mg		ASP1941 50/100 mg	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Week 28	41	−0.04 (0.175)	12	−0.27 (0.156)	27	−0.04 (0.254)	22	−0.14 (0.224)
Week 32	40	−0.04 (0.212)	11	−0.30 (0.286)	24	−0.11 (0.267)	21	−0.16 (0.350)
Week 36	40	0.02 (0.221)	11	−0.13 (0.287)	24	−0.03 (0.276)	21	−0.19 (0.520)
Week 40	39	0.05 (0.220)	11	−0.04 (0.294)	22	−0.02 (0.293)	20	−0.14 (0.529)
Week 44	38	0.04 (0.215)	11	0.01 (0.365)	21	0.05 (0.346)	20	−0.12 (0.508)
Week 48	38	0.03 (0.200)	11	0.02 (0.397)	21	0.12 (0.710)	20	−0.16 (0.541)
Week 52	38	0.01 (0.210)	11	0.01 (0.375)	21	0.14 (0.762)	20	−0.23 (0.477)
End of administration of ASP1941	41	0.03 (0.227)	12	−0.02 (0.369)	27	0.07 (0.703)	22	−0.22 (0.459)
Follow-up period	40	0.16 (0.232)	12	0.13 (0.425)	26	0.15 (0.811)	21	−0.15 (0.553)

The severity of renal impairment is categorized by eGFR at Visit 2 into mild (60≤eGFR<90 mL/min/1.73 m^2) or moderate (30≤eGFR<60 mL/min/1.73 m^2).

FAS: full analysis set, HbA1c: hemoglobin A1c

Source: Table 12.3B.1.3.2

Table 9 Percentages of Subjects with HbA1c Level Less Than 7.0%: FAS (52 Weeks)

	ASP1941 50 mg Randomization		Study drug in treatment period I/treatment period II			
			ASP1941 50/50 mg		ASP1941 50/100 mg	
	n	Number (rate) of subjects	n	Number (rate) of subjects	n	Number (rate) of subjects
Start of treatment period (baseline)	118	54 (45.8%)	68	36 (52.9%)	34	12 (35.3%)
Week 4	116	72 (62.1%)	68	51 (75.0%)	33	14 (42.4%)
Week 8	116	84 (72.4%)	68	60 (88.2%)	34	17 (50.0%)
Week 12	113	83 (73.5%)	68	64 (94.1%)	33	13 (39.4%)
Week 16	113	85 (75.2%)	68	65 (95.6%)	34	14 (41.2%)
Week 20	108	79 (73.1%)	68	66 (97.1%)	34	10 (29.4%)
Week 24†	107	82 (76.6%)	68	65 (95.6%)	34	15 (44.1%)
Week 28	102	80 (78.4%)	68	61 (89.7%)	34	19 (55.9%)
Week 32	96	74 (77.1%)	64	58 (90.6%)	32	16 (50.0%)
Week 36	96	68 (70.8%)	64	56 (87.5%)	32	12 (37.5%)
Week 40	92	66 (71.7%)	61	56 (91.8%)	31	10 (32.3%)
Week 44	90	66 (73.3%)	59	53 (89.8%)	31	13 (41.9%)
Week 48	90	64 (71.1%)	59	52 (88.1%)	31	12 (38.7%)
Week 52	90	64 (71.1%)	59	50 (84.7%)	31	14 (45.2%)
End of treatment period I	118	88 (74.6%)	68	65 (95.6%)	34	15 (44.1%)
End of administration of ASP1941	118	80 (67.8%)	68	56 (82.4%)	34	16 (47.1%)
Follow-up period	113	69 (61.1%)	66	48 (72.7%)	33	15 (45.5%)

FAS: full analysis set, HbA1c: hemoglobin A1c

†: Week 24 is the time point to proceed from treatment period I to treatment period II.

Source: Tables 12.3B.1.4.1 and 12.3B.1.4.2

Table 10 Percentages of Subjects with HbA1c Level Less Than 7.0% by Severity of Renal Impairment: FAS (52 Weeks)

	Subjects with mild renal impairment						Subjects with moderate renal impairment					
	ASP1941 50 mg Randomization		Study drug in treatment period I/treatment period II				ASP1941 50 mg Randomization		Study drug in treatment period I/treatment period II			
			ASP1941 50/50 mg		ASP1941 50/100 mg				ASP1941 50/50 mg		ASP1941 50/100 mg	
	n	Number (rate) of subjects	n	Number (rate) of subjects	n	Number (rate) of subjects	n	Number (rate) of subjects	n	Number (rate) of subjects	n	Number (rate) of subjects
Start of treatment period	60	30 (50.0%)	41	23 (56.1%)	12	4 (33.3%)	58	24 (41.4%)	27	13 (48.1%)	22	8 (36.4%)
Week 4	60	41 (68.3%)	41	33 (80.5%)	12	5 (41.7%)	56	31 (55.4%)	27	18 (66.7%)	21	9 (42.9%)
Week 8	59	48 (81.4%)	41	38 (92.7%)	12	7 (58.3%)	57	36 (63.2%)	27	22 (81.5%)	22	10 (45.5%)
Week 12	57	48 (84.2%)	41	40 (97.6%)	11	5 (45.5%)	56	35 (62.5%)	27	24 (88.9%)	22	8 (36.4%)
Week 16	57	49 (86.0%)	41	40 (97.6%)	12	6 (50.0%)	56	36 (64.3%)	27	25 (92.6%)	22	8 (36.4%)
Week 20	56	45 (80.4%)	41	40 (97.6%)	12	3 (25.0%)	52	34 (65.4%)	27	26 (96.3%)	22	7 (31.8%)
Week 24†	55	47 (85.5%)	41	40 (97.6%)	12	5 (41.7%)	52	35 (67.3%)	27	25 (92.6%)	22	10 (45.5%)
Week 28	53	49 (92.5%)	41	38 (92.7%)	12	11 (91.7%)	49	31 (63.3%)	27	23 (85.2%)	22	8 (36.4%)
Week 32	51	46 (90.2%)	40	37 (92.5%)	11	9 (81.8%)	45	28 (62.2%)	24	21 (87.5%)	21	7 (33.3%)
Week 36	51	43 (84.3%)	40	36 (90.0%)	11	7 (63.6%)	45	25 (55.6%)	24	20 (83.3%)	21	5 (23.8%)
Week 40	50	41 (82.0%)	39	36 (92.3%)	11	5 (45.5%)	42	25 (59.5%)	22	20 (90.9%)	20	5 (25.0%)
Week 44	49	41 (83.7%)	38	35 (92.1%)	11	6 (54.5%)	41	25 (61.0%)	21	18 (85.7%)	20	7 (35.0%)
Week 48	49	42 (85.7%)	38	36 (94.7%)	11	6 (54.5%)	41	22 (53.7%)	21	16 (76.2%)	20	6 (30.0%)
Week 52	49	42 (85.7%)	38	36 (94.7%)	11	6 (54.5%)	41	22 (53.7%)	21	14 (66.7%)	20	8 (40.0%)
End of treatment period I	60	49 (81.7%)	41	40 (97.6%)	12	5 (41.7%)	58	39 (67.2%)	27	25 (92.6%)	22	10 (45.5%)
End of administration	60	48 (80.0%)	41	37 (90.2%)	12	7 (58.3%)	58	32 (55.2%)	27	19 (70.4%)	22	9 (40.9%)
Follow-up period	57	39 (68.4%)	40	31 (77.5%)	12	6 (50.0%)	56	30 (53.6%)	26	17 (65.4%)	21	9 (42.9%)

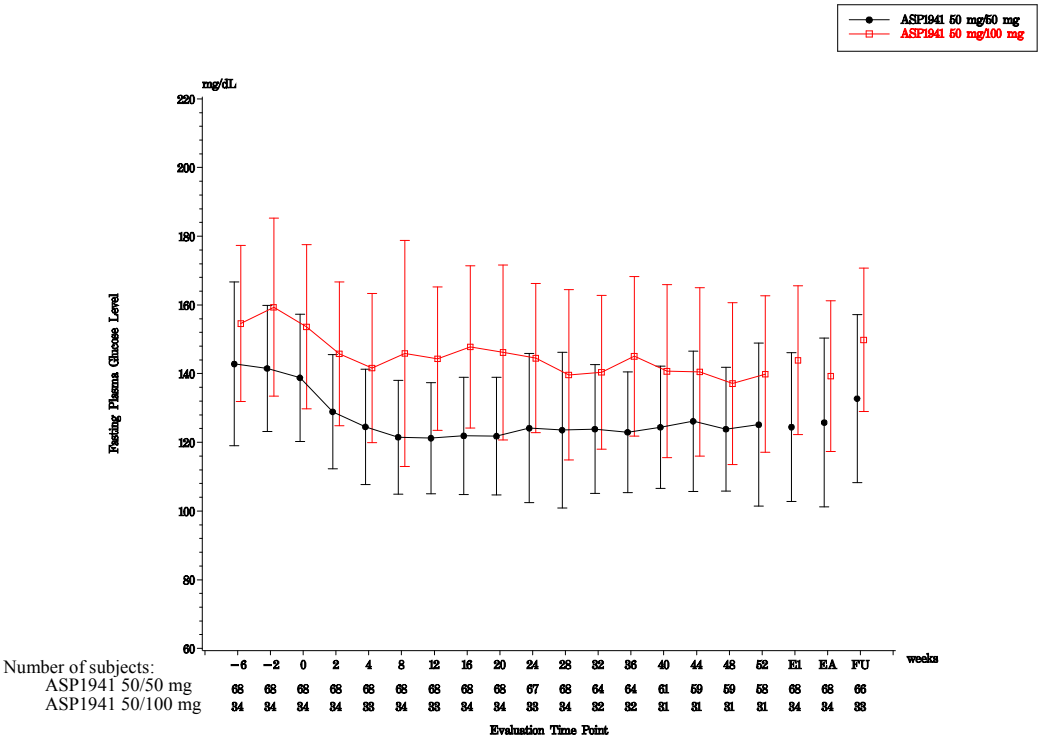
The severity of renal impairment is categorized by eGFR at Visit 2 into mild ($60 \leq eGFR < 90$ mL/min/1.73 m^2) or moderate ($30 \leq eGFR < 60$ mL/min/1.73 m^2).

End of administration: end of administration of ASP1941, FAS: full analysis set, HbA1c: hemoglobin A1c

†: Week 24 is the time point to proceed from treatment period I to treatment period II.

Source: Tables 12.3B.1.4.3 and 12.3B.1.4.5

Figure 4 Changes over Time in Fasting Plasma Glucose (mg/dL) (Mean and SD): FAS (52 Weeks)



E1: end of treatment period I, EA: end of administration of ASP1941, FAS: full analysis set, FU: follow-up

Source: Figure 12.3B.2.1.3

Table 11 Changes over Time in Fasting Plasma Glucose (mg/dL) from the End of Treatment Period I: FAS (52 Weeks)

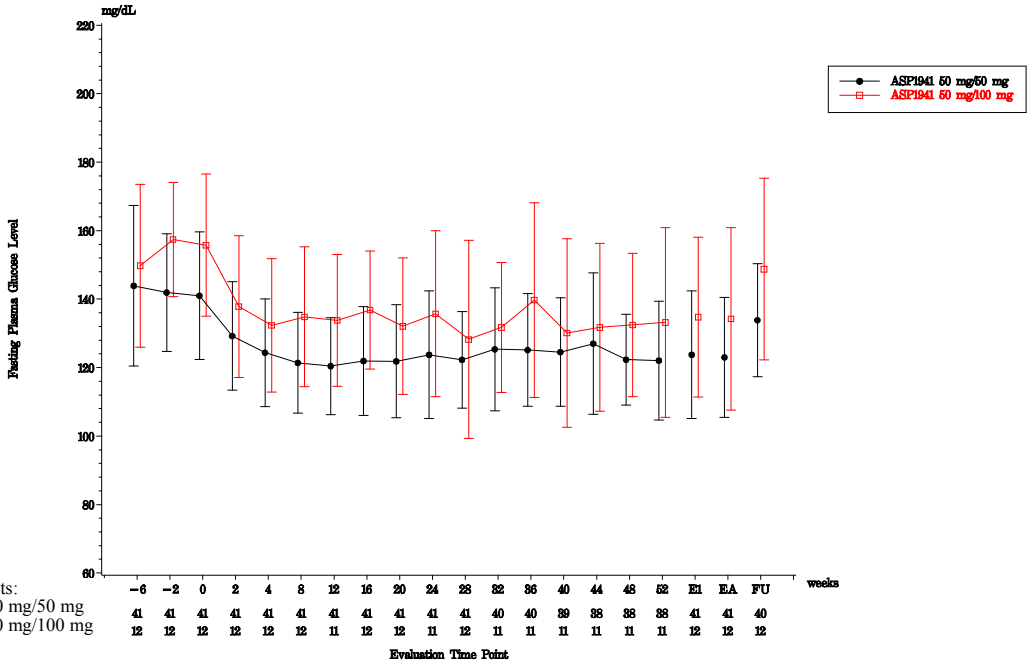
	Study drug in treatment period I/treatment period II			
	ASP1941 50/50 mg		ASP1941 50/100 mg	
	n	Mean (SD)	n	Mean (SD)
Week 28	68	−0.9 (12.13)	34	−4.3 (17.96)
Week 32	64	0.9 (13.12)	32	−3.7 (21.43)
Week 36	64	0.0 (11.80)	32	1.0 (19.85)
Week 40	61	1.3 (13.74)	31	−3.0 (18.91)
Week 44	59	3.3 (13.56)	31	−3.2 (19.96)
Week 48	59	0.9 (16.81)	31	−6.6 (18.90)
Week 52	58	2.7 (19.40)	31	−3.9 (14.10)
End of administration of ASP1941	68	1.3 (19.03)	34	−4.6 (14.23)
Follow-up period	66	10.1 (19.80)	33	5.8 (19.57)

FAS: full analysis set

Source: Table 12.3B.2.3.1

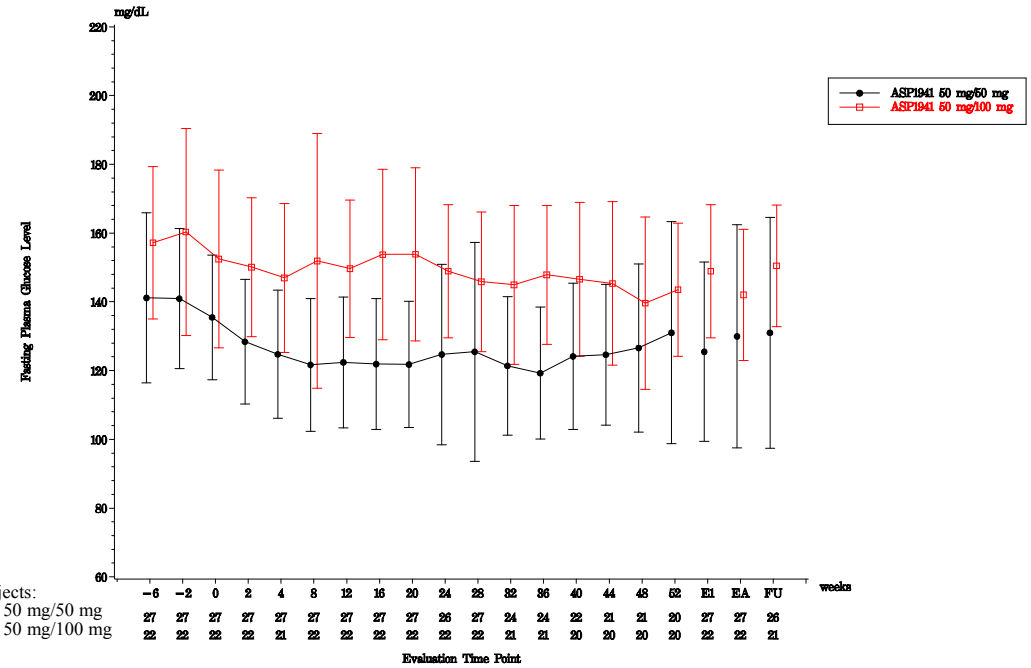
Figure 5 Changes over Time in Fasting Plasma Glucose (mg/dL) by Severity of Renal Impairment (Mean and SD): FAS (52 Weeks)

A. ASP1941 50/50 mg Group, ASP1941 50/100 mg Group: Subjects with Mild Renal Impairment



Number of subjects:	−6	−2	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	E1	EA	FU
ASP1941 50 mg/50 mg	41	41	41	41	41	41	41	41	41	41	41	40	40	39	38	38	38	41	41	40
ASP1941 50 mg/100 mg	12	12	12	12	12	12	11	12	12	11	12	11	11	11	11	11	11	12	12	12

B. ASP1941 50/50 mg Group, ASP1941 50/100 mg Group: Subjects with Moderate Renal Impairment



Number of subjects:	−6	−2	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	E1	EA	FU
ASP1941 50 mg/50 mg	27	27	27	27	27	27	27	27	27	26	27	24	24	22	21	21	20	27	27	26
ASP1941 50 mg/100 mg	22	22	22	22	21	22	22	22	22	22	22	21	21	20	20	20	20	22	22	21

The severity of renal impairment is categorized by eGFR at Visit 2 into mild (60≤eGFR<90 mL/min/1.73 m^2) or moderate (30≤eGFR<60 mL/min/1.73 m^2).

E1: end of treatment period I, EA: end of administration of ASP1941, FAS: full analysis set, FU: follow-up

Source: Figure 12.3B.2.1.7

Table 12 Summary Statistics of Plasma Concentration of the Unchanged Drug (ng/mL) in the ASP1941 50 mg Group: PKAS (24 Weeks)

Visit	No. of subjects	Mean	SD	Minimum	Maximum	Median	Geometric mean	No. of subjects†	Coefficient of variation (%)
Week 8	115	96.34	137.482	0.00	1113.15	65.13	71.24	113	142.71
Week 16	112	81.54	92.578	0.00	864.60	63.59	64.66	109	113.54
Week 24	107	94.54	135.549	0.00	1210.48	69.56	72.30	106	143.38

PKAS: pharmacokinetics analysis set

†: Number of subjects used for calculating geometric mean

Source: Attachment 1.1 Table 1.1

Table 13 Summary Statistics of Plasma Concentration of the Unchanged Drug (ng/mL) in the ASP1941 50 mg Group by Severity of Renal Impairment: PKAS (24 Weeks)

Severity of renal impairment	Visit	No. of subjects	Mean	SD	Minimum	Maximum	Median	Geometric mean	No. of subjects†	Coefficient of Variation (%)
Mild	Week 8	59	80.01	76.980	0.00	598.24	65.13	65.80	58	96.21
	Week 16	57	71.34	52.714	0.00	358.17	59.38	62.08	55	73.89
	Week 24	55	98.21	159.703	0.00	1210.48	71.42	71.83	54	162.61
Moderate	Week 8	56	113.54	179.836	0.00	1113.15	64.31	77.46	55	158.40
	Week 16	55	92.11	120.467	0.00	864.60	68.91	67.39	54	130.79
	Week 24	52	90.65	105.607	27.77	786.31	66.15	72.78	52	116.51

The severity of renal impairment is categorized by eGFR at Visit 2 into mild ($60 \leq eGFR < 90$ mL/min/1.73 m^2) or moderate ($30 \leq eGFR < 60$ mL/min/1.73 m^2).

PKAS: pharmacokinetics analysis set

†: Number of subjects used for calculating geometric mean

Source: Attachment 1.1 Tables 2.1 and 2.2

Table 14 Summary Statistics of Plasma Concentration of the Unchanged Drug (ng/mL) in the ASP1941 50/50 mg Group: PKAS (52 Weeks)

Visit	No. of subjects	Mean	SD	Minimum	Maximum	Median	Geometric mean	No. of subjects†	Coefficient of variation (%)
Week 8	68	87.01	78.920	28.80	598.24	67.27	72.32	68	90.70
Week 16	68	78.86	53.406	1.91	358.17	64.06	64.59	68	67.73
Week 24‡	68	108.98	167.142	8.85	1210.48	72.21	76.45	68	153.37
Week 32	64	97.73	98.865	20.05	576.83	69.81	76.23	64	101.16
Week 40	61	98.73	142.978	11.04	1121.01	70.77	73.42	61	144.82
Week 52	59	88.73	63.609	16.48	401.60	71.72	74.78	59	71.69

PKAS: pharmacokinetics analysis set

†: Number of subjects used for calculating geometric mean

‡: Week 24 is the time point to proceed from treatment period I to treatment period II.

Source: Attachment 1.2 Table 1.3.1

Table 15 Summary Statistics of Plasma Concentration of the Unchanged Drug (ng/mL) in ASP1941 50/100 mg Group: PKAS (52 Weeks)

Visit	No. of subjects	Mean	SD	Minimum	Maximum	Median	Geometric mean	No. of subjects†	Coefficient of variation (%)
Week 8	34	123.83	222.143	25.90	1113.15	66.60	73.57	34	179.40
Week 16	34	86.81	140.524	16.00	864.60	62.92	61.03	34	161.87
Week 24‡	34	68.99	28.510	26.41	146.71	63.15	63.49	34	41.32
Week 32	32	132.51	58.864	34.14	289.48	120.91	119.32	32	44.42
Week 40	31	140.77	63.035	24.57	267.75	126.12	126.41	31	44.78
Week 52	31	140.43	52.226	44.50	255.44	132.11	130.17	31	37.19

PKAS: pharmacokinetics analysis set

†: Number of subjects used for calculating geometric mean

‡: Week 24 is the time point to proceed from treatment period I to treatment period II.

Source: Attachment 1.2 Table 1.4.1

Table 16 Summary Statistics of Plasma Concentration of the Unchanged Drug (ng/mL) in the ASP1941 50/50 mg Group by Severity of Renal Impairment: PKAS (52 Weeks)

Severity of renal impairment	Visit	No. of subjects	Mean	SD	Minimum	Maximum	Median	Geometric mean	No. of subjects†	Coefficient of Variation (%)
Mild	Week 8	41	85.41	86.625	29.21	598.24	65.13	71.22	41	101.42
	Week 16	41	77.03	55.400	20.63	358.17	59.38	65.39	41	71.92
	Week 24‡	41	108.08	182.905	8.85	1210.48	72.42	74.23	41	169.23
	Week 32	40	81.08	82.429	20.05	550.72	65.14	65.89	40	101.67
	Week 40	39	81.28	53.222	30.47	339.81	70.08	71.06	39	65.48
	Week 52	38	80.99	47.585	16.48	275.81	66.18	70.49	38	58.75
Moderate	Week 8	27	89.44	67.047	28.80	358.49	72.27	74.03	27	74.96
	Week 16	27	81.62	51.138	1.91	201.30	70.44	63.41	27	62.65
	Week 24‡	27	110.34	143.242	27.77	786.31	72.00	79.94	27	129.81
	Week 32	24	125.49	118.178	40.77	576.83	83.45	97.19	24	94.18
	Week 40	22	129.67	227.407	11.04	1121.01	71.98	77.81	22	175.38
	Week 52	21	102.73	85.000	35.76	401.60	75.03	83.23	21	82.74

The severity of renal impairment is categorized by eGFR at Visit 2 into mild (60≤eGFR<90 mL/min/1.73 m^2) or moderate (30≤eGFR<60 mL/min/1.73 m^2).

PKAS: pharmacokinetics analysis set
†: Number of subjects used for calculating geometric mean
‡: Week 24 is the time point to proceed from treatment period I to treatment period II.

Source: Attachment 1.2 Tables 2.1.3 and 2.2.3

Table 17 Summary Statistics of Plasma Concentration of the Unchanged Drug (ng/mL) in the ASP1941 50/100 mg Group by Severity of Renal Impairment: PKAS (52 Weeks)

Severity of renal impairment	Visit	No. of subjects	Mean	SD	Minimum	Maximum	Median	Geometric mean	No. of subjects†	Coefficient of Variation (%)
Mild	Week 8	12	79.41	49.705	25.90	192.75	79.91	65.71	12	62.59
	Week 16	12	64.19	41.620	16.00	156.10	62.92	51.94	12	64.84
	Week 24‡	12	71.21	38.599	26.41	146.71	66.53	61.71	12	54.21
	Week 32	11	128.23	75.060	34.14	289.48	108.10	108.38	11	58.54
	Week 40	11	140.64	82.856	24.57	267.75	119.94	116.45	11	58.91
	Week 52	11	138.15	67.314	44.50	228.42	148.26	120.81	11	48.72
Moderate	Week 8	22	148.05	272.966	26.00	1113.15	62.40	78.25	22	184.37
	Week 16	22	99.15	172.254	23.53	864.60	62.44	66.65	22	173.73
	Week 24‡	22	67.78	22.192	34.44	113.72	61.86	64.48	22	32.74
	Week 32	21	134.76	50.381	44.71	248.43	122.19	125.49	21	37.39
	Week 40	20	140.84	51.582	72.18	254.61	131.66	132.25	20	36.63
	Week 52	20	141.68	43.785	74.06	255.44	131.47	135.63	20	30.91

The severity of renal impairment is categorized by eGFR at Visit 2 into mild ($60 \leq eGFR < 90$ mL/min/1.73 m^2) or moderate ($30 \leq eGFR < 60$ mL/min/1.73 m^2).

PKAS: pharmacokinetics analysis set

†: Number of subjects used for calculating geometric mean

‡: Week 24 is the time point to proceed from treatment period I to treatment period II.

Source: Attachment 1.2 Tables 2.1.4 and 2.2.4

Table 18 Adverse Events with an Incidence of 2% or Higher in Any Group: SAF (24 Weeks)

MedDRA Version 12.1 System Organ Class (SOC)† Preferred Term (PT)	Placebo (n=46)	ASP1941 50 mg (n=119)
Number of subjects who experienced an AE †	34 (73.9%)	97 (81.5%)
Blood and lymphatic system disorders	0	3 (2.5%)
Anaemia	0	3 (2.5%)
Cardiac disorders	2 (4.3%)	2 (1.7%)
Atrioventricular block complete	1 (2.2%)	0
Ventricular extrasystoles	1 (2.2%)	0
Eye disorders	4 (8.7%)	6 (5.0%)
Cataract	1 (2.2%)	1 (0.8%)
Conjunctivitis	1 (2.2%)	2 (1.7%)
Corneal erosion	1 (2.2%)	0
Diabetic retinopathy	1 (2.2%)	1 (0.8%)
Punctate keratitis	1 (2.2%)	0
Gastrointestinal disorders	6 (13.0%)	25 (21.0%)
Abdominal pain upper	0	3 (2.5%)
Colonic polyp	1 (2.2%)	2 (1.7%)
Constipation	2 (4.3%)	9 (7.6%)
Dental caries	1 (2.2%)	3 (2.5%)
Diarrhoea	0	4 (3.4%)
Gastritis	1 (2.2%)	3 (2.5%)
Periodontitis	1 (2.2%)	1 (0.8%)
Peritonitis	1 (2.2%)	0
Salivary gland calculus	1 (2.2%)	0
Stomatitis	1 (2.2%)	1 (0.8%)
General disorders and administration site conditions	4 (8.7%)	6 (5.0%)
Chest pain	1 (2.2%)	0
Fatigue	2 (4.3%)	0
Malaise	1 (2.2%)	0
Thirst	1 (2.2%)	3 (2.5%)
Hepatobiliary disorders	1 (2.2%)	2 (1.7%)
Hepatic function abnormal	1 (2.2%)	0
Infections and infestations	21 (45.7%)	36 (30.3%)
Appendicitis perforated	1 (2.2%)	0
Bronchitis	1 (2.2%)	1 (0.8%)
Gastroenteritis	1 (2.2%)	3 (2.5%)
Herpes zoster	1 (2.2%)	0
Nasopharyngitis	16 (34.8%)	25 (21.0%)
Pharyngitis	1 (2.2%)	1 (0.8%)
Postoperative wound infection	1 (2.2%)	0
Asymptomatic bacteriuria	2 (4.3%)	0
Abdominal abscess	1 (2.2%)	0
Oral herpes	1 (2.2%)	0
Injury, poisoning and procedural complications	4 (8.7%)	10 (8.4%)
Arthropod bite	1 (2.2%)	1 (0.8%)
Excoriation	1 (2.2%)	0
Wound complication	1 (2.2%)	0
Procedural pain	1 (2.2%)	0
Investigations	5 (10.9%)	14 (11.8%)
Beta 2 microglobulin urine increased	0	3 (2.5%)
Blood creatine phosphokinase increased	1 (2.2%)	2 (1.7%)
Blood pressure increased	1 (2.2%)	0
Blood triglycerides increased	2 (4.3%)	0
Weight loss	1 (2.2%)	4 (3.4%)
Metabolism and nutrition disorders	2 (4.3%)	9 (7.6%)
Diabetes mellitus‡	1 (2.2%)	4 (3.4%)
Hyperkalaemia	1 (2.2%)	0
Musculoskeletal and connective tissue disorders	8 (17.4%)	20 (16.8%)
Back pain	4 (8.7%)	5 (4.2%)

MedDRA Version 12.1 System Organ Class (SOC)† Preferred Term (PT)	Placebo (n=46)	ASP1941 50 mg (n=119)
Muscle spasms	1 (2.2%)	1 (0.8%)
Myalgia	2 (4.3%)	2 (1.7%)
Neck pain	1 (2.2%)	0
Pain in extremity	1 (2.2%)	4 (3.4%)
Nervous system disorders	1 (2.2%)	16 (13.4%)
Carotid artery stenosis	1 (2.2%)	1 (0.8%)
Dizziness	0	5 (4.2%)
Headache	0	3 (2.5%)
Hypoaesthesia	0	3 (2.5%)
Psychiatric disorders	3 (6.5%)	1 (0.8%)
Insomnia	3 (6.5%)	1 (0.8%)
Renal and urinary disorders	2 (4.3%)	10 (8.4%)
Pollakiuria	2 (4.3%)	10 (8.4%)
Respiratory, thoracic and mediastinal disorders	3 (6.5%)	4 (3.4%)
Rhinitis allergic	1 (2.2%)	1 (0.8%)
Rhinorrhoea	1 (2.2%)	0
Allergic bronchitis	1 (2.2%)	0
Oropharyngeal pain	1 (2.2%)	1 (0.8%)
Skin and subcutaneous tissue disorders	8 (17.4%)	12 (10.1%)
Dermatitis contact	1 (2.2%)	5 (4.2%)
Eczema asteatotic	1 (2.2%)	0
Erythema	1 (2.2%)	0
Hyperkeratosis	1 (2.2%)	0
Nail disorder	1 (2.2%)	0
Pruritus	2 (4.3%)	2 (1.7%)
Pustular psoriasis	1 (2.2%)	0
Urticaria	1 (2.2%)	0

Number of subjects (%)

SAF: safety analysis set

†: Adverse events with an incidence of less than 2% are included in both groups.

‡: Reported as [redacted].

Source: Table 12.6A.1.5.1

Table 19 Adverse Events with an Incidence of 2% or Higher in Any Group (by Severity of Renal Impairment): SAF (24 Weeks)

MedDRA Version 12.1 System Organ Class (SOC) † Preferred Term (PT)	Subjects with mild renal impairment		Subjects with moderate renal impairment	
	Placebo (n=23)	ASP1941 50 mg (n=61)	Placebo (n=23)	ASP1941 50 mg (n=58)
Number of subjects who experienced an AE	18 (78.3%)	49 (80.3%)	16 (69.6%)	48 (82.8%)
Blood and lymphatic system disorders	0	0	0	3 (5.2%)
Anaemia	0	0	0	3 (5.2%)
Cardiac disorders	1 (4.3%)	0	1 (4.3%)	2 (3.4%)
Atrioventricular block complete	0	0	1 (4.3%)	0
Ventricular extrasystoles	1 (4.3%)	0	0	0
Eye disorders	2 (8.7%)	2 (3.3%)	2 (8.7%)	4 (6.9%)
Cataract	1 (4.3%)	0	0	1 (1.7%)
Conjunctivitis	0	1 (1.6%)	1 (4.3%)	1 (1.7%)
Corneal erosion	0	0	1 (4.3%)	0
Diabetic retinopathy	1 (4.3%)	0	0	1 (1.7%)
Punctate keratitis	0	0	1 (4.3%)	0
Gastrointestinal disorders	4 (17.4%)	11 (18.0%)	2 (8.7%)	14 (24.1%)
Abdominal pain upper	0	1 (1.6%)	0	2 (3.4%)
Colonic polyp	1 (4.3%)	1 (1.6%)	0	1 (1.7%)
Constipation	1 (4.3%)	5 (8.2%)	1 (4.3%)	4 (6.9%)
Dental caries	1 (4.3%)	0	0	3 (5.2%)
Diarrhoea	0	3 (4.9%)	0	1 (1.7%)
Dyspepsia	0	0	0	2 (3.4%)
Gastritis	0	1 (1.6%)	1 (4.3%)	2 (3.4%)
Periodontitis	1 (4.3%)	0	0	1 (1.7%)
Peritonitis	1 (4.3%)	0	0	0
Salivary gland calculus	1 (4.3%)	0	0	0
Stomatitis	1 (4.3%)	1 (1.6%)	0	0
General disorders and administration site conditions	2 (8.7%)	3 (4.9%)	2 (8.7%)	3 (5.2%)
Chest pain	0	0	1 (4.3%)	0
Fatigue	1 (4.3%)	0	1 (4.3%)	0
Malaise	0	0	1 (4.3%)	0
Thirst	1 (4.3%)	2 (3.3%)	0	1 (1.7%)
Hepatobiliary disorders	1 (4.3%)	2 (3.3%)	0	0
Hepatic function abnormal	1 (4.3%)	0	0	0
Hepatic steatosis	0	2 (3.3%)	0	0
Infections and infestations	8 (34.8%)	16 (26.2%)	13 (56.5%)	20 (34.5%)
Appendicitis perforated	1 (4.3%)	0	0	0
Bronchitis	1 (4.3%)	0	0	1 (1.7%)
Gastroenteritis	0	2 (3.3%)	1 (4.3%)	1 (1.7%)
Herpes zoster	1 (4.3%)	0	0	0
Nasopharyngitis	5 (21.7%)	13 (21.3%)	11 (47.8%)	12 (20.7%)
Pharyngitis	0	1 (1.6%)	1 (4.3%)	0
Postoperative wound infection	1 (4.3%)	0	0	0
Asymptomatic bacteriuria	0	0	2 (8.7%)	0
Abdominal abscess	1 (4.3%)	0	0	0
Oral herpes	1 (4.3%)	0	0	0
Injury, poisoning and procedural complications	1 (4.3%)	7 (11.5%)	3 (13.0%)	3 (5.2%)
Arthropod bite	0	1 (1.6%)	1 (4.3%)	0
Excoriation	0	0	1 (4.3%)	0
Wound complication	0	0	1 (4.3%)	0
Procedural pain	1 (4.3%)	0	0	0
Investigations	4 (17.4%)	10 (16.4%)	1 (4.3%)	4 (6.9%)
Beta 2 microglobulin urine increased	0	2 (3.3%)	0	1 (1.7%)
Blood creatine phosphokinase increased	1 (4.3%)	2 (3.3%)	0	0
Blood creatinine increased	0	2 (3.3%)	0	0
Blood pressure increased	1 (4.3%)	0	0	0
Blood triglycerides increased	1 (4.3%)	0	1 (4.3%)	0

MedDRA Version 12.1 System Organ Class (SOC) † Preferred Term (PT)	Subjects with mild renal impairment		Subjects with moderate renal impairment	
	Placebo (n=23)	ASP1941 50 mg (n=61)	Placebo (n=23)	ASP1941 50 mg (n=58)
Weight loss	1 (4.3%)	2 (3.3%)	0	2 (3.4%)
Cystatin C increased	0	2 (3.3%)	0	0
Metabolism and nutrition disorders	0	0	2 (8.7%)	9 (15.5%)
Diabetes mellitus ‡	0	0	1 (4.3%)	4 (6.9%)
Hyperkalaemia	0	0	1 (4.3%)	0
Hyperuricaemia	0	0	0	2 (3.4%)
Hyperlipidaemia	0	0	0	2 (3.4%)
Musculoskeletal and connective tissue disorders	5 (21.7%)	12 (19.7%)	3 (13.0%)	8 (13.8%)
Back pain	2 (8.7%)	3 (4.9%)	2 (8.7%)	2 (3.4%)
Muscle spasms	1 (4.3%)	0	0	1 (1.7%)
Myalgia	2 (8.7%)	2 (3.3%)	0	0
Neck pain	0	0	1 (4.3%)	0
Pain in extremity	0	2 (3.3%)	1 (4.3%)	2 (3.4%)
Nervous system disorders	0	7 (11.5%)	1 (4.3%)	9 (15.5%)
Carotid artery stenosis	0	0	1 (4.3%)	1 (1.7%)
Dizziness	0	1 (1.6%)	0	4 (6.9%)
Headache	0	2 (3.3%)	0	1 (1.7%)
Hypoaesthesia	0	2 (3.3%)	0	1 (1.7%)
Psychiatric disorders	1 (4.3%)	0	2 (8.7%)	1 (1.7%)
Insomnia	1 (4.3%)	0	2 (8.7%)	1 (1.7%)
Renal and urinary disorders	2 (8.7%)	5 (8.2%)	0	5 (8.6%)
Pollakiuria	2 (8.7%)	5 (8.2%)	0	5 (8.6%)
Respiratory, thoracic and mediastinal disorders	2 (8.7%)	2 (3.3%)	1 (4.3%)	2 (3.4%)
Rhinitis allergic	0	1 (1.6%)	1 (4.3%)	0
Rhinorrhoea	1 (4.3%)	0	0	0
Allergic bronchitis	0	0	1 (4.3%)	0
Oropharyngeal pain	1 (4.3%)	0	0	1 (1.7%)
Skin and subcutaneous tissue disorders	4 (17.4%)	6 (9.8%)	4 (17.4%)	6 (10.3%)
Dermatitis contact	1 (4.3%)	2 (3.3%)	0	3 (5.2%)
Eczema asteatotic	0	0	1 (4.3%)	0
Erythema	0	0	1 (4.3%)	0
Hyperkeratosis	1 (4.3%)	0	0	0
Nail disorder	0	0	1 (4.3%)	0
Pruritus	0	1 (1.6%)	2 (8.7%)	1 (1.7%)
Pustular psoriasis	1 (4.3%)	0	0	0
Urticaria	1 (4.3%)	0	0	0

Number of subjects (%)

The severity of renal impairment is categorized by eGFR at Visit 2 into mild (60≤eGFR<90 mL/min/1.73 m^2) or moderate (30≤eGFR<60 mL/min/1.73 m^2).

SAF: safety analysis set

†: Adverse events with an incidence of less than 2% are included in both groups.

‡: Reported as [redacted].

Source: Table 12.6A.1.5.2

Table 20 Adverse Events with an Incidence of 2% or Higher in the ASP1941 50 mg Randomization Group: SAF (52 Weeks)

MedDRA Version 12.1 System Organ Class (SOC) † Preferred Term (PT)	ASP1941 50 mg Randomization (n=119)	Study drug in treatment period I/treatment period II ASP1941 50/50 mg (n=68)	 ASP1941 50/100 mg (n=34)
Number of subjects who experienced an AE†	111 (93.3%)	62 (91.2%)	33 (97.1%)
Blood and lymphatic system disorders	6 (5.0%)	4 (5.9%)	0
Anaemia	5 (4.2%)	3 (4.4%)	0
Eye disorders	17 (14.3%)	11 (16.2%)	5 (14.7%)
Conjunctivitis	3 (2.5%)	2 (2.9%)	1 (2.9%)
Gastrointestinal disorders	48 (40.3%)	26 (38.2%)	14 (41.2%)
Abdominal pain upper	4 (3.4%)	1 (1.5%)	2 (5.9%)
Constipation	14 (11.8%)	7 (10.3%)	4 (11.8%)
Dental caries	6 (5.0%)	1 (1.5%)	4 (11.8%)
Diarrhoea	5 (4.2%)	4 (5.9%)	0
Dyspepsia	3 (2.5%)	1 (1.5%)	2 (5.9%)
Gastritis	6 (5.0%)	2 (2.9%)	2 (5.9%)
Haemorrhoids	3 (2.5%)	3 (4.4%)	0
Periodontal disease	4 (3.4%)	2 (2.9%)	2 (5.9%)
Periodontitis	4 (3.4%)	3 (4.4%)	1 (2.9%)
Reflux oesophagitis	5 (4.2%)	2 (2.9%)	2 (5.9%)
Vomiting	3 (2.5%)	2 (2.9%)	0
General disorders and administration site conditions	15 (12.6%)	9 (13.2%)	5 (14.7%)
Thirst	6 (5.0%)	3 (4.4%)	2 (5.9%)
Hepatobiliary disorders	4 (3.4%)	3 (4.4%)	1 (2.9%)
Hepatic steatosis	3 (2.5%)	2 (2.9%)	1 (2.9%)
Infections and infestations	64 (53.8%)	43 (63.2%)	15 (44.1%)
Bronchitis	5 (4.2%)	3 (4.4%)	2 (5.9%)
Gastroenteritis	5 (4.2%)	2 (2.9%)	1 (2.9%)
Influenza	3 (2.5%)	2 (2.9%)	1 (2.9%)
Nasopharyngitis	42 (35.3%)	31 (45.6%)	8 (23.5%)
Helicobacter infection	3 (2.5%)	1 (1.5%)	1 (2.9%)
Injury, poisoning and procedural complications	18 (15.1%)	8 (11.8%)	8 (23.5%)
Scratch	3 (2.5%)	1 (1.5%)	2 (5.9%)
Contusion	5 (4.2%)	3 (4.4%)	2 (5.9%)
Investigations	17 (14.3%)	9 (13.2%)	5 (14.7%)
Beta 2 microglobulin urine increased	4 (3.4%)	4 (5.9%)	0
Weight loss	6 (5.0%)	5 (7.4%)	1 (2.9%)
Metabolism and nutrition disorders	11 (9.2%)	5 (7.4%)	5 (14.7%)
Diabetes mellitus‡	5 (4.2%)	2 (2.9%)	2 (5.9%)
Hyperuricaemia	3 (2.5%)	1 (1.5%)	2 (5.9%)
Musculoskeletal and connective tissue disorders	30 (25.2%)	20 (29.4%)	6 (17.6%)
Arthritis	3 (2.5%)	2 (2.9%)	1 (2.9%)
Back pain	6 (5.0%)	5 (7.4%)	1 (2.9%)
Pain in extremity	4 (3.4%)	3 (4.4%)	0
Spinal osteoarthritis	3 (2.5%)	2 (2.9%)	1 (2.9%)
Intervertebral disc protrusion	3 (2.5%)	1 (1.5%)	2 (5.9%)
Musculoskeletal stiffness	3 (2.5%)	3 (4.4%)	0
Nervous system disorders	25 (21.0%)	14 (20.6%)	7 (20.6%)
Dizziness	7 (5.9%)	2 (2.9%)	4 (11.8%)
Headache	4 (3.4%)	3 (4.4%)	1 (2.9%)
Hypoaesthesia	4 (3.4%)	4 (5.9%)	0
Tremor	4 (3.4%)	2 (2.9%)	2 (5.9%)
Renal and urinary disorders	19 (16.0%)	12 (17.6%)	6 (17.6%)
Pollakiuria	12 (10.1%)	6 (8.8%)	5 (14.7%)
Renal impairment	3 (2.5%)	2 (2.9%)	1 (2.9%)
Skin and subcutaneous tissue disorders	24 (20.2%)	14 (20.6%)	6 (17.6%)
Dermatitis contact	6 (5.0%)	3 (4.4%)	2 (5.9%)
Dry skin	3 (2.5%)	2 (2.9%)	1 (2.9%)

MedDRA Version 12.1 System Organ Class (SOC) † Preferred Term (PT)	ASP1941 50 mg Randomization (n=119)	Study drug in treatment period I/treatment period II ASP1941 50/50 mg (n=68)	 ASP1941 50/100 mg (n=34)
Eczema	3 (2.5%)	1 (1.5%)	1 (2.9%)
Pruritus	4 (3.4%)	2 (2.9%)	0
Rash	4 (3.4%)	2 (2.9%)	1 (2.9%)
Vascular disorders	3 (2.5%)	2 (2.9%)	1 (2.9%)
Orthostatic hypotension	3 (2.5%)	2 (2.9%)	1 (2.9%)

Number of subjects (%)

SAF: safety analysis set

†: Adverse events with an incidence of less than 2% in the ASP1941 50 mg randomization group are included.

‡: Reported as [redacted].

Source: Tables 12.6B.1.4.1 and 12.6B.1.4.2

Table 21 Adverse Events with an Incidence of 2% or Higher in the ASP1941 50 mg Randomization Group (by Severity of Renal Impairment): SAF (52 Weeks)

MedDRA Version 12.1 System Organ Class (SOC) Preferred Term (PT)	Subjects with mild renal impairment			Subjects with moderate renal impairment		
	ASP1941 50 mg Randomization (n=61)	Study drug in treatment period I/treatment period II		ASP1941 50 mg Randomization (n=58)	Study drug in treatment period I/treatment period II	
		ASP1941 50/50 mg (n=41)	ASP1941 50/100 mg (n=12)		ASP1941 50/50 mg (n=27)	ASP1941 50/100 mg (n=22)
Number of subjects who experienced an AE†	57 (93.4%)	39 (95.1%)	11 (91.7%)	54 (93.1%)	23 (85.2%)	22 (100.0%)
Blood and lymphatic system disorders	1 (1.6%)	1 (2.4%)	0	5 (8.6%)	3 (11.1%)	0
Anaemia	1 (1.6%)	1 (2.4%)	0	4 (6.9%)	2 (7.4%)	0
Eye disorders	9 (14.8%)	7 (17.1%)	2 (16.7%)	8 (13.8%)	4 (14.8%)	3 (13.6%)
Conjunctivitis	1 (1.6%)	1 (2.4%)	0	2 (3.4%)	1 (3.7%)	1 (4.5%)
Dry eye	2 (3.3%)	1 (2.4%)	1 (8.3%)	0	0	0
Gastrointestinal disorders	24 (39.3%)	16 (39.0%)	4 (33.3%)	24 (41.4%)	10 (37.0%)	10 (45.5%)
Abdominal discomfort	0	0	0	2 (3.4%)	0	2 (9.1%)
Abdominal pain upper	1 (1.6%)	0	0	3 (5.2%)	1 (3.7%)	2 (9.1%)
Constipation	7 (11.5%)	4 (9.8%)	1 (8.3%)	7 (12.1%)	3 (11.1%)	3 (13.6%)
Dental caries	1 (1.6%)	1 (2.4%)	0	5 (8.6%)	0	4 (18.2%)
Diarrhoea	3 (4.9%)	2 (4.9%)	0	2 (3.4%)	2 (7.4%)	0
Dyspepsia	1 (1.6%)	1 (2.4%)	0	2 (3.4%)	0	2 (9.1%)
Gastric ulcer	2 (3.3%)	1 (2.4%)	0	0	0	0
Gastritis	2 (3.3%)	1 (2.4%)	0	4 (6.9%)	1 (3.7%)	2 (9.1%)
Haemorrhoids	2 (3.3%)	2 (4.9%)	0	1 (1.7%)	1 (3.7%)	0
Hiatus hernia	0	0	0	2 (3.4%)	1 (3.7%)	1 (4.5%)
Periodontal disease	2 (3.3%)	1 (2.4%)	1 (8.3%)	2 (3.4%)	1 (3.7%)	1 (4.5%)
Periodontitis	2 (3.3%)	2 (4.9%)	0	2 (3.4%)	1 (3.7%)	1 (4.5%)
Reflux oesophagitis	1 (1.6%)	0	1 (8.3%)	4 (6.9%)	2 (7.4%)	1 (4.5%)
Vomiting	2 (3.3%)	1 (2.4%)	0	1 (1.7%)	1 (3.7%)	0
General disorders and administration site conditions	6 (9.8%)	2 (4.9%)	3 (25.0%)	9 (15.5%)	7 (25.9%)	2 (9.1%)
Malaise	2 (3.3%)	1 (2.4%)	1 (8.3%)	0	0	0
Oedema	0	0	0	2 (3.4%)	2 (7.4%)	0
Thirst	4 (6.6%)	2 (4.9%)	1 (8.3%)	2 (3.4%)	1 (3.7%)	1 (4.5%)
Hepatobiliary disorders	2 (3.3%)	2 (4.9%)	0	2 (3.4%)	1 (3.7%)	1 (4.5%)
Hepatic steatosis	2 (3.3%)	2 (4.9%)	0	1 (1.7%)	0	1 (4.5%)
Immune system disorders	0	0	0	2 (3.4%)	2 (7.4%)	0
Seasonal allergy	0	0	0	2 (3.4%)	2 (7.4%)	0
Infections and infestations	32 (52.5%)	27 (65.9%)	3 (25.0%)	32 (55.2%)	16 (59.3%)	12 (54.5%)
Bronchitis	0	0	0	5 (8.6%)	3 (11.1%)	2 (9.1%)
Cystitis	0	0	0	2 (3.4%)	1 (3.7%)	0
Folliculitis	0	0	0	2 (3.4%)	0	2 (9.1%)
Gastroenteritis	2 (3.3%)	1 (2.4%)	0	3 (5.2%)	1 (3.7%)	1 (4.5%)
Influenza	2 (3.3%)	1 (2.4%)	1 (8.3%)	1 (1.7%)	1 (3.7%)	0
Nasopharyngitis	24 (39.3%)	21 (51.2%)	2 (16.7%)	18 (31.0%)	10 (37.0%)	6 (27.3%)
Pneumonia	0	0	0	2 (3.4%)	2 (7.4%)	0
Helicobacter infection	2 (3.3%)	1 (2.4%)	0	1 (1.7%)	0	1 (4.5%)
Injury, poisoning and procedural complications	9 (14.8%)	4 (9.8%)	3 (25.0%)	9 (15.5%)	4 (14.8%)	5 (22.7%)
Scratch	0	0	0	3 (5.2%)	1 (3.7%)	2 (9.1%)
Contusion	1 (1.6%)	1 (2.4%)	0	4 (6.9%)	2 (7.4%)	2 (9.1%)
Investigations	11 (18.0%)	5 (12.2%)	4 (33.3%)	6 (10.3%)	4 (14.8%)	1 (4.5%)
Beta 2 microglobulin urine increased	2 (3.3%)	2 (4.9%)	0	2 (3.4%)	2 (7.4%)	0
Blood creatine phosphokinase increased	2 (3.3%)	1 (2.4%)	1 (8.3%)	0	0	0
Blood creatinine increased	2 (3.3%)	0	1 (8.3%)	0	0	0
Weight loss	2 (3.3%)	2 (4.9%)	0	4 (6.9%)	3 (11.1%)	1 (4.5%)
Cystatin C increased	2 (3.3%)	0	1 (8.3%)	0	0	0

MedDRA Version 12.1 System Organ Class (SOC) Preferred Term (PT)	Subjects with mild renal impairment			Subjects with moderate renal impairment		
	ASP1941 50 mg Randomization (n=61)	Study drug in treatment period I/treatment period II		ASP1941 50 mg Randomization (n=58)	Study drug in treatment period I/treatment period II	
		ASP1941 50/50 mg (n=41)	ASP1941 50/100 mg (n=12)		ASP1941 50/50 mg (n=27)	ASP1941 50/100 mg (n=22)
Metabolism and nutrition disorders	1 (1.6%)	1 (2.4%)	0	10 (17.2%)	4 (14.8%)	5 (22.7%)
Diabetes mellitus‡	0	0	0	5 (8.6%)	2 (7.4%)	2 (9.1%)
Hyperuricaemia	0	0	0	3 (5.2%)	1 (3.7%)	2 (9.1%)
Hyperlipidaemia	0	0	0	2 (3.4%)	0	2 (9.1%)
Musculoskeletal and connective tissue disorders	15 (24.6%)	11 (26.8%)	3 (25.0%)	15 (25.9%)	9 (33.3%)	3 (13.6%)
Arthritis	1 (1.6%)	0	1 (8.3%)	2 (3.4%)	2 (7.4%)	0
Back pain	4 (6.6%)	4 (9.8%)	0	2 (3.4%)	1 (3.7%)	1 (4.5%)
Musculoskeletal pain	0	0	0	2 (3.4%)	2 (7.4%)	0
Myalgia	2 (3.3%)	1 (2.4%)	1 (8.3%)	0	0	0
Pain in extremity	2 (3.3%)	2 (4.9%)	0	2 (3.4%)	1 (3.7%)	0
Spinal osteoarthritis	1 (1.6%)	0	1 (8.3%)	2 (3.4%)	2 (7.4%)	0
Intervertebral disc protrusion	2 (3.3%)	1 (2.4%)	1 (8.3%)	1 (1.7%)	0	1 (4.5%)
Musculoskeletal stiffness	0	0	0	3 (5.2%)	3 (11.1%)	0
Nervous system disorders	14 (23.0%)	9 (22.0%)	3 (25.0%)	11 (19.0%)	5 (18.5%)	4 (18.2%)
Cerebral infarction	2 (3.3%)	1 (2.4%)	0	0	0	0
Cervicobrachial syndrome	2 (3.3%)	2 (4.9%)	0	0	0	0
Dizziness	2 (3.3%)	1 (2.4%)	1 (8.3%)	5 (8.6%)	1 (3.7%)	3 (13.6%)
Headache	3 (4.9%)	2 (4.9%)	1 (8.3%)	1 (1.7%)	1 (3.7%)	0
Hypoaesthesia	2 (3.3%)	2 (4.9%)	0	2 (3.4%)	2 (7.4%)	0
Tremor	3 (4.9%)	2 (4.9%)	1 (8.3%)	1 (1.7%)	0	1 (4.5%)
Psychiatric disorders	0	0	0	2 (3.4%)	0	1 (4.5%)
Insomnia	0	0	0	2 (3.4%)	0	1 (4.5%)
Renal and urinary disorders	8 (13.1%)	6 (14.6%)	1 (8.3%)	11 (19.0%)	6 (22.2%)	5 (22.7%)
Hydronephrosis	0	0	0	2 (3.4%)	2 (7.4%)	0
Pollakiuria	6 (9.8%)	4 (9.8%)	1 (8.3%)	6 (10.3%)	2 (7.4%)	4 (18.2%)
Renal impairment	0	0	0	3 (5.2%)	2 (7.4%)	1 (4.5%)
Respiratory, thoracic and mediastinal disorders	7 (11.5%)	3 (7.3%)	2 (16.7%)	2 (3.4%)	1 (3.7%)	0
Cough	2 (3.3%)	1 (2.4%)	0	0	0	0
Upper respiratory tract inflammation	2 (3.3%)	1 (2.4%)	1 (8.3%)	0	0	0
Skin and subcutaneous tissue disorders	13 (21.3%)	11 (26.8%)	1 (8.3%)	11 (19.0%)	3 (11.1%)	5 (22.7%)
Dermatitis contact	3 (4.9%)	3 (7.3%)	0	3 (5.2%)	0	2 (9.1%)
Dry skin	2 (3.3%)	2 (4.9%)	0	1 (1.7%)	0	1 (4.5%)
Eczema	1 (1.6%)	1 (2.4%)	0	2 (3.4%)	0	1 (4.5%)
Pruritus	2 (3.3%)	1 (2.4%)	0	2 (3.4%)	1 (3.7%)	0
Rash	1 (1.6%)	1 (2.4%)	0	3 (5.2%)	1 (3.7%)	1 (4.5%)
Vascular disorders	2 (3.3%)	1 (2.4%)	1 (8.3%)	1 (1.7%)	1 (3.7%)	0
Orthostatic hypotension	2 (3.3%)	1 (2.4%)	1 (8.3%)	1 (1.7%)	1 (3.7%)	0

Number of subjects (%)

The severity of renal impairment is categorized by eGFR at Visit 2 into mild (60≤eGFR<90 mL/min/1.73 m^2) or moderate (30≤eGFR<60 mL/min/1.73 m^2).

SAF: safety analysis set

†: Adverse events with an incidence of less than 2% in the ASP1941 50 mg randomization group are included.

‡: Reported as [redacted].

Source: Tables 12.6B.1.4.3 and 12.6B.1.4.5

Table 22 List of Serious Adverse Events

Subject ID	Sex/age/ Severity of renal impairment	ASP1941 Treatment duration† (starting date of treatment period II‡)	Adverse event (MedDRA§ PT)	Date of occurrence (treatment period)/ date of resolution ‡	Severity	Outcome	Causal relationship to the study drug	Actions taken against the study drug
Placebo/-								
[redacted]	[redacted]	15	Atrioventricular block complete	15 (I)/32	Moderate	Recovered	Possible	Discontinued
[redacted]	[redacted]	55	Appendicitis perforated	21 (I)/23	Moderate	Recovered	Not related	Not changed
			Peritonitis	21 (I)/45	Moderate	Recovered	Not related	Not changed
			Postoperative wound infection	32 (I)/45	Moderate	Recovered	Not related	Not changed
			Abdominal abscess	54 (I)/106	Moderate	Recovered	Not related	Discontinued
Placebo/ASP1941 100 mg								
[redacted]	[redacted]	56 (169)	Death	247 (II')/247	Severe	Death	Possible	Discontinued
[redacted]	[redacted]	183 (180)	Rotator cuff syndrome	187 (II)/-	Mild	Not recovered	Not related	Not changed
ASP1941 50 mg/-								
[redacted]	[redacted]	125	Hepatic neoplasm malignant	158 (I')/-	Moderate	Not recovered	Not related	Not applicable
[redacted]	[redacted]	168	Spinal ligament ossification	151 (I)/-	Mild	Not recovered	Not related	Discontinued
[redacted]	[redacted]	56	Small intestine carcinoma	49 (I)/-	Mild	Not recovered	Not related	Discontinued
[redacted]	[redacted]	74	Thyroid cancer	57 (I)/-	Mild	Not recovered	Not related	Discontinued
[redacted]	[redacted]	161	Osteoarthritis	112 (I)/225	Moderate	Recovered	Not related	Discontinued
			Postoperative thrombosis	172 (I')/190	Mild	Recovered	Not related	Not applicable
[redacted]	[redacted]	77	Cerebral infarction	97 (I)/-	Moderate	Not recovered	]Not related	Discontinued
[redacted]	[redacted]	131	Atrial flutter	69 (I)/74	Moderate	Recovered	Not related	Not changed
			Upper gastrointestinal haemorrhage	131 (I)/142	Moderate	Recovered	Possible	Discontinued
ASP1941 50/50 mg								
[redacted]	[redacted]	364 (176)	Appendicitis perforated	381 (II')/392	Moderate	Recovered	Not related	Not applicable
[redacted]	[redacted]	186 (169)	Uterine cancer¶	175 (II)/-	Mild	Not recovered	Possible	Discontinued
[redacted]	[redacted]	286 (162)	Cerebral infarction	286 (II)/318	Severe	With sequelae	Not related	Discontinued
[redacted]	[redacted]	364 (168)	Benign prostatic hyperplasia	309 (II)/-	Moderate	Not recovered	Not related	Not changed
[redacted]	[redacted]	290 (169)	Angina unstable	252 (II)/-	Severe	Recovering	Possible	Discontinued
[redacted]	[redacted]	351 (171)	Large intestine carcinoma	371 (II')/-	Mild	Not recovered	Possible	Not applicable
[redacted]	[redacted]	203 (169)	Haemolytic anaemia	141 (I)/-	Moderate	Not recovered	Possible	Discontinued
			Diabetes mellitus	169 (I)/288	Moderate	Recovered	Not related	Not changed
			Cystitis haemorrhagic	262 (II')/267	Moderate	Recovered	Not related	Not applicable
			Inflammation	240 (II')/-	Moderate	Recovering	Not related	Not applicable
[redacted]	[redacted]	206 (169)	Pneumonia pneumococcal	199 (II)/-	Moderate	Not recovered	Not related	Discontinued
[redacted]	[redacted]	364 (169)	Heat illness	382 (II')/383	Moderate	Recovered	Not related	Not applicable
ASP1941 50/100 mg								
[redacted]	[redacted]	364 (161)	Colonic polyp	15 (I)/136	Moderate	Recovered	Not related	Not changed
[redacted]	[redacted]	204 (176)	Still's disease adult onset	194 (II)/-	Moderate	Recovering	Not related	Discontinued
[redacted]	[redacted]	378 (169)	Cataract	360 (II)/-	Mild	Not recovered	Not related	Not changed

The analytical results at the end of the treatment periods I and II are presented.

Starting date of treatment period II: starting date of administration of the study drug for treatment period II

(I): from the first administration to Visit 10/discontinuation, (I'): Visit 10/discontinuation (subjects who did not proceed to treatment period II), (II): after the firstl administration in treatment period II, (II'): after the final administration in treatment period II

†: Placebo group shows the treatment duration with the placebo.

‡: The day of the first prescription of the study drug for treatment period I is considered as Day 1.

§: MedDRA Version 12.1

¶: Reported as [redacted]

Source: Appendices 13.2.7A.4 and 13.2.7B.4

Table 23 List of Adverse Events Leading to the Discontinuation of the Drug Administration

Subject ID	Sex/age/ Severity of renal impairment	ASP1941 Treatment duration† (treatment period II starting date ‡)	Adverse event (MedDRA§ PT)	Date of occurrence (treatment period)/ date of resolution ‡	Severity	Outcome	Causal relationship to the study drug	Actions taken against the study drug
Placebo/-								
[redacted]	[redacted]	15	Atrioventricular block complete	15 (I)/32	Moderate	Recovered	Possible	Discontinued
[redacted]	[redacted]	55	Abdominal abscess	54 (I)/106	Moderate	Recovered	Not related	Discontinued
[redacted]	[redacted]	168	Malaise	155 (I)/162	Mild	Recovered	Possible	Discontinued
[redacted]	[redacted]	84	Diabetes mellitus¶	57 (I)/-	Mild	Recovering	Not related	Discontinued
Placebo/ASP1941 100 mg								
[redacted]	[redacted]	56 (169)	Death	247 (II')/247	Severe	Death	Possible	Discontinued
ASP1941 50 mg/-								
[redacted]	[redacted]	29	Pruritus	18 (I)/35	Mild	Recovered	Possible	Discontinued
		125	Gastroenteritis	117 (I)/158	Moderate	Recovered	Possible	Discontinued
		168	Spinal ligament ossification	151 (I)/-	Mild	Not recovered	Not related	Discontinued
		143	Blood creatinine increased	134 (I)/149	Mild	Recovered	Not related	Discontinued
		56	Small intestine carcinoma	49 (I)/-	Mild	Not recovered	Not related	Discontinued
		12	Pruritus	2 (I)/19	Mild	Recovered	Possible	Discontinued
		74	Thyroid cancer	57 (I)/-	Mild	Not recovered	Not related	Discontinued
		161	Osteoarthritis	112 (I)/225	Moderate	Recovered	Not related	Discontinued
		77	Cerebral infarction	97 (I)/-	Moderate	Not recovered	Not related	Discontinued
		168	Tachycardia	169 (I)/202	Moderate	Recovered	Not related	Discontinued
		111	Diabetic retinopathy	108 (I)/-	Mild	Not recovered	Not related	Discontinued
		131	Upper gastrointestinal haemorrhage	131 (I)/142	Moderate	Recovered	Possible	Discontinued
ASP1941 50/50 mg								
[redacted]	[redacted]	252 (166)	Oedema	246 (II)/267	Mild	Recovered	Not related	Discontinued
			Renal impairment	253 (II')/-	Mild	Not recovered	Not related	Discontinued
		186 (169)	Uterine cancer ††	175 (II)/-	Mild	Not recovered	Possible	Discontinued
		286 (162)	Cerebral infarction	286 (II)/318	Severe	With sequelae	Not related	Discontinued
		290 (169)	Angina unstable	252 (II)/-	Severe	Recovering	Possible	Discontinued
		203 (169)	Haemolytic anaemia	141 (I)/-	Moderate	Not recovered	Possible	Discontinued
		206 (169)	Pneumonia pneumococcal	199 (II)/-	Moderate	Not recovered	Not related	Discontinued
ASP1941 50/100 mg								
[redacted]	[redacted]	245 (169)	Diabetes mellitus¶	113 (I)/-	Mild	Not recovered	Not related	Discontinued
		202 (170)	Vulvitis	170 (II)/225	Mild	Recovered	Possible	Discontinued
		204 (176)	Still's disease adult onset	194 (II)/-	Moderate	Recovering	Not related	Discontinued

The analytical results at the end of the treatment periods I and II are presented.

Starting date of treatment period II: starting date of administration of the study drug for treatment period II

(I): from the first administration to Visit 10 or discontinuation, (II): after the first administration in treatment period II, (II'): after the final administration in treatment period II

†: Placebo/- group shows the treatment duration with the placebo.

‡: The day of the first prescription of the study drug for treatment period I is considered as Day 1.

§: MedDRA Version 12.1

¶: Reported as [redacted].

††: Reported as [redacted]
Source: Appendices 13.2.7A.6 and 13.2.7B.6