SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	For National Authority Use only
Name of Finished Product: To be determined		
Name of Active Ingredient: ASP1517 (International Nonproprietary Name: to be determined)		

Title of Study: ASP1517 Clinical Pharmacological Study
Examination of Pharmacokinetics and Pharmacodynamics in Patients with Renal Anemia Undergoing Hemodialysis (Protocol No. 1517-CL-0203)

Person Responsible for Clinical Study Report: [redacted]

Investigator: [redacted]

Investigational Center: [redacted]

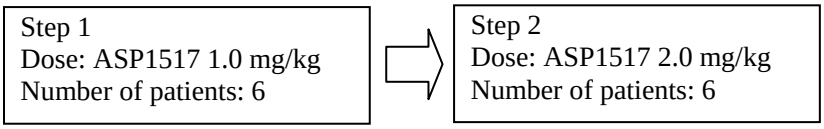
Publication (References): None

Study Period: 4 months **Study Initiation Date:** 15 February 2010 (date of first signed consent) **Study Completion Date:** 7 June 2010 (date of last subject evaluation)	**Phase of Development:** Clinical pharmacology study

Objectives:

- To study pharmacokinetics (PK) and pharmacodynamics (PD) as well as the safety and tolerability of ASP1517 orally administered to patients with renal anemia undergoing hemodialysis.
- To assess the influence of hemodialysis on the PK of ASP1517.

Design and Methodology:
This Japanese clinical pharmacology study was an open-label, uncontrolled, dose escalation study in patients with renal anemia undergoing hemodialysis (target number of patients: 12 patients [6 each for Step 1 and Step 2]). Step 2 (ASP1517 2.0 mg/kg) was to be carried out after safety was confirmed in Step 1 (ASP1517 1.0 mg/kg).



A single oral dose of ASP1517 was administered to patients on Days 1 and 8 in each step, as described below.

- On Day 1, the earliest hemodialysis day in the week with the longest period after the last hemodialysis, the first dose of ASP1517 was administered after hemodialysis.
- On Day 8, the earliest hemodialysis day in the week with the longest period after the last hemodialysis on Day 1, the second dose of ASP1517 was administered, and hemodialysis was started 2.5 hours post-dose.

Target Number of Patients: 12 patients (6 patients each for Steps 1 and 2)
[Rationale]
The sample size was set based on the feasibility of the study.

Diagnosis and Main Criteria for Inclusion and Exclusion:
The study included patients with renal anemia undergoing hemodialysis who met all of the following inclusion criteria and who did not meet any of the following exclusion criteria.

1. Inclusion Criteria

1. Written informed consent has been obtained from the patient†
2. Age (at informed consent acquisition): ≥ 20 years old and < 75 years old
3. Patients on stable chronic maintenance dialysis who were scheduled to undergo hemodialysis three times a week during the study period
4. Body weight (after hemodialysis at screening and pre-washout visit): ≥ 40.0 kg and < 80.0 kg
5. The dose of intravenous erythropoiesis stimulating agent (ESA) at screening and pre-washout visit was no greater than the approved dose range in Japan.
6. Mean hemoglobin (Hb) at screening and pre-washout visit was ≥ 10.0 g/dL and ≤ 12.0 g/dL and a difference between these Hb values was within 1.0 g/dL.

† When a patient participating in Step 1 moved on to Step 2, the patient was to give consent to participate in Step 2 at least 4 weeks after the follow-up visit in Step 1.

2. Exclusion Criteria

1. Inability to comply with requirements for hemodialysis defined in the protocol
2. Necessity of using any of the prohibited treatments (drug and nondrug treatments) during the period defined in the protocol
3. Severe inflammatory or infectious disease (white blood count [WBC] at pre-washout visit exceeded the upper limit of the normal range)
4. Previous gastric/intestinal resection that might affect drug absorption in the

gastrointestinal tract
5. Uncontrollable hypertension (systolic blood pressure ≥ 170 mmHg and diastolic blood pressure ≥ 110 mmHg, both before hemodialysis, at screening and pre-washout visit)
6. Complicated with severe heart disease (e.g. congestive cardiac failure [NYHA classification III or greater], myocardial infarction) or previous hospitalization for the treatment of cerebrovascular or heart disease within 12 weeks prior to informed consent
7. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin or γ-GTP exceeded the upper limit of the normal range at screening and pre-washout visit or previous serious hepatic disease (e.g. acute or active chronic hepatitis, cirrhosis)
8. Previous or concurrent malignant tumor
9. Previous blood transfusion or surgery (excluding shunting) within 4 weeks before pre-washout visit
10. History of serious drug allergies including anaphylactic shock
11. Women who were pregnant, lactating, might be pregnant, wished to get pregnant during the study period, or were unwilling to practice contraception instructed by the investigator
12. Participation in any of other clinical or post-marketing studies (including those of medical devices) within 12 weeks before informed consent†
13. Employees of the sponsor, contract research organizations (CROs), site management organizations (SMOs) or study sites related to the present study
14. Other patients considered ineligible for the study by the investigator/subinvestigator
15. Occurrence of a serious adverse event (SAE) in Step 1 whose relationship to the study drug could not be ruled out‡
16. Either AST or ALT exceeded 2.5 times the upper limit of the normal range after study treatment in Step 1 and total bilirubin exceeded 1.5 times the upper limit of the normal range on the same day‡
17. Either AST or ALT exceeded 2.5 times the upper limit of the normal range after study treatment in Step 1 and any symptoms likely caused by hepatic impairment (e.g. fever, rash, malaise, nausea/vomiting, jaundice, right hypochondrial pain) were present on the same day‡

† Exclusion criterion 12 did not apply for patients who continued to participate in Step 2 after completing Step 1.

‡ Exclusion criteria 15 to 17 applied only for patients who continued to participate in Step 2 after completing Step 1 without meeting any of criteria for study discontinuation.

Test Product, Dose, and Mode of Administration:

1. Test Product and Lot Number

Study drug	Contents and dosage form	Lot No.
ASP1517 20-mg capsule	#3 capsule containing 20 mg of ASP1517	[redacted]
ASP1517 50-mg capsule	#3 capsule containing 50 mg of ASP1517	[redacted]
ASP1517 100-mg capsule	#1 capsule containing 100 mg of ASP1517	[redacted]

2. Dose and Mode of Administration

A dose of ASP1517 1.0 mg/kg was used in Step 1 and a dose of ASP1517 2.0 mg/kg was used in Step 2. A single dose of ASP1517 capsule(s) was orally administered with ≤ 150 mL of water on Days 1 and 8 in each step to patients who had fasted for 4 hours. The timing of study treatment on Days 1 and 8 is described below. Patients were allowed to take a meal at least 2 hours post-dose.

- Day 1: ASP1517 was to be administered within 1 hour after completion of hemodialysis.
- Day 8: ASP1517 was to be administered 2.5 hours before initiation of hemodialysis.

[Rationale]

In order to compare the PK and PD profiles of ASP1517 between the present study (1517-CL-203) and the single-dose study planned in the U.S. (FGCL-SM4592-039) in patients with renal failure undergoing hemodialysis, the same doses (1.0 and 2.0 mg/kg) as used in the U.S. study were selected. A single oral dose toxicology study in rats produced no toxicologically significant findings at dose levels of up to 30 mg/kg. The no-observed-adverse-effect level (NOAEL) was 30 mg/kg/day in cynomolgus monkeys receiving multiple oral doses three times a week for 22 weeks. In the FGCL-SM4592-016 study, moreover, the tolerability of ASP1517 was confirmed up to 4.0 mg/kg for single dosing and up to 3.75 mg/kg for intermittent repeated dosing; thus, the doses selected for the present study were considered to be safe for the patients.

For the purpose of evaluating the influence of hemodialysis on ASP1517 PK profile, the study drug was administered after hemodialysis on Day 1 and before hemodialysis on Day 8 and the post- and pre-dialysis PK profiles were compared. A food effect (pilot) study in the U.S. (FGCL-SM4592-027) revealed that food reduced the maximum concentration (C_{max}) and AUC from the time of dosing up to infinity with extrapolation of the terminal phase (AUC_{inf}) by approximately 35% and 11%, respectively, on average and prolonged terminal elimination half-life (t_{max}) by 2 hours. Based on these findings, all patients were required to fast from 4 hours before study treatment until 2 hours after study treatment.

Duration of Evaluation:

Pre-investigational period: 7 to 30 days; Investigational period: 29 to 43 days

Concomitant Medication (Drugs and Therapies):

1. Concomitant Treatment (Drug and Nondrug Treatment)

In principle, if a patient was on medication for primary disease or complications, such concomitant drugs and their dosing regimens remained unchanged from pre-washout visit until follow-up visit.

2. Prohibited Concomitant Treatment (Drug and Nondrug Treatment)

The following concomitant drugs were prohibited from completion of hemodialysis at pre-washout visit until Day 10.

- Epoetin drugs (pre-washout visit on Day –7)
- Darbepoetin alfa drugs (pre-washout visit on Day –14)
- Iron preparations

The following concomitant treatments (drug and nondrug treatments) were prohibited from pre-washout visit until follow-up visit.

- Drugs metabolized mainly by CYP2C8
- Drugs containing acetaminophen
- Blood transfusion or surgeries (except shunting)

3. Hemodialysis Conditions

Hemodialysis was performed under the following conditions from Day 1 through Day 10.

Day of dialysis	Mon-Wed-Fri or Tue-Thu-Sat
Duration of dialysis (per day)	240 ± 30 minutes
Blood flow rate	180 to 260 mL/min
Dialysate flow rate	500 ± 100 mL/min
Type of dialyzer	Functional classification III, IV or V
Vascular access	Internal shunt with autologous arterial and venous vessels

Variables, Evaluation Schedule and Criteria for Evaluation:

1. Schedule of Clinical Study

Pre-investigational period			Investigational period										
			For study treatment on Day 1				For study treatment on Day 8						
Screening visit (Day -30 to Day -7)	Pre-washout visit	Day -1 (Hospitalization)	Day 1 (Study treatment)	Day 2 (Discharge)	Day 3	Day 5	Day 7 (Hospitalization)	Day 8 (Study treatment)	Day 9 (Discharge)	Day 10	Follow-up visit (Day 12)	Post-study visit (Day 29-Day 43)
Day of dialysis	Day of dialysis		Day of dialysis		Day of dialysis	Day of dialysis		Day of dialysis		Day of dialysis	Day of dialysis	Day of dialysis

- The screening visit, pre-washout visit, Day 1, Day 8 and post-study visit occurred on the day of dialysis after the longest dialysis interval.
- The screening visit and pre-washout visit were at least 1 week apart from each other.
- The washout of ESA was started post-dialysis on Day –7 for patients receiving epoetin and post-dialysis on Day –14 for those receiving darbepoetin alfa.

2. Pharmacokinetic and Pharmacodynamic Variables

After an oral dose of ASP1517 before or after hemodialysis, plasma ASP1517 concentrations, erythropoietin (EPO) concentrations and ASP1517 concentrations in the dialysate were measured and the following parameters were calculated.

- Plasma ASP1517 concentration: C_{max}, t_{max}, AUC from the time of dosing to the last measurable concentration (AUC_{last}), AUC extrapolated to infinity (AUC_{inf}), AUC from the time of dosing until to 24 hours (AUC_{24}), $t_{1/2}$, oral clearance (CL/F), volume of distribution (Vd/F), mean residence time from time 0 to infinity by extrapolation (MRT_{inf}) and hemodialysis clearance based on plasma ASP1517 concentrations at the dialyzer's inlet (arterial) side and outlet (venous) side (CL_{DP})
- EPO concentration: maximum concentration of EPO ($C_{max,EPO}$), AUC from the time of dosing to the last measurable concentration of EPO ($AUC_{last,EPO}$), maximum amount of change from baseline of EPO ($C_{max,\Delta EPO}$), AUC for amount of change of EPO from the time of dosing to the last measurable concentration ($AUC_{last,\ \Delta EPO}$) and time to attain C_{max} of EPO ($t_{max,EPO}$)
- ASP1517 concentration in dialysate: hemodialysis clearance based on the amount of ASP1517 collected from dialysate (CL_{DD})

- Hepcidin concentration: minimum concentration of hepcidin ($C_{min,Hep}$), AUC from the time of dosing to the last measurable concentration of hepcidin ($AUC_{last,Hep}$), maximum change value of C_{min} from baseline of hepcidin ($C_{min,\ \Delta Hep}$), AUC for amount of change of hepcidin from the time of dosing to the last measurable concentration ($AUC_{last,\ \Delta Hep}$) and time to attain C_{min} of hepcidin ($t_{min,Hep}$)

3. Safety Variables

- Adverse events (AEs)
- Laboratory tests (hematology, blood chemistry, vascular endothelial growth factor [VEGF] and plasminogen activator inhibitor 1 [PAI-1])
- Vital signs (supine blood pressure, supine pulse rate and body temperature)
- Standard 12-lead electrocardiogram (ECG)

Criteria for Causal Relationships to the Study Drug

Causal relationships to the study drug were evaluated based on the following criteria. AEs that fell under either "Possibly related" or "Probably related" were defined as "AEs whose relationship with the study drug could not be ruled out."

Causal relationship to the study drug	Criteria for causal relationship
Not related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, applying to any of the items below; • which could also be explained by concurrent disease or other drugs or chemicals • information on drug discontinuation may be lacking or unclear
Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, applying to these items below; • recurrence on re-administration or resolved or less severe on discontinuation • unlikely to be attributed to concurrent disease or other drugs or chemicals

Statistical Methods:

1. Analysis Sets

- Safety analysis set (SAF)
  The SAF consisted of all patients who received the study drug.
- Pharmacokinetic analysis set (PKAS)
  The PKAS consisted of patients who received the study drug and who had PK measurements in at least one time point.
- Pharmacodynamic analysis set (PDAS)
  The PDAS consisted of patients who received the study drug and who had PD measurements in at least one time point.

2. PK Analysis

PK analysis was performed for ASP1517 concentrations in plasma and dialysate. PK parameters were calculated and summary statistics were provided. CL_{DP} values were shown in the list but the summary statistics were not tabulated because the individual values were negative.

3. PD Analysis

Summary statistics and individual plotting were provided. PD parameters were calculated and summary statistics were provided.

4. Safety Analysis

Frequencies of AEs were tabulated by System Organ Class (SOC) and symptom. Summary statistics and individual plotting were provided for laboratory tests and vital signs.

Date of Report: 25 October 2013 (Version 2.0)

1. DISPOSITION OF PATIENTS AND ANALYSIS SETS

Of 10 and 8 patients who gave consent to participate in Step 1 and Step 2, respectively, 6 patients each received the study drug. All randomized patients completed study treatment. Five of these patients participated in both Step 1 and Step 2, and received the study treatments with 1.0 and 2.0 mg/kg doses.

All patients treated with the study drug were included in the SAF. The PKAS and PDAS were identical to the SAF.

Table 1 Disposition of Patients Participating in the Study

	ASP1517		Total
	1.0 mg/kg	2.0 mg/kg	
Informed consent	10	8	–
Study treatment	6	6	12
Study treatment completed	6 (100.0%)	6 (100.0%)	12 (100.0%)
Study treatment discontinued	0	0	0

Number of patients (%)
Source: Table 12.1.1.1, Table 12.1.1.2 and Table 12.1.1.3

2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Main demographics were similar between the treatment groups in the PKAS. No other baseline characteristics were considered to have a clear effect on the evaluation of the test drug.

Table 2 Main Demographics: PKAS

		ASP1517	
		1.0 mg/kg (n=6)	2.0 mg/kg (n=6)
Age (years)†		59.2 (6.52)	61.2 (8.40)
Sex	Male	4 (66.7%)	4 (66.7%)
	Female	2 (33.3%)	2 (33.3%)
Height (cm)‡		158.27 (12.189)	158.67 (12.684)
Body weight (kg)‡		53.22 (8.461)	54.63 (9.762)

Mean (SD) or number of patients (%)
† at informed consent, ‡ at screening
Source: Table 12.1.2.1.2

3. EXPOSURE TO THE STUDY DRUG

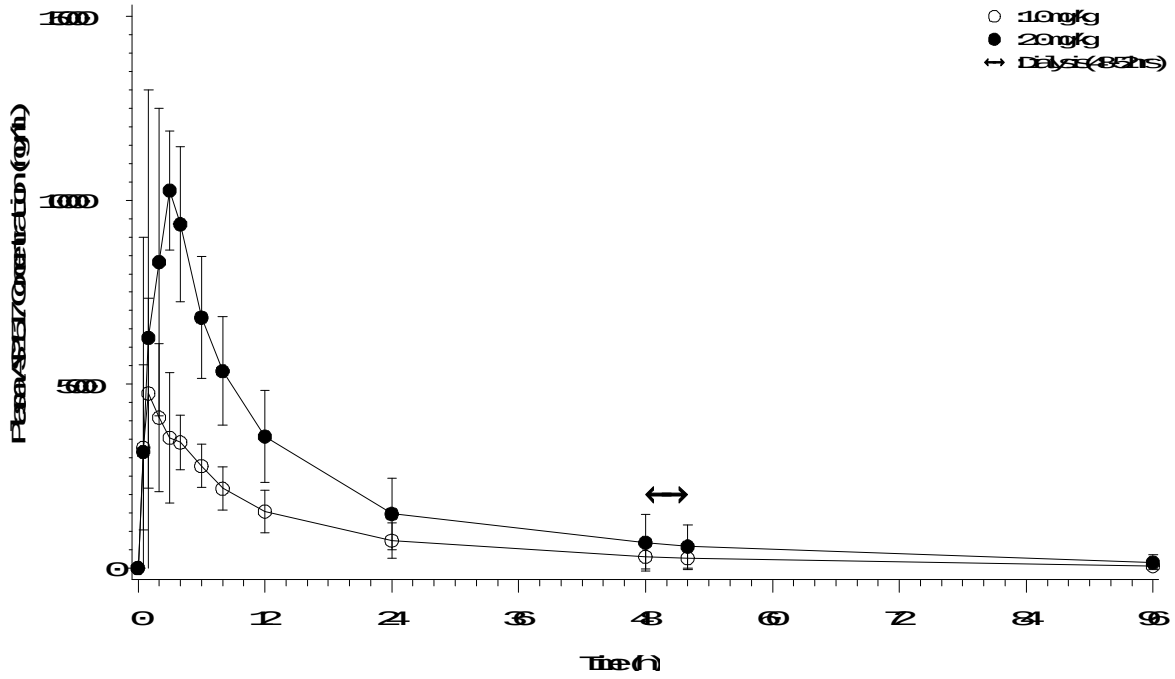
In the study, the study drug was ingested by patients in the presence of the investigator, subinvestigator or study drug manager as a witness to prove that the study drug was administered appropriately.

4. PHARMACOKINETICS

The mean AUC_{inf} in patients receiving 1.0 and 2.0 mg/kg on Day 1 was 65588.7 and 149873.9 ng·h/mL, respectively. The mean C_{max} was 5561.782 and 13006.055 ng/mL, respectively. The mean CL/F was 16.862 and 15.716 mL/h/kg, respectively. The mean $t_{1/2}$ was 15.471 and 20.881 h, respectively. T_{max} was 2.33 h for both treatment groups.

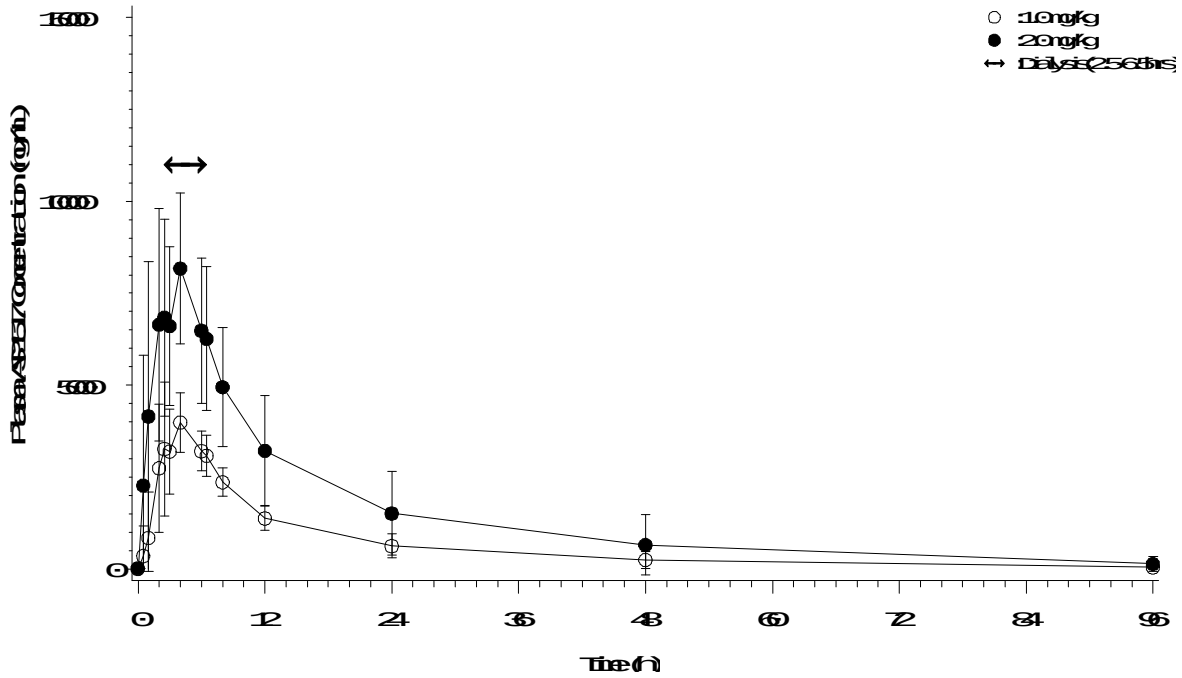
Mean plasma concentrations of unchanged ASP1517 peaked at a lower level on Day 8, when hemodialysis was started 2.5 hours post-dose, than on Day 1 when study medication occurred after hemodialysis. The mean C_{max} in the 1.0 and 2.0 mg/kg groups decreased by approximately 20% and 28%, respectively, and the mean t_{max} was prolonged by approximately 25% and 21%, respectively, on Day 8 compared to Day 1. For both groups, mean AUC_{24} on Day 8 was approximately 12% lower than that on Day 1. The mean CL/F in the 1.0 and 2.0 mg/kg groups increased by approximately 14% and 20%, respectively, on Day 8 compared to Day 1.

Figure 1 Mean Plasma Concentrations of Unchanged ASP1517 over Time (Day 1)



Mean ± SD (n = 6 for each treatment group)
Source: Figure 12.4.1

Figure 2 Mean Plasma Concentrations of Unchanged ASP1517 over Time (Day 8)



Mean ± SD (n = 6 for each treatment group)
Source: Figure 12.4.1

Table 3 Main Summary Statistics for Plasma PK Parameters after ASP1517 Administration (Day 1)

	1.0 mg/kg (n=6)	2.0 mg/kg (n=6)
AUC_{24} (ng·h/mL)	45805.5 (5194.90)	103431.6 (27713.02)
AUC_{48} (ng·h/mL)	57437.3 (14530.10)	127760.2 (48082.21)
AUC_{inf} (ng·h/mL)	65588.7 (24261.38)	149873.9 (73298.04)
AUC_{last} (ng·h/mL)	64288.8 (22496.95)	144292.3 (66333.76)
CL/F (mL/h/kg)	16.862 (5.3090)	15.716 (6.0410)
Vd/F (mL/kg)	362.410 (97.6227)	445.065 (278.5548)
C_{max} (ng/mL)	5561.782 (1294.0564)	13006.055 (1966.4694)
MRT_{inf} (h)	18.226 (10.0162)	20.478 (8.7267)
$t_{1/2}$ (h)	15.471 (3.1351)	20.881 (10.4919)
t_{max} (h)	2.33 (1.966)	2.33 (1.211)

Mean (SD)
Source: Table 12.4.7

Table 4 Main Summary Statistics for Plasma PK Parameters after ASP1517 Administration (Day 8)

	1.0 mg/kg (n=6)	2.0 mg/kg (n=6)
AUC_{24} (ng·h/mL)	40233.4 (5450.54)	90751.3 (30440.80)
AUC_{48} (ng·h/mL)	49815.9 (11382.31)	114798.2 (53230.84)
AUC_{inf} (ng·h/mL)	56628.5 (18732.60)	135303.8 (80530.69)
AUC_{last} (ng·h/mL)	55325.3 (16955.15)	130502.2 (73686.31)
CL/F (mL/h/kg)	19.165 (5.5695)	18.895 (8.7229)
Vd/F (mL/kg)	411.041 (90.0142)	378.986 (101.7260)
C_{max} (ng/mL)	4443.433 (521.8223)	9417.115 (1152.2877)
MRT_{inf} (h)	19.205 (8.7254)	19.684 (10.4382)
$t_{1/2}$ (h)	15.789 (5.0694)	16.196 (7.0600)
t_{max} (h)	2.91 (0.866)	2.83 (1.329)

Mean (SD)
Source: Table 12.4.7

5. PHARMACODYNAMICS

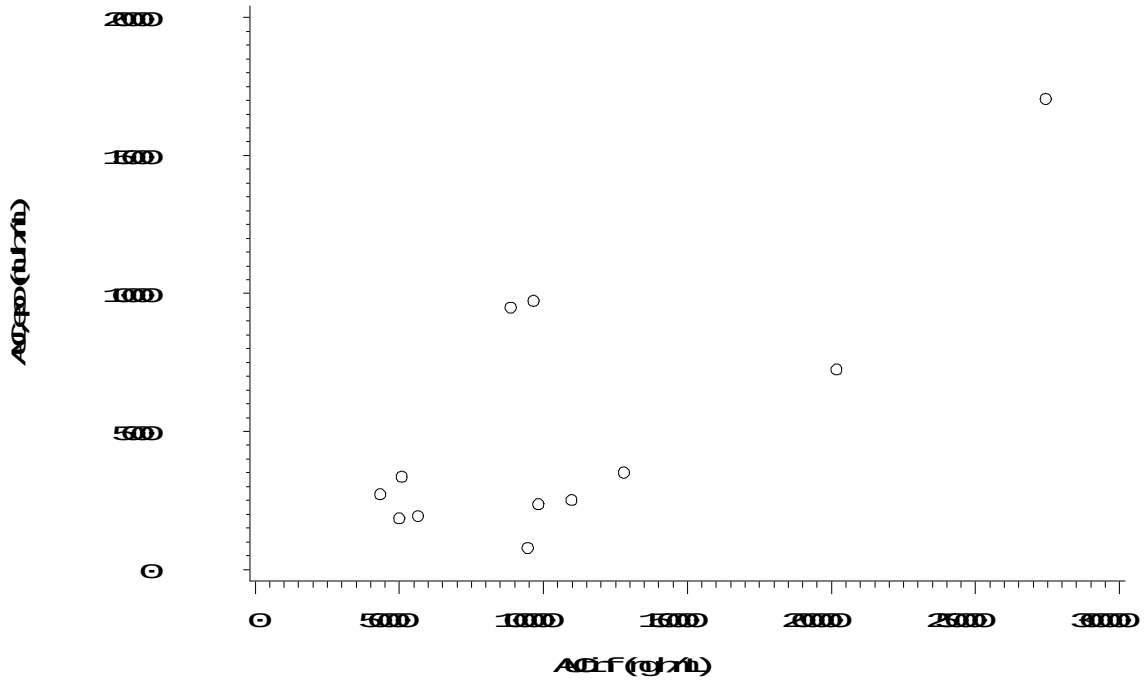
After administration of ASP1517 1.0 and 2.0 mg/kg on Day 1, EPO markedly increased from baseline in a dose-dependent manner. It peaked at approximately 8 to 12 hours post-dose and decreased nearly to half of the peak level at approximately 24 hours post-dose. The mean $t_{max,EPO}$ for the 1.0 and 2.0 mg/kg groups was 9.67 and 11.33 hours, respectively. There was a correlation between AUC_{EPO} and AUC_{inf} of ASP1517.

Table 5 Main Summary Statistics for PD Parameters of Erythropoietin after ASP1517 Administration (Day 1)

	1.0 mg/kg (n=6)	2.0 mg/kg (n=6)
$AUC_{last,EPO}$ (mU·h/mL)	2172.4 (879.62)	8262.9 (5245.45)
$AUC_{last,\Delta EPO}$ (mU·h/mL)	1730.1 (808.22)	7929.7 (5208.22)
$C_{max,EPO}$ (mU/mL)	141.48 (55.251)	559.33 (340.177)
$C_{max,\Delta EPO}$ (mU/mL)	123.13 (52.215)	545.55 (338.653)
$t_{max,EPO}$ (h)	9.67 (2.658)	11.33 (1.633)

Mean (SD)
Source: Table 12.5.2

Figure 3 Scatter Plot of AUC_{inf} and AUC_{EPO} after ASP1517 Administration (Day 1)



Source: Figure 12.4.12

PD parameters of hepcidin showed no evident change related to the dose. No evident relation was noted between AUC_{Hep} and AUC_{inf} of ASP1517.

6. SAFETY

(1) Adverse events

Two AEs (altered state of consciousness and body temperature increased) were reported in 2 of 6 patients receiving ASP1517 1.0 mg/kg and three AEs (renal cancer, nausea and nasopharyngitis) were reported in 3 of 6 patients receiving ASP1517 2.0 mg/kg. No AEs resulted in study discontinuation. All AEs except nausea were considered not related to the study drug. The AE of altered state of consciousness occurred when the relevant patient dozed off and accidentally swallowed a piece of candy during hemodialysis, resulting in a suffocated state. The AE of renal cancer was serious; however, a comparative review of CT and MRI images obtained before study participation with those obtained after study treatment indicated that the onset of cancer had likely occurred before the study.

Table 6 List of Adverse Events

Subject number	Group	MedDRA Preferred Term†	Day of onset (Day)	Day of offset (Day)	Severity/ Seriousness	Study treatment	Outcome	Causal relationship to study drug
S00105	1.0 mg/kg	Altered state of consciousness	19	19	Moderate/ non-serious	Not applicable‡	Resolved	Not related
S00110	1.0 mg/kg	Body temperature increased	1	2	Mild/ non-serious	Continued	Resolved	Not related
S00152	2.0 mg/kg	Renal cancer	17	–	Moderate/ serious	Not applicable‡	Not resolved	Not related
S00155	2.0 mg/kg	Nausea	8	8	Mild/ non-serious	Not applicable‡	Resolved	Possibly related
S00160	2.0 mg/kg	Nasopharyn-gitis	22	–	Mild/ non-serious	Not applicable‡	Not resolved	Not related

† MedDRA/J v12.0

‡ AEs occurred after the last study medication on Day 8.
Source: Appendix 13.2.7.2

(2) Laboratory values, vital signs and ECG findings

VEGF markedly increased from baseline approximately 8 to 12 hours after administration of ASP1517 2.0 mg/kg and returned almost to baseline 24 hours post-dose, whereas no evident increase in VEGF from baseline was noted in the 1.0 mg/kg group. PAI-1 tended to dose-dependently increase from baseline approximately 8 hours after administration of ASP1517 1.0 and 2.0 mg/kg. Mean changes in pulse rate from baseline to 8 hours post-dose, which represented almost the largest increases, in the ASP1517 1.0 and 2.0 mg/kg groups were 3.7 and 9.0 bpm, respectively on Day 1, and 6.5 and 9.8 bpm respectively, on Day 8. No clear dose-related changes from baseline were noted for laboratory test parameters (hematology and blood chemistry) and vital signs (supine blood pressure and body temperature) except VEGF, PAI-1 and supine pulse rate.

There were no particular safety concerns about standard 12-lead ECGs.

7. CONCLUSION

No significant safety concerns arose in patients with renal anemia undergoing hemodialysis and who received a single oral dose of ASP1517 1.0 and 2.0 mg/kg on Days 1 and 8, though PAI-1 increased dose-dependently from baseline and VEGF and pulse rate increased from baseline at a dose of 2.0 mg/kg. Compared with Day 1 on which the study drug was administered after hemodialysis, the study treatment given on Day 8, on which hemodialysis was started 2.5 hours post-dose, resulted in approximately 20% to 28% decreases in C_{max}, approximately 12% decrease in AUC_{24}, and approximately 14% to 20% increases in CL/F; this shows that the pharmacokinetics of ASP1517 is slightly affected by hemodialysis. After administration of ASP1517 1.0 and 2.0 mg/kg, EPO markedly increased from baseline in a dose-dependent manner. AUC_{EPO} correlated with AUC_{inf}.