Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Not available		
Name of Active Ingredient: Roxadustat (ASP1517)		

SYNOPSIS

Title of Study: A Phase 3, Multi-center, Randomized, 2-arm Parallel, Double-blind, Active-comparator (Darbepoetin Alfa) Conversion Study of Intermittent Oral Dosing of ASP1517 in Hemodialysis Chronic Kidney Disease Patients with Anemia

Investigators/Coordinating Investigator: [redacted], [redacted], Japan and others

Study Center(s): 58 sites in Japan

Publication Based on the Study: None to date

Study Period: 1 year and 4 months

Study Initiation Date (Date of First Enrollment): 30 Nov 2016

Study Completion Date (Date of Last Evaluation): 15 Mar 2018

Phase of Development: Phase 3

Objectives:

Non-inferiority of the efficacy, by conversion from recombinant human erythropoietin (rHuEPO) or darbepoetin alfa to ASP1517, was examined by using darbepoetin alfa as a comparator in patients with renal anemia on hemodialysis (HD). The safety was also comparatively evaluated.

Methodology:

This study was conducted as a multicenter, randomized, darbepoetin alfa-controlled, and double-blind study.

After obtaining written informed consent from patients, the prescreening assessments were performed on the day of dialysis after the longest dialysis interval. After confirming that the patients satisfied the inclusion/exclusion criteria, the screening assessments were performed at least 1 week after the prescreening assessments on the day of dialysis after the longest dialysis interval. When the patients were confirmed to satisfy all the inclusion/exclusion criteria by assessments performed within 10 weeks after the prescreening assessments, the investigator or sub-investigator registered the eligible patients, and the treatment period was conducted on the day of dialysis after the longest dialysis interval in the week when the dose of erythropoiesis stimulating agent (ESA) had been administered (within 1 to 2 weeks in principal).

Patients were randomized to the ASP1517 or darbepoetin alfa treatment arm, and then the drug number and dose were notified by the web registration system at registration. Patients randomized to the ASP1517 treatment arm received ASP1517 from the day or following day of prescription and darbepoetin alfa placebo

from the day of prescription. Patients randomized to the darbepoetin alfa treatment arm received ASP1517 placebo from the day or following day of prescription and darbepoetin alfa from the prescription day.

The investigator or sub-investigator prescribed the study drug on the basis of the drug number and dose directions notified by the web registration system under double-blind condition (double-dummy method).

ASP1517 was administered 3 times a week for a maximum of 24 weeks. Darbepoetin alfa was administered once a week for a maximum of 24 weeks.

Number of Patients (Planned, Enrolled and Analyzed):

Planned: 300 patients in total (150 patients per treatment arm)

Randomized: 303 patients (151 in the ASP1517 group, and 152 in the darbepoetin alfa group)

[Analysis sets]

- Safety analysis set (SAF): 302 patients (150 in the ASP1517 group, and 152 in the darbepoetin alfa group)
- Full analysis set (FAS): 301 patients (150 in the ASP1517 group, and 151 in the darbepoetin alfa group)
- Per protocol set (PPS): 245 patients (114 in the ASP1517 group, and 131 in the darbepoetin alfa group)
- Pharmacokinetics analysis set (PKAS): 301 patients (150 in the ASP1517 group, and 151 in the darbepoetin alfa group)

Diagnosis and Main Criteria for Inclusion:

Patients with renal anemia on HD were enrolled in this study. Patients who were candidates for participation in the study were screened in accordance with the following inclusion criteria before enrollment into the study.

1. Patients who had given written informed consent by themselves
2. Patients who were diagnosed with chronic kidney disease (CKD), had been receiving stable chronic maintenance HD 3 times a week for more than 12 weeks before the prescreening assessments, and were scheduled to undergo HD 3 times a week during the study period
3. Patients with renal anemia who had been receiving intravenous treatment of rHuEPO (twice a week or 3 times a week) or darbepoetin alfa within the doses approved in Japan for more than 8 weeks before the prescreening assessments
4. Mean of the patient's 2 most recent hemoglobin (Hb) levels just before registration (before dialysis after the longest dialysis interval) during the screening period had to be 10.0 to 12.0 g/dL (2 Hb levels had to be measured with at least a week interval)
5. Patients with either transferrin saturation (TSAT) of ≥ 20% or serum ferritin of ≥ 100 ng/mL during the screening period
6. Patients aged 20 years or more at informed consent acquisition
7. Patients had been receiving HD via arteriovenous fistula or graft or subcutaneously fixed superficial artery.
8. Female patients had to fulfill following conditions:
   Non-childbearing potential female patients:
   - Post-menopausal (defined as at least 1 year without any menses) prior to the prescreening assessments, or
   - Documented surgically sterile

   Childbearing potential female patients (patients who did not correspond above):

- Agreed not to try to become pregnant during the study after informed consent acquisition and for 28 days after the final study drug administration
- And had a negative pregnancy test at the prescreening assessments
- And, if heterosexually active, agreed to consistently use two forms of highly effective birth control (at least one of which had to be a barrier method) starting at screening and throughout the study period and for 28 days after the final study drug administration

9. Female patients had to agree not to breastfeed starting at screening and throughout the study period, and for 28 days after the final study drug administration.
10. Female patients had not to donate ova starting at screening and throughout the study period, and for 28 days after the final study drug administration.
11. Male patients and their female spouse/partners who were of childbearing potential had to be using 2 forms of highly effective birth control (at least one of which had to be a barrier method) starting at screening and continue throughout the study period, and for 12 weeks after the final study drug administration.
12. Male patients had not to donate sperm starting at screening and throughout the study period, and for 12 weeks after the final study drug administration.

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

<Test drug>

ASP1517 tablets were tablets containing 20 mg, 50 mg or 100 mg as ASP1517 (Lot No. of formulation: [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted])

ASP1517 placebo tablets were tablets, the appearance of which was indistinguishable from ASP1517 20-mg, 50-mg or 100-mg tablet (Lot No. of formulation: [redacted], [redacted], [redacted] and [redacted])

<Dose and mode of administration>

The investigator or sub-investigator prescribed ASP1517 or ASP1517 placebo on the basis of the initial conversion dose shown in [Table for dose conversion at start of ASP1517] notified by the web registration system under double-blind condition in registered patients on the day of dialysis after the longest dialysis interval in the week when the dose of ESA would have been administered. Dose adjustment was managed on the web registration system based on the dose adjustment rule defined in <Increase or reduction in dose of the study drugs>. The dose of ASP1517 was determined in a blind manner based on the Hb level entered into the web registration system. The investigator or sub-investigator prescribed the test drug on the basis of the drug number and dose notified by the web registration system.

Initial conversion dose of ASP1517

The dose was determined on the basis of the average weekly dose of rHuEPO or darbepoetin alfa during 4 weeks prior to registration according to the following dose conversion shown in [Table for dose conversion at start of ASP1517].

[Table for dose conversion at start of ASP1517]

rHuEPO (IU/week)	Darbepoetin alfa (μg/week)	ASP1517 (mg/time)
< 4500	< 20	70
≥ 4500	≥ 20	100

rHuEPO: recombinant human erythropoietin

Dose adjustment rule of ASP1517

Dose was adjusted according to the rules defined <Increase or reduction in dose of the study drugs> so that the Hb level could be maintained within the target range (10.0 to 12.0 g/dL).

According to the following rules, patients took ASP1517 3 times a week for a maximum of 24 weeks:

- The first dosing was taken on the day or the next day of prescription.
- Patients took the study drug at 2- or 3-day intervals (Monday-Wednesday-Friday, Tuesday-Thursday-Saturday, etc.; dosing days had to remain consistent) throughout the administration period. Only the last dose was taken from the previous day of the week 24 visit to no later than the test and assessment on the day of week 24 visit.
- The study drug was administered after completion of dialysis if dosing was scheduled on a dialysis day (excluding the day of week 24 visit).
- When coadministered with phosphate binders (bixalomer, sevelamer hydrochloride, precipitated calcium carbonate, lanthanum carbonate hydrate, ferric citrate hydrate, sucroferric oxyhydroxide, etc.), patients had to take ASP1517 at least 1 hour before or 1 hour after dosing phosphate binder.

<Increase or reduction in dose of the study drugs>

The below instructions regarding dose adjustment of ASP1517 after the start of administration.

[Dose adjustment rule of ASP1517]

1. A decision on whether to perform dose adjustment or not was made at every even-week visit from week 4, if both the Hb level before dialysis after the longest dialysis interval and the change in the Hb levels over the past 4 weeks (difference between the Hb levels before dialysis after the longest dialysis interval in the concerned week and 4 weeks earlier) met the criteria defined in the [Dose increase/reduction rules of ASP1517 (even weeks from week 4 to week 22)], except as shown in [Dose adjustment in case of temporary dose hold] and [Dose adjustment in case of excessive Hb elevation]. Patients started taking the study drug at the post-adjustment dose after completion of dialysis after the longest dialysis interval.
2. If a dose reduction was required at the lowest dose or a dose increase was required at the highest dose, the dose had to remain the same.
3. The dose for each patient could not be permitted to be increased to more than 3.0 mg/kg.
4. If a dose increase or reduction was performed, the adjusted dose had to remain the same for at least 4 weeks (except in cases shown in [Dose adjustment in case of temporary dose hold] and [Dose adjustment in case of excessive Hb elevation]).

[Table for dose adjustment of ASP1517]

Stage	1	2	3	4	5	6	7	8	9	10
Dose (mg)	20	40	50	70	100	120	150	200	250	300

The highest dose did not exceed 3.0 mg/kg (dose calculation was made using the body weight after the end of dialysis performed just before registration after the longest dialysis interval).
[Example] The maximum dose of ASP1517 could be 150 mg in a patient weighing 60.0 kg after the end of dialysis performed just before registration after the longest dialysis interval.

[Dose increase/reduction rules (even weeks from week 4 to week 22)]

Dose increase/reduction had to be conducted if both the Hb level before dialysis after the longest dialysis interval and the change in the Hb levels over the past 4 weeks (difference between the Hb levels before dialysis

after the longest dialysis interval in the concerned week and 4 weeks earlier) met the following rule shown in [Table for dose increase/reduction rules of ASP1517].

[Table for dose increase/reduction rules of ASP1517]

Change of Hb Levels Before Dialysis After the Longest Dialysis Interval From 4 Weeks Ago to the Concerned Week	**Hb Level in the Week Before Dialysis After the Longest Dialysis Interval**		
	< 10.5 g/dL	**≥ 10.5 g/dL ≤ 11.5 g/dL**	**> 11.5 g/dL ≤ 12.5 g/dL**
< -1.0 g/dL	One-step dose increase	One-step dose increase	No change
≥ -1.0 g/dL ≤ 1.0 g/dL	One-step dose increase	No change	One-step dose reduction
> 1.0 g/dL	No change	One-step dose reduction	One-step dose reduction

[Dose adjustment in case of temporary dose hold]

At any time when the Hb level was more than 12.5 g/dL, dosing was stopped, then resumed dosing when the Hb level was less than 11.0 g/dL at a dose that was reduced by one step.

[Dose adjustment in case of excessive Hb reduction]

If the Hb level was less than 9.0 g/dL by week 3, the dose had to be increased by one step. This rule was applied only once.

[Dose adjustment in case of excessive Hb elevation]

If the Hb level increased by above 2.0 g/dL at any time within 4 weeks, the dose had to be reduced by one step. If dose adjustment was performed on the basis of excessive Hb elevation, the adjusted dose had to remain the same for at least 4 weeks.

Duration of Treatment (or Duration of Study, if applicable):

A maximum of 24 weeks

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

<Reference drug>

Darbepoetin alfa syringes were syringes containing 10 μg, 15 μg, 20 μg, 40 μg, 60 μg or 120 μg as darbepoetin alfa (Lot No. of formulation: [redacted]).

Darbepoetin alfa placebo syringes were syringes, the appearance of which was indistinguishable from darbepoetin alfa 10-μg, 15-μg, 20-μg, 40-μg, 60-μg or 120-μg syringe (Lot No. of formulation: [redacted]).

<Dose and mode of administration>

The investigator or sub-investigator prescribed darbepoetin alfa (comparator) or darbepoetin alfa placebo on the basis of the initial conversion dose shown in [Table for dose conversion at start of darbepoetin alfa] notified by the web registration system under double-blind condition in registered patients on the day of dialysis after the longest dialysis interval in the week when ESA would be administered. Dose adjustment was managed on the web registration system based on the dose adjustment rule defined in <Increase or reduction in dose of darbepoetin alfa>. The dose of darbepoetin alfa (comparator) was determined in a blind manner based on the

Hb level entered into the web registration system. The investigator or sub-investigator prescribed the comparator on the basis of the drug number and dose notified by the web registration system.

Initial conversion dose of darbepoetin alfa

The dose was determined on the basis of the average weekly dose of rHuEPO or darbepoetin alfa during 4 weeks prior to registration according to the following dose conversion shown in [Table for dose conversion at start of darbepoetin alfa].

[Table for dose conversion at start of darbepoetin alfa]

rHuEPO (IU/week)	Darbepoetin alfa (μg/week)	Comparator (Darbepoetin alfa) (μg/week)
-	< 12.5	10
≤ 3000	≥ 12.5 to < 17.5	15
> 3000 to ≤ 4500	≥ 17.5 to < 25	20
> 4500 to ≤ 6000	≥ 25 to < 35	30
> 6000	≥ 35 to < 45	40
-	≥ 45 to < 55	50
-	≥ 55	60

rHuEPO: recombinant human erythropoietin

Dose adjustment criteria of darbepoetin alfa

The dose was adjusted according to the ruled defined in <Increase or reduction in dose of darbepoetin alfa> so that the Hb level could be maintained within the target range (10.0 to 12.0 g/dL).

Darbepoetin alfa (comparator) was intravenously administered once per week to patients at the completion of dialysis on the dialysis day after the longest dialysis interval, for a maximum of 24 weeks. The last dose was administered at completion of dialysis on the day of week 23 visit.

<Increase or reduction in dose of darbepoetin alfa>

The below instructions regarding dose adjustment of darbepoetin alfa after the start of administration.

[Dose adjustment rule of darbepoetin alfa]

1. After start dosing of the comparator, dose was adjusted to maintain the Hb in the target range (10.0 to 12.0 g/dL) at every even week. If both the Hb levels at 2 consecutive weeks of the concerned week (even week) and the previous week were above 11.5 g/dL, the dose had to be reduced by one step. If both the Hb levels at 2 consecutive weeks of the concerned week (even week) and the previous week were below 10.5 g/dL, the dose had to be increased by one step.
2. Dose was changed from the date on dialysis of the concerned week.
3. If the Hb level above 12.5 g/dL was confirmed, dosing of the comparator was on hold and then resumed when the Hb level below 11.0 g/dL was confirmed at a dose that was reduced by one step. When a dose on hold was 10 μg, the same dose was used at resumption of treatment.
4. Dose was adjusted according to the following rule shown in [Table for adjustment of darbepoetin alfa]. If a dose reduction was required at the lowest dose of the comparator or a dose increase was required at the highest dose of the comparator, the dose had to remain the same because adjustment of comparator dose could not be conducted.

[Table for dose adjustment of darbepoetin alfa]

Stage	1	2	3	4	5	6	7	8	9	10	11	12	13
Dose (μg)	10	15	20	30	40	50	60	80	100	120	140	160	180

Criteria for Evaluation:

Efficacy endpoints

Primary endpoint:

- Change of Hb levels from baseline during the evaluation period (Evaluation period: weeks 18 to 24)

Secondary endpoints:

- Average Hb levels of weeks 18 to 24
- Maintenance rate of the target Hb level (proportion of patients who achieved the average Hb level of 10.0 to 12.0 g/dL for weeks 18 to 24)
- Proportion of patients who achieved the target Hb level (10.0 to 12.0 g/dL) at each week
- Change of Hb levels from week 0 to each week
- Proportion of measurement points that met the target Hb level (10.0 to 12.0 g/dL) from weeks 18 to 24
- Rate of rise in Hb levels (g/dL/week) from week 0 to at the earliest date of week 4, time of discontinuation, or time of dose adjustment
- Hematocrit (Ht), reticulocyte (Ret), ferrum (Fe), ferritin, transferrin, total iron binding capacity (TIBC), soluble transferrin receptor (sTfR), TSAT, and reticulocyte hemoglobin content (CHr)
- Quality of life (QOL) survey (SF-36, EQ-5D-5L, and FACT-An)
- Occurrence (number) of hospitalizations and duration of hospitalization

Exploratory endpoint

- Hepcidin

Pharmacokinetics

- Plasma concentration of unchanged form of ASP1517 (ASP1517 arm only)

Safety endpoints

- Adverse events (AEs)
- Laboratory data (excluding Hb, Ht, Ret, Fe, ferritin, transferrin, TIBC, sTfR, TSAT and CHr)
- Vital signs (pulse rate and blood pressure in supine position)
- 12-lead electrocardiogram (ECG)
- Ophthalmological examination (funduscopic photograph, optical coherence tomography [OCT], visual acuity)

Statistical Methods:

[Analysis of efficacy endpoints]

Analysis of the primary endpoint was performed on the PPS as the primary analysis set. The efficacy of ASP1517 was confirmed if the 95% confidence interval (CI) of the average Hb level in the evaluation period was within the range of 10.0 to 12.0 g/dL in the ASP1517 treatment arm. To confirm the non-inferiority of ASP1517 to darbepoetin alfa, the 95% CI in the difference of ASP1517 and darbepoetin alfa (ASP1517 -

darbepoetin alfa) as the change of Hb levels from baseline during the evaluation period was analyzed by a mixed model of repeated measurements with an unstructured covariance matrix within patients. The model considered treatment arms (ASP1517 or darbepoetin alfa), visit, baseline Hb, ESA dose just before registration, previous or concurrent retinal vascular disorder, diabetes mellitus, and visit by treatment arm interaction as explanatory variables. The non-inferiority was confirmed if the lower limit of the 95% CI for the difference lied entirely above -0.75 g/dL. Similar analysis was conducted with the FAS as the secondary analysis against the primary analysis. In addition, change of average Hb levels of weeks 18 to 24 from baseline was summarized by descriptive statistics on PPS and FAS. Difference between treatment arms in the change of average Hb levels and its 95% CI were also calculated. As sensitivity analysis of the primary analysis, analysis of covariance (ANCOVA) and analyses taking into account multiple missing data mechanisms were conducted. Analyses of the secondary endpoints and other variables were performed on the FAS. Unless designated otherwise, analysis was conducted by treatment arm (ASP1517 or darbepoetin alfa).

[Analysis of exploratory endpoint]

Hepcidin

Hepcidin was summarized using mean, standard deviation, minimum, maximum and median by treatment arm (ASP1517 or darbepoetin alfa), and by visit for the FAS. Additionally, a within-patient change was calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

[Analysis of pharmacokinetics]

The analyses of pharmacokinetics were performed using the PKAS. No statistical analyses were conducted.

[Analysis of safety endpoints]

All analysis of safety was presented by treatment arm (ASP1517 or darbepoetin alfa) for the SAF unless specified otherwise.

Summary of Results/Conclusions:

Population:

A total of 415 patients provided informed consent and 112 patients discontinued before randomization due to screen failures [Figure 1]. The number of randomized patients was 303 (151 in the ASP1517 group and 152 in the darbepoetin alfa group). All 303 patients were treated with the study drug. A total of 250 (82.5%) patients (119 [78.8%] in the ASP1517 group and 131 [86.2%] in the darbepoetin alfa group) completed the study and 53 (17.5%) patients (32 [21.2%] in the ASP1517 group and 21 [13.8%] in the darbepoetin alfa group) discontinued [Table 1]. Of the 303 randomized patients, 302 (99.7%) were included in the SAF, 301 (99.3%) were included in the FAS and PKAS, and 245 (80.9%) were included in the PPS. A total of 58 (19.1%) patients (37 [24.5%] in the ASP1517 group and 21 [13.8%] in darbepoetin alfa group) were excluded from the PPS. The most common reason for exclusion was “Hb was not measured at baseline or less than 4 points from weeks 18 to 24” (16.2%, 49/303 patients), followed by “duration of administration period was less than 18 weeks (126 days)” (14.9%, 45/303 patients).

In the FAS, 101 (67.3%) patients were male and 49 (32.7%) patients were female in the ASP1517 group and 107 (70.9%) patients were male and 44 (29.1%) patients were female in the darbepoetin alfa group. The mean (SD) age was 64.6 (11.7) years in the ASP1517 group and 64.9 (10.1) years in the darbepoetin alfa group. The

mean (SD) weight at prescreening was 57.85 (11.94) kg in the ASP1517 group and 58.77 (12.92) kg in the darbepoetin alfa group. The mean (SD) and median of HD vintage were 92.77 (89.78) and 59.45 months in the ASP1517 group and 99.66 (101.63) and 54.34 months in the darbepoetin alfa group. The mean (SD) duration of anemia associated with CKD was 91.27 (73.71) months in the ASP1517 group and 95.17 (80.93) months in the darbepoetin alfa group. The common primary diseases of CKD were chronic glomerular nephritis (35.3%, 53/150 patients) and diabetic nephropathy (31.3%, 47/150 patients) in the ASP1517 group and chronic glomerular nephritis (35.1%, 53/151 patients) and diabetic nephropathy (32.5%, 49/151 patients) in the darbepoetin alfa group. Previous or concurrent retinal vascular disorder was present in 62 (41.3%) patients in the ASP1517 group and 57 (37.7%) patients in the darbepoetin alfa group. Diabetes mellitus was present in 54 (36.0%) patients in the ASP1517 group and 54 (35.8%) patients in the darbepoetin alfa group. Overall, the baseline characteristics were similar between the ASP1517 and darbepoetin alfa groups [Table 2].

Efficacy and Exploratory Endpoint Results:

- The mean (SE) of average Hb levels of weeks 18 to 24 in the ASP1517 group was 10.99 (0.06) g/dL with the 95% CI of 10.88 to 11.10 g/dL, which was within the range of 10.0 to 12.0 g/dL [Table 3]. Thus, the efficacy of ASP1517 was confirmed.
- The least square (LS) mean (SE) of change of average Hb levels of weeks 18 to 24 from baseline was -0.04 (0.06) g/dL in the ASP1517 group and -0.03 (0.06) g/dL in the darbepoetin alfa group. The estimated difference between the ASP1517 and darbepoetin alfa groups in the LS mean of change of average Hb levels of weeks 18 to 24 from baseline was -0.02 g/dL with the lower limit of 95% CI of -0.18 g/dL, which was above the pre-defined non-inferiority margin of -0.75 g/dL [Table 4]. Thus, the non-inferiority of ASP1517 to darbepoetin alfa was confirmed.
- The results of secondary and sensitivity analyses showed that the lower limits of 95% CI for the difference between the ASP1517 and darbepoetin alfa groups in the mean change of average Hb levels of weeks 18 to 24 from baseline were above -0.75 g/dL, which confirmed the robustness of the results of primary analysis.
- The mean (SD) of average Hb level of weeks 18 to 24 was 11.00 (0.60) g/dL in the ASP1517 group and 10.95 (0.63) g/dL in the darbepoetin alfa group. The difference (95% CI) between the ASP1517 and darbepoetin alfa groups in the average Hb levels of weeks 18 to 24 was 0.05 (-0.10, 0.20) g/dL [Table 5].
- The maintenance rate (95% CI) during weeks 18 to 24 was 79.3 (72.0, 85.5) % in the ASP1517 group and 83.4 (76.5, 89.0) % in the darbepoetin alfa group [Table 6]. The difference (95% CI) between the ASP1517 and darbepoetin alfa groups in the maintenance rate of target Hb level was -4.1 (-13.6, 5.3) %. In the patients with at least one Hb value during weeks 18 to 24, the maintenance rate (95% CI) was 95.2 (89.8, 98.2) % in the ASP1517 group and 91.3 (85.3, 95.4) % in the darbepoetin alfa group. The difference (95% CI) between the ASP1517 and darbepoetin alfa groups in the maintenance rate of target Hb level for the patients with at least one Hb value during weeks 18 to 24 was 3.9 (-2.9, 10.7) % [Table 7].
- The proportion (95% CI) of patients who achieved target Hb level (10.0 to 12.0 g/dL) at end of treatment (EOT) was 78.7 (71.2, 84.9) % in the ASP1517 group and 85.4 (78.8, 90.6) % in the darbepoetin alfa group. The difference (95% CI) between the ASP1517 and darbepoetin alfa groups in the proportion of patients who achieved target Hb level at EOT was -6.8 (-16.1, 2.5) %. In the ASP1517 group, the proportion of patients who achieved target Hb level temporarily decreased from week 1 through week 3 and then improved the decreasing trend from week 6 through week 12 and then became stable through

EOT. In the darbepoetin alfa group, the proportion of patients who achieved target Hb level was stable through EOT [Figure 2].

- The mean Hb values were maintained at the target Hb level (10.0 to 12.0 g/dL) in both the ASP1517 and darbepoetin alfa groups through EOT, and no remarkable changes were observed. The difference between the ASP1517 and darbepoetin alfa groups in the change of Hb levels from week 0 was 0.21 to 0.29 g/dL from week 3 through week 5 because a temporal increase of Hb levels from week 0 was observed in the ASP1517 group, but otherwise small (-0.17 to 0.18 g/dL) through EOT [Figure 3].
- The mean (SD) proportion of measurement points that met target Hb level (10.0 to 12.0 g/dL) from weeks 18 to 24 was 85.67 (22.66) % in the ASP1517 group and 86.99 (22.21) % in the darbepoetin alfa group. The difference (95% CI) between the ASP1517 and darbepoetin alfa groups in the proportion of measurement points that met the target Hb level was -1.32 (-6.77, 4.14) % [Table 8].
- The mean (SD) rate of rise in Hb levels was 0.129 (0.331) g/dL/week in the ASP1517 group and -0.017 (0.195) g/dL/week in the darbepoetin alfa group [Table 9]. The proportion of patients whose rate of rise in Hb levels exceeded 0.5 g/dL/week was 10.7% (16/150 patients) in the ASP1517 group and 0.7% (1/151 patients) in the darbepoetin alfa group [Table 10].
- The mean Ht values increased from week 0 through week 4 and then decreased through week 8 and then became stable through EOT in the ASP1517 group, while no remarkable change was observed in the darbepoetin alfa group. The mean reticulocytes/erythrocytes values increased from week 0 through week 2 and then decreased through week 4 and then became stable through EOT in the ASP1517 group, while no remarkable change was observed in the darbepoetin alfa group. The mean ferritin values slightly decreased from week 0 through week 2 and then became stable through EOT in both the ASP1517 and darbepoetin alfa groups. The mean transferrin and TIBC values increased from week 0 through week 4 and then became stable through EOT in the ASP1517 group, while no remarkable change was observed in the darbepoetin alfa group. No remarkable changes in the mean values for Fe, sTfR, TSAT, or CHr values were observed at each visit and EOT in both the ASP1517 and darbepoetin alfa groups, and no remarkable difference between the groups was observed.
- The mean changes during weeks 0 to 24 in SF-36, EQ-5D-5L and FACT-An scores were small, and no apparent change was observed during the study in either the ASP1517 or darbepoetin alfa group. No apparent difference between the ASP1517 and darbepoetin alfa groups in SF-36, EQ-5D-5L and FACT-An scores was observed.
- The proportion of patients who were admitted to the hospital during treatment period was 17.3% (26/150 patients) in the ASP1517 group and 13.2% (20/151 patients) in the darbepoetin alfa group. The mean (SD) number of hospitalizations was 0.2 (0.6) times in the ASP1517 group and 0.2 (0.5) times in the darbepoetin alfa group. No apparent difference between the ASP1517 and darbepoetin alfa groups in occurrence of hospitalizations was observed. The mean (SD) total duration of hospitalization was 9.1 (16.9) days in the ASP1517 group and 15.1 (32.4) days in the darbepoetin alfa group.
- Subgroup analyses showed that the mean (SD) of change of average Hb levels of weeks 18 to 24 from baseline in the ASP1517 and darbepoetin alfa groups was -0.03 (0.79) and -0.03 (0.88) g/dL in C-reactive protein (CRP) < 28.57 nmol/L subgroup and -0.13 (0.81) and -0.18 (0.94) g/dL in ≥ 28.57 nmol/L subgroup, respectively. In the darbepoetin alfa group, it was necessary to administer darbepoetin alfa at

higher doses to patients with high CRP levels, than to patients with low CRP levels, to maintain their Hb levels. However, in the ASP1517 group, there was no major change in ASP1517 dose associated with CRP levels.

- No remarkable changes in the mean hepcidin levels were observed in either the ASP1517 or darbepoetin alfa group from week 0 through EOT.

Safety Results:

- The incidence of treatment-emergent adverse events (TEAEs) was 86.0% (129/150 patients) in the ASP1517 group and 82.9% (126/152 patients) in the darbepoetin alfa group. The common (incidence ≥ 5% in any randomization arm) TEAEs were nasopharyngitis, shunt stenosis, diarrhea, contusion and vomiting. Of these, the events occurring more frequently in the ASP1517 group compared with the darbepoetin alfa group included nasopharyngitis (34.7% versus 26.3%) and vomiting (6.7% versus 2.0%). Retinal hemorrhage was reported in 3.3% (5/150 patients) in the ASP1517 group and 3.9% (6/152 patients) in the darbepoetin alfa group [Table 11]. Severe TEAEs were reported in 2.7% (4/150 patients) in the ASP1517 group and 2.0% (3/152 patients) in the darbepoetin alfa group. All other TEAEs were mild or moderate in severity.
- The incidence of drug-related TEAEs was 22.0% (33/150 patients) in the ASP1517 group and 13.2% (20/152 patients) in the darbepoetin alfa group. The drug-related TEAEs with an incidence ≥ 1% in the ASP1517 group were hypertension (3.3%), retinal hemorrhage, vomiting and hypoalbuminemia (2.0% each), nausea, diarrhea, malaise and hyperkalemia (1.3% each). The drug-related TEAEs with an incidence ≥ 1% in the darbepoetin alfa group were retinal hemorrhage (2.6%), hypertension (2.0%) and vertigo (1.3%). No particular pattern of drug-related TEAEs was identified in either the ASP1517 or darbepoetin alfa group [Table 12]. Severe drug-related TEAEs were reported in 0.7% (1/150 patients) in the ASP1517 group and 1.3% (2/152 patients) in the darbepoetin alfa group. All other drug-related TEAEs were mild or moderate in severity.
- The incidence of treatment-emergent serious adverse events (TESAEs) was 20.7% (31/150 patients) in the ASP1517 group and 14.5% (22/152 patients) in the darbepoetin alfa group. TESAEs observed in 2 or more patients in the ASP1517 group were shunt stenosis (4.0%, 6/150 patients), shunt occlusion (2.0%, 3/150 patients), cellulitis and deep vein thrombosis (1.3%, 2/150 patients each). TESAEs observed in 2 or more patients in the darbepoetin alfa group were shunt stenosis (4.6%, 7/152 patients), angina pectoris and shunt occlusion (1.3%, 2/152 patients each) [Table 13]. The incidence of drug-related TESAEs was 3.3% (5/150 patients) in the ASP1517 group and 3.9% (6/152 patients) in the darbepoetin alfa group. There were no drug-related TESAEs observed in 2 or more patients in either the ASP1517 or darbepoetin alfa group.
- The incidence of TEAEs leading to withdrawal of treatment was 8.7% (13/150 patients) in the ASP1517 group and 5.3% (8/152 patients) in the darbepoetin alfa group [Table 14]. The incidence of drug-related TEAEs leading to withdrawal of treatment was 5.3% (8/150 patients) in the ASP1517 group and 3.3% (5/152 patients) in the darbepoetin alfa group. No TEAEs leading to withdrawal of treatment occurred in 2 or more patients in either treatment group.
- Deaths were reported only in the ASP1517 group and the incidence was 1.3% (2/150 patients). One of these 2 patients died of cardiac failure congestive on day 97. The investigator considered that a causal

relationship between this event and ASP1517 could not be ruled out. However, the patient was a HD-introduced patient and had a medical history of hypertension, angina pectoris and dyslipidemia as complications. Thus, the sponsor's assessment concluded that the event of cardiac failure congestive was likely to be induced by the patient's predisposing factors, such as poor body fluid management, and that the event was not causally related to the study drug.

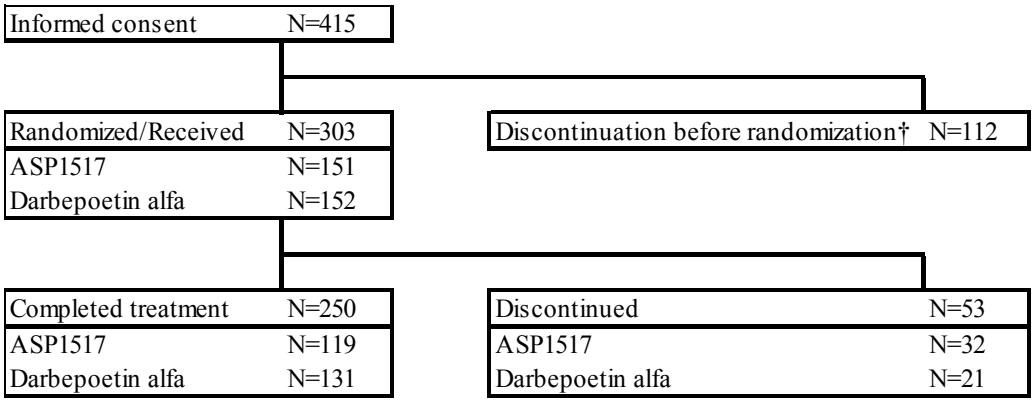
- In the subgroup analyses, no remarkable difference regarding the incidence of TEAEs was found between the subgroups or between the ASP1517 and darbepoetin alfa groups.
- As a result of clinical laboratory evaluation, no clinically meaningful mean changes from week 0 for safety relevant hematology and biochemistry variables were found in either the ASP1517 or darbepoetin alfa group at each visit and EOT.
- As a result of vital sign evaluation, no clinically meaningful mean changes from week 0 for safety relevant vital signs variables (systolic blood pressure [SBP], diastolic blood pressure [DBP] and pulse rate) were found in either the ASP1517 or darbepoetin alfa group at each visit and EOT.
- As a result of ECG evaluation, no clinically remarkable differences depending on the measurement timing or between the ASP1517 and darbepoetin alfa groups were found.
- As a result of ophthalmological examination, the proportion of patients with new or worsening retinal hemorrhages during the treatment period in the ASP1517 and darbepoetin alfa groups was 32.4% (46/142 patients) and 36.6% (53/145 patients), respectively [Table 15]. No clinically meaningful mean changes from week 0 in the retinal thickness were found in either the ASP1517 or darbepoetin alfa group at each visit and EOT. These findings suggest that there is absence of increased risk of ophthalmological abnormalities including retinal hemorrhages in patients treated with ASP1517 compared to darbepoetin alfa.

CONCLUSIONS:

- The study reached its objective and confirmed the efficacy of ASP1517 and its non-inferiority to darbepoetin alfa in terms of maintaining Hb levels within the target range in patients with renal anemia on HD.
- ASP1517 was well tolerated and the safety profile of ASP1517 was comparable to that of darbepoetin alfa.
- The rate of new or worsening retinal hemorrhages in the ASP1517 group was not higher than that in the darbepoetin alfa group.

Date of Report: 9 Aug 2018

Figure 1 Disposition of Patients



† Patients who signed informed consent but discontinued before randomization were screening failures.

Source: Table 12.1.1.1, Table 12.1.1.2, Table 12.1.1.3.2

Table 1 Study Disposition (All Randomized Patients)

Parameter	Category	Darbepoetin alfa (N=152)	ASP1517 (N=151)	Total (N=303)
Study Discontinuation	No	131 (86.2%)	119 (78.8%)	250 (82.5%)
	Yes	21 (13.8%)	32 (21.2%)	53 (17.5%)
Primary End of Study Reason †	Completed	131 (86.2%)	119 (78.8%)	250 (82.5%)
	Adverse Event	8 (5.3%)	12 (7.9%)	20 (6.6%)
	Death	0	2 (1.3%)	2 (0.7%)
	Lack of Efficacy	1 (0.7%)	1 (0.7%)	2 (0.7%)
	Lost to Follow-up	0	0	0
	Progressive Disease	0	0	0
	Protocol Deviation	4 (2.6%)	7 (4.6%)	11 (3.6%)
	Withdrawal by Subject	4 (2.6%)	5 (3.3%)	9 (3.0%)
	Study Terminated by Sponsor	0	0	0
	Non-Compliance With Study Drug	0	0	0
	Recovery	0	0	0
	Pregnancy	0	0	0
	Site Terminated by Sponsor	0	0	0
	Other	4 (2.6%)	5 (3.3%)	9 (3.0%)

† Only the primary end of study reason was collected.

Source: Table 12.1.1.3.2

Table 2 Demographic Characteristics (FAS)

	Darbepoetin alfa (N=151)	ASP1517 (N=150)	Total (N=301)
Sex			
Male	107 (70.9%)	101 (67.3%)	208 (69.1%)
Female	44 (29.1%)	49 (32.7%)	93 (30.9%)
Age (Years) [Informed Consent]			
n	151	150	301
Mean	64.9	64.6	64.7
SD	10.1	11.7	10.9
Min	37	24	24
Median	66.0	65.5	66.0
Max	85	89	89
Age Group (Years) [Informed Consent]			
< 65	62 (41.1%)	67 (44.7%)	129 (42.9%)
≥ 65	89 (58.9%)	83 (55.3%)	172 (57.1%)
Height (cm) [Prescreening]			
n	151	150	301
Mean	161.76	160.16	160.96
SD	8.88	8.65	8.79
Min	137.5	140.8	137.5
Median	163.00	160.30	162.30
Max	181.1	181.5	181.5
Weight (kg) [Prescreening]			
n	151	150	301
Mean	58.77	57.85	58.31
SD	12.92	11.94	12.43
Min	36.4	36.5	36.4
Median	58.00	56.85	57.40
Max	109.2	99.6	109.2
Weight Group (kg) [Prescreening]			
< 60	84 (55.6%)	94 (62.7%)	178 (59.1%)
≥ 60	67 (44.4%)	56 (37.3%)	123 (40.9%)
Weight (kg) [Week 0 (After Hemodialysis)]			
n	151	150	301
Mean	58.78	57.82	58.30
SD	12.90	11.97	12.43
Min	36.3	36.8	36.3
Median	58.10	57.10	57.40
Max	107.0	99.7	107.0
Weight Group (kg) [Week 0 (After Hemodialysis)]			
< 60	82 (54.3%)	93 (62.0%)	175 (58.1%)
≥ 60	69 (45.7%)	57 (38.0%)	126 (41.9%)
BMI (kg/m^2) [Prescreening]			
n	151	150	301
Mean	22.32	22.43	22.37
SD	3.78	3.55	3.66
Min	15.8	16.2	15.8
Median	21.71	21.63	21.67
Max	37.3	35.0	37.3

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	Darbepoetin alfa (N=151)	ASP1517 (N=150)	Total (N=301)
Duration of Anemia associated with CKD (Months)			
n	89	96	185
Mean	95.17	91.27	93.15
SD	80.93	73.71	77.08
Min	4.7	7.2	4.7
Median	58.71	68.37	66.17
Max	349.4	365.7	365.7
Duration of Anemia associated with CKD Group (Months)			
< 6	1 (0.7%)	0	1 (0.3%)
≥ 6 to < 12	1 (0.7%)	2 (1.3%)	3 (1.0%)
≥ 12 to < 36	20 (13.2%)	23 (15.3%)	43 (14.3%)
≥ 36 to < 60	24 (15.9%)	17 (11.3%)	41 (13.6%)
≥ 60 to < 120	14 (9.3%)	29 (19.3%)	43 (14.3%)
≥ 120 to < 240	22 (14.6%)	22 (14.7%)	44 (14.6%)
≥ 240	7 (4.6%)	3 (2.0%)	10 (3.3%)
Unknown	62 (41.1%)	54 (36.0%)	116 (38.5%)
Primary Disease of CKD			
Chronic Glomerular Nephritis	53 (35.1%)	53 (35.3%)	106 (35.2%)
Diabetic Nephropathy	49 (32.5%)	47 (31.3%)	96 (31.9%)
Chronic Pyelonephritis	1 (0.7%)	0	1 (0.3%)
Polycystic Kidney	10 (6.6%)	12 (8.0%)	22 (7.3%)
Nephrosclerosis	19 (12.6%)	18 (12.0%)	37 (12.3%)
Other	19 (12.6%)	20 (13.3%)	39 (13.0%)
Duration of CKD (Months)			
n	83	78	161
Mean	192.34	181.43	187.06
SD	137.36	136.38	136.57
Min	25.7	21.1	21.1
Median	138.84	139.29	138.84
Max	566.1	626.3	626.3
Duration of CKD Group (Months)			
< 6	0	0	0
≥ 6 to < 12	0	0	0
≥ 12 to < 36	2 (1.3%)	4 (2.7%)	6 (2.0%)
≥ 36 to < 60	9 (6.0%)	10 (6.7%)	19 (6.3%)
≥ 60 to < 120	22 (14.6%)	17 (11.3%)	39 (13.0%)
≥ 120 to < 240	23 (15.2%)	30 (20.0%)	53 (17.6%)
≥ 240	27 (17.9%)	17 (11.3%)	44 (14.6%)
Unknown	68 (45.0%)	72 (48.0%)	140 (46.5%)
Hemodialysis Vintage (Months)			
n	151	150	301
Mean	99.66	92.77	96.23
SD	101.63	89.78	95.81
Min	4.3	3.4	3.4
Median	54.34	59.45	57.92
Max	422.4	488.7	488.7
Hemodialysis Vintage Group 1 (Months)			
< 60	78 (51.7%)	75 (50.0%)	153 (50.8%)
≥ 60	73 (48.3%)	75 (50.0%)	148 (49.2%)
Unknown	0	0	0

Table continued on next page

	Darbepoetin alfa (N=151)	ASP1517 (N=150)	Total (N=301)
Hemodialysis Vintage Group 2 (Months)			
< 6	3 (2.0%)	2 (1.3%)	5 (1.7%)
≥ 6 to < 12	9 (6.0%)	7 (4.7%)	16 (5.3%)
≥ 12 to < 36	47 (31.1%)	42 (28.0%)	89 (29.6%)
≥ 36 to < 60	19 (12.6%)	24 (16.0%)	43 (14.3%)
≥ 60 to < 120	26 (17.2%)	32 (21.3%)	58 (19.3%)
≥ 120 to < 240	28 (18.5%)	35 (23.3%)	63 (20.9%)
≥ 240	19 (12.6%)	8 (5.3%)	27 (9.0%)
Unknown	0	0	0
Previous or Concurrent Retinal Vascular Disorder †			
Absent	94 (62.3%)	88 (58.7%)	182 (60.5%)
Present	57 (37.7%)	62 (41.3%)	119 (39.5%)
Diabetes Mellitus			
Absent	97 (64.2%)	96 (64.0%)	193 (64.1%)
Present	54 (35.8%)	54 (36.0%)	108 (35.9%)
C-Reactive Protein High Sensitivity (nmol/L) [Week 0]			
n	151	150	301
Mean	13.926	12.615	13.273
SD	21.855	22.976	22.393
Min	0.48	0.48	0.48
Median	5.370	5.380	5.370
Max	127.62	180.96	180.96
C-Reactive Protein High Sensitivity Group (nmol/L) [Week 0]			
< 28.57	129 (85.4%)	136 (90.7%)	265 (88.0%)
≥ 28.57	22 (14.6%)	14 (9.3%)	36 (12.0%)
History of Ocular Intervention ‡ (Type: Focal Laser)			
No	144 (95.4%)	137 (91.3%)	281 (93.4%)
Yes	7 (4.6%)	13 (8.7%)	20 (6.6%)
History of Ocular Intervention ‡ (Type: Panretinal Photocoagulation)			
No	123 (81.5%)	116 (77.3%)	239 (79.4%)
Yes	28 (18.5%)	34 (22.7%)	62 (20.6%)
History of Ocular Intervention ‡ (Type: Vitrectomy)			
No	139 (92.1%)	129 (86.0%)	268 (89.0%)
Yes	12 (7.9%)	21 (14.0%)	33 (11.0%)
History of Ocular Intervention ‡ (Type: Cataract Surgery/Phacoemulsification)			
No	109 (72.2%)	102 (68.0%)	211 (70.1%)
Yes	42 (27.8%)	48 (32.0%)	90 (29.9%)
History of Ocular Intervention ‡ (Type: Other)			
No	146 (96.7%)	147 (98.0%)	293 (97.3%)
Yes	5 (3.3%)	3 (2.0%)	8 (2.7%)
History of Hypertension			
No	10 (6.6%)	12 (8.0%)	22 (7.3%)
Yes	141 (93.4%)	138 (92.0%)	279 (92.7%)

Table continued on next page

	Darbepoetin alfa (N=151)	ASP1517 (N=150)	Total (N=301)
Mean Arterial Blood Pressure (MAP) (mmHg) § [Week 0]			
n	151	150	301
Mean	102.8	103.6	103.2
SD	13.1	13.7	13.4
Min	59	57	57
Median	102.0	102.0	102.0
Max	134	144	144
Mean Arterial Blood Pressure (MAP) Group (mmHg) § [Week 0]			
< 100	65 (43.0%)	59 (39.3%)	124 (41.2%)
≥ 100	86 (57.0%)	91 (60.7%)	177 (58.8%)
History of Diabetic Mellitus and/or Hypertension			
No/No	8 (5.3%)	12 (8.0%)	20 (6.6%)
Yes/No	2 (1.3%)	0	2 (0.7%)
No/Yes	89 (58.9%)	84 (56.0%)	173 (57.5%)
Yes/Yes	52 (34.4%)	54 (36.0%)	106 (35.2%)
History of Diabetic Mellitus and/or Retinal Vascular Disease †			
No/No	82 (54.3%)	83 (55.3%)	165 (54.8%)
Yes/No	12 (7.9%)	5 (3.3%)	17 (5.6%)
No/Yes	15 (9.9%)	13 (8.7%)	28 (9.3%)
Yes/Yes	42 (27.8%)	49 (32.7%)	91 (30.2%)
History of Diabetic Mellitus and/or Mean Arterial Blood Pressure (MAP) § Group (< 100, ≥ 100) [Week 0]			
No/< 100	43 (28.5%)	39 (26.0%)	82 (27.2%)
Yes/< 100	22 (14.6%)	20 (13.3%)	42 (14.0%)
No/≥ 100	54 (35.8%)	57 (38.0%)	111 (36.9%)
Yes/≥ 100	32 (21.2%)	34 (22.7%)	66 (21.9%)
History of Retinal Diseases Currently Treated with Medication			
No	149 (98.7%)	146 (97.3%)	295 (98.0%)
Yes	2 (1.3%)	4 (2.7%)	6 (2.0%)

BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; MAP: mean arterial blood pressure; SBP: systolic blood pressure

† Refers to retinal hemorrhage, vitreous hemorrhage, non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, macular edema, retinal vein occlusion, and retinal artery occlusion.

‡ Both eyes are combined.

§ MAP is derived for each visit from the above averaged SBP and DBP using the following equation: MAP = (2/3) * DBP + (1/3) * SBP.

Source: Table 12.1.2.1.1

Table 3 Average Hb Levels of Weeks 18 to 24 (PPS)

Parameter	Treatment Group	N	Mean (SE) (95% CI)	Reference Range
Average Hb Levels of Weeks 18 to 24 (g/dL)	ASP1517	114	10.99 (0.06) (10.88, 11.10)	(10.0, 12.0)

CI: confidence interval

Hb values in analysis visit windows at weeks 18, 19, 20, 21, 22, 23 and 24 are used for calculating the average of weeks 18 to 24.

Source: Table 12.3.1.1.1

Table 4 Change of Average Hb Levels of Weeks 18 to 24 From Baseline (PPS)

Parameter	Treatment Group	LS Mean (SE) (95% CI) †	Estimated Difference (SE) (95% CI) †	Non-inferiority Margin
Change of Average Hb Levels of Weeks 18 to 24 from Baseline (g/dL)	Darbepoetin alfa	-0.03 (0.06) (-0.14, 0.09)	-	-
	ASP1517	-0.04 (0.06) (-0.16, 0.08)	-0.02 (0.08) (-0.18, 0.15)	-0.75

CI: confidence interval; ESA: erythropoiesis stimulating agent; LS: least square; MMRM: mixed-effects models for repeated measures

Hb values in analysis visit windows at weeks 18, 19, 20, 21, 22, 23 and 24 are used for calculating the average of weeks 18 to 24.

† MMRM with an unstructured covariance matrix within subjects was used. The model considered randomization arms (ASP1517 or darbepoetin alfa), visit, baseline Hb, ESA dose just before registration, previous or concurrent retinal vascular disorder, diabetes mellitus, and visit by randomization arm interaction as explanatory variables.

Source: Table 12.3.1.1.2

Table 5 Average Hb Levels of Weeks 18 to 24 (FAS)

Statistic	Darbepoetin alfa (N=151)	ASP1517 (N=150)
Average Hb Levels of Weeks 18 to 24 (g/dL)		
n	138	125
Mean	10.95	11.00
SD	0.63	0.60
Min	9.0	8.7
Median	10.95	11.00
Max	12.8	12.2
95% CI	(10.84, 11.05)	(10.89, 11.10)
Difference of Means	-	0.05
95% CI of Difference	-	(-0.10, 0.20)

CI: confidence interval

Hb values in analysis visit windows at weeks 18, 19, 20, 21, 22, 23 and 24 are used for calculating the average of weeks 18 to 24.

Source: Table 12.3.2.1, Table 12.3.2.2

Table 6 Maintenance Rate of Target Hb Level (Average Hb Level of 10.0 to 12.0 g/dL for Weeks 18 to 24) (FAS)

	Darbepoetin alfa (N=151)	ASP1517 (N=150)
Average Hb Levels of Weeks 18 to 24		
Number of Subjects Who Maintain Target Hb Level †	126 (83.4%)	119 (79.3%)
95% CI of Maintenance Rate ‡	(76.5%, 89.0%)	(72.0%, 85.5%)
Difference of Maintenance Rates	-	-4.1%
95% CI of Difference §	-	(-13.6%, 5.3%)

CI: confidence interval

Hb values in analysis visit windows at weeks 18, 19, 20, 21, 22, 23 and 24 are used for calculating the average of weeks 18 to 24.

† Defined as average Hb level of 10.0 to 12.0 g/dL for weeks 18 to 24

‡ Clopper-Pearson method

§ Normal approximation with continuity correction

Source: Table 12.3.3.1

Table 7 Maintenance Rate of Target Hb Level (Average Hb Level of 10.0 to 12.0 g/dL for Weeks 18 to 24) for Patients With at Least One Hb Value (FAS)

	Darbepoetin alfa (N=151)	ASP1517 (N=150)
Average Hb Levels of Weeks 18 to 24		
Number of Subjects Who Maintain Target Hb Level †	126/138 (91.3%)	119/125 (95.2%)
95% CI of Maintenance Rate ‡	(85.3%, 95.4%)	(89.8%, 98.2%)
Difference of Maintenance Rates	-	3.9%
95% CI of Difference §	-	(-2.9%, 10.7%)

CI: confidence interval

Hb values in analysis visit windows at weeks 18, 19, 20, 21, 22, 23 and 24 are used for calculating the average of weeks 18 to 24.

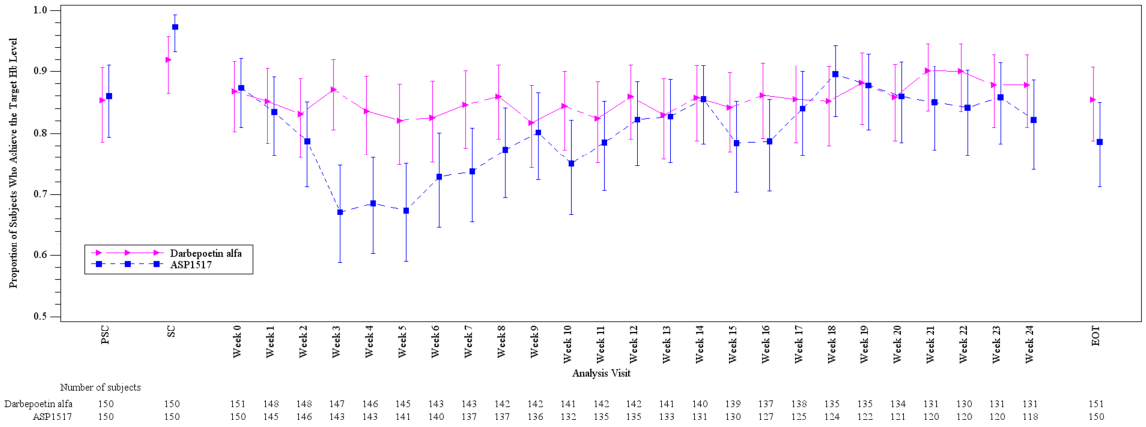
† Defined as average Hb level of 10.0 to 12.0 g/dL for weeks 18 to 24

‡ Clopper-Pearson method

§ Normal approximation with continuity correction

Source: Table 12.3.3.2

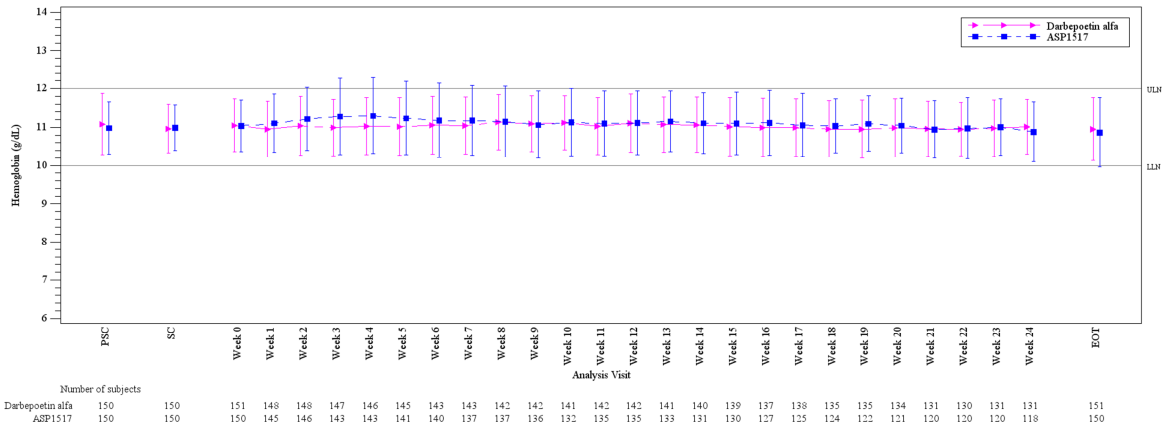
Figure 2 **Proportion and 95% Confidence Interval Plot of Patients Who Achieved the Target Hb Level (10.0 to 12.0 g/dL) (FAS)**



EOT: end of treatment; PSC: prescreening; SC: screening

Source: Figure 12.3.1.2.1

Figure 3 **Mean and Standard Deviation Plot of Hemoglobin (FAS)**



EOT: end of treatment; LLN: lower limit of normal; PSC: prescreening; SC: screening; ULN: upper limit of normal

Source: Figure 12.3.1.1.1

Table 8 Proportion of Measurement Points That Met the Target Hb Level (10.0 to 12.0 g/dL) from Weeks 18 to 24 (FAS)

	Darbepoetin alfa (N=151)	ASP1517 (N=150)
Proportion of Measurement Points That Met the Target Hb Level from Weeks 18 to 24 (%)		
n	138	125
Mean	86.99	85.67
SD	22.21	22.66
Min	0.0	0.0
Median	100.00	100.00
Max	100.0	100.0
Difference of Means	-	-1.32
95% CI of Difference	-	(-6.77, 4.14)

CI: confidence interval

Source: Table 12.3.6.1, Table 12.3.6.2

Table 9 Rate of Rise in Hb Levels (FAS)

	Darbepoetin alfa (N=151)	ASP1517 (N=150)
Rate of Rise in Hb Levels (g/dL/week) †		
n	151	150
Mean	-0.017	0.129
SD	0.195	0.331
Min	-0.50	-0.95
Median	-0.030	0.060
Max	0.65	1.30

† Rate of rise in Hb levels (g/dL/week) from week 0 to at earliest date of week 4, discontinuation or dose adjustment.

Source: Table 12.3.12.1

Table 10 Categorized Rate of Rise in Hb Levels, Pattern 1 (FAS)

	Darbepoetin alfa (N=151)	ASP1517 (N=150)
Rate of Rise in Hb Levels (g/dL/week) †		
≤ 0.1	114 (75.5%)	81 (54.0%)
> 0.1 to ≤ 0.2	20 (13.2%)	17 (11.3%)
> 0.2 to ≤ 0.3	11 (7.3%)	14 (9.3%)
> 0.3 to ≤ 0.4	3 (2.0%)	16 (10.7%)
> 0.4 to ≤ 0.5	2 (1.3%)	6 (4.0%)
> 0.5	1 (0.7%)	16 (10.7%)

† Rate of rise in Hb levels (g/dL/week) from week 0 to at earliest date of week 4, discontinuation or dose adjustment.

Source: Table 12.3.12.2

Table 11 Common (≥ 3% in Any Randomization Arm) Treatment-emergent Adverse Events (SAF)

MedDRA version 19.0 System Organ Class Preferred Term	Darbepoetin alfa (N=152)	ASP1517 (N=150)	Total (N=302)
Overall	**126 (82.9%)**	**129 (86.0%)**	**255 (84.4%)**
Eye disorders	**13 (8.6%)**	**18 (12.0%)**	**31 (10.3%)**
Retinal haemorrhage	6 (3.9%)	5 (3.3%)	11 (3.6%)
Gastrointestinal disorders	**28 (18.4%)**	**42 (28.0%)**	**70 (23.2%)**
Diarrhoea	12 (7.9%)	11 (7.3%)	23 (7.6%)
Vomiting	3 (2.0%)	10 (6.7%)	13 (4.3%)
Dental caries	0	5 (3.3%)	5 (1.7%)
Infections and infestations	**58 (38.2%)**	**67 (44.7%)**	**125 (41.4%)**
Nasopharyngitis	40 (26.3%)	52 (34.7%)	92 (30.5%)
Upper respiratory tract infection	2 (1.3%)	5 (3.3%)	7 (2.3%)
Injury, poisoning and procedural complications	**45 (29.6%)**	**41 (27.3%)**	**86 (28.5%)**
Shunt stenosis	13 (8.6%)	11 (7.3%)	24 (7.9%)
Contusion	10 (6.6%)	10 (6.7%)	20 (6.6%)
Shunt occlusion	3 (2.0%)	7 (4.7%)	10 (3.3%)
Wound	5 (3.3%)	3 (2.0%)	8 (2.6%)
Procedural hypotension	1 (0.7%)	5 (3.3%)	6 (2.0%)
Metabolism and nutrition disorders	**3 (2.0%)**	**12 (8.0%)**	**15 (5.0%)**
Hyperkalaemia	1 (0.7%)	5 (3.3%)	6 (2.0%)
Musculoskeletal and connective tissue disorders	**22 (14.5%)**	**18 (12.0%)**	**40 (13.2%)**
Back pain	7 (4.6%)	3 (2.0%)	10 (3.3%)
Skin and subcutaneous tissue disorders	**13 (8.6%)**	**18 (12.0%)**	**31 (10.3%)**
Skin exfoliation	2 (1.3%)	6 (4.0%)	8 (2.6%)
Vascular disorders	**15 (9.9%)**	**14 (9.3%)**	**29 (9.6%)**
Hypertension	7 (4.6%)	5 (3.3%)	12 (4.0%)
Internal haemorrhage	6 (3.9%)	2 (1.3%)	8 (2.6%)

Source: Table 12.6.1.2

Table 12 Drug-related Treatment-emergent Adverse Events (SAF)

MedDRA version 19.0 System Organ Class Preferred Term	Darbepoetin alfa (N=152)	ASP1517 (N=150)	Total (N=302)
Overall	**20 (13.2%)**	**33 (22.0%)**	**53 (17.5%)**
Cardiac disorders	**3 (2.0%)**	**2 (1.3%)**	**5 (1.7%)**
Angina pectoris	1 (0.7%)	0	1 (0.3%)
Atrioventricular block complete	1 (0.7%)	0	1 (0.3%)
Bradycardia	1 (0.7%)	0	1 (0.3%)
Cardiac failure congestive	0	1 (0.7%)	1 (0.3%)
Coronary artery stenosis	0	1 (0.7%)	1 (0.3%)
Ear and labyrinth disorders	**2 (1.3%)**	**2 (1.3%)**	**4 (1.3%)**
Vertigo	2 (1.3%)	1 (0.7%)	3 (1.0%)
Sudden hearing loss	0	1 (0.7%)	1 (0.3%)
Eye disorders	**4 (2.6%)**	**5 (3.3%)**	**9 (3.0%)**
Retinal haemorrhage	4 (2.6%)	3 (2.0%)	7 (2.3%)
Diabetic retinopathy	0	1 (0.7%)	1 (0.3%)
Macular oedema	0	1 (0.7%)	1 (0.3%)
Retinal exudates	1 (0.7%)	0	1 (0.3%)
Gastrointestinal disorders	**3 (2.0%)**	**8 (5.3%)**	**11 (3.6%)**
Nausea	1 (0.7%)	2 (1.3%)	3 (1.0%)
Vomiting	0	3 (2.0%)	3 (1.0%)
Abdominal pain upper	1 (0.7%)	1 (0.7%)	2 (0.7%)
Diarrhoea	0	2 (1.3%)	2 (0.7%)
Constipation	0	1 (0.7%)	1 (0.3%)
Dyspepsia	0	1 (0.7%)	1 (0.3%)
Faeces soft	1 (0.7%)	0	1 (0.3%)
General disorders and administration site conditions	**1 (0.7%)**	**3 (2.0%)**	**4 (1.3%)**
Malaise	0	2 (1.3%)	2 (0.7%)
Chest pain	0	1 (0.7%)	1 (0.3%)
Gait disturbance	1 (0.7%)	0	1 (0.3%)
Oedema	0	1 (0.7%)	1 (0.3%)
Injury, poisoning and procedural complications	**2 (1.3%)**	**1 (0.7%)**	**3 (1.0%)**
Shunt occlusion	1 (0.7%)	1 (0.7%)	2 (0.7%)
Shunt stenosis	1 (0.7%)	1 (0.7%)	2 (0.7%)
Investigations	**2 (1.3%)**	**2 (1.3%)**	**4 (1.3%)**
Haemoglobin decreased	1 (0.7%)	1 (0.7%)	2 (0.7%)
Blood creatine phosphokinase increased	0	1 (0.7%)	1 (0.3%)
Lipase increased	1 (0.7%)	0	1 (0.3%)
Metabolism and nutrition disorders	**0**	**6 (4.0%)**	**6 (2.0%)**
Hypoalbuminaemia	0	3 (2.0%)	3 (1.0%)
Hyperkalaemia	0	2 (1.3%)	2 (0.7%)
Hyperphosphataemia	0	1 (0.7%)	1 (0.3%)
Decreased appetite	0	1 (0.7%)	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (1.3%)**	**0**	**2 (0.7%)**
Malignant neoplasm of renal pelvis	1 (0.7%)	0	1 (0.3%)
Lip and/or oral cavity cancer	1 (0.7%)	0	1 (0.3%)

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MedDRA version 19.0 System Organ Class Preferred Term	Darbepoetin alfa (N=152)	ASP1517 (N=150)	Total (N=302)
Nervous system disorders	**2 (1.3%)**	**2 (1.3%)**	**4 (1.3%)**
Cerebral infarction	0	1 (0.7%)	1 (0.3%)
Headache	1 (0.7%)	0	1 (0.3%)
Hypoaesthesia	0	1 (0.7%)	1 (0.3%)
Orthostatic intolerance	1 (0.7%)	0	1 (0.3%)
Psychiatric disorders	**0**	**2 (1.3%)**	**2 (0.7%)**
Anxiety	0	1 (0.7%)	1 (0.3%)
Insomnia	0	1 (0.7%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Pleural effusion	0	1 (0.7%)	1 (0.3%)
Skin and subcutaneous tissue disorders	**1 (0.7%)**	**0**	**1 (0.3%)**
Eczema	1 (0.7%)	0	1 (0.3%)
Vascular disorders	**5 (3.3%)**	**6 (4.0%)**	**11 (3.6%)**
Hypertension	3 (2.0%)	5 (3.3%)	8 (2.6%)
Jugular vein thrombosis	0	1 (0.7%)	1 (0.3%)
Deep vein thrombosis	0	1 (0.7%)	1 (0.3%)
Peripheral arterial occlusive disease	1 (0.7%)	0	1 (0.3%)
Internal haemorrhage	1 (0.7%)	0	1 (0.3%)

Source: Table 12.6.1.3

Table 13 Treatment-emergent Serious Adverse Events (SAF)

MedDRA version 19.0 System Organ Class Preferred Term	Darbepoetin alfa (N=152)	ASP1517 (N=150)	Total (N=302)
Overall	**22 (14.5%)**	**31 (20.7%)**	**53 (17.5%)**
Cardiac disorders	**4 (2.6%)**	**5 (3.3%)**	**9 (3.0%)**
Angina pectoris	2 (1.3%)	1 (0.7%)	3 (1.0%)
Acute myocardial infarction	0	1 (0.7%)	1 (0.3%)
Aortic valve stenosis	1 (0.7%)	0	1 (0.3%)
Atrioventricular block complete	1 (0.7%)	0	1 (0.3%)
Bradycardia	0	1 (0.7%)	1 (0.3%)
Cardiac failure	1 (0.7%)	0	1 (0.3%)
Cardiac failure congestive	0	1 (0.7%)	1 (0.3%)
Coronary artery stenosis	0	1 (0.7%)	1 (0.3%)
Myocardial ischaemia	1 (0.7%)	0	1 (0.3%)
Ear and labyrinth disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Sudden hearing loss	0	1 (0.7%)	1 (0.3%)
Gastrointestinal disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Gastrointestinal haemorrhage	0	1 (0.7%)	1 (0.3%)
General disorders and administration site conditions	**0**	**1 (0.7%)**	**1 (0.3%)**
Vascular stent occlusion	0	1 (0.7%)	1 (0.3%)
Infections and infestations	**0**	**3 (2.0%)**	**3 (1.0%)**
Cellulitis	0	2 (1.3%)	2 (0.7%)
Urinary tract infection	0	1 (0.7%)	1 (0.3%)
Injury, poisoning and procedural complications	**10 (6.6%)**	**11 (7.3%)**	**21 (7.0%)**
Shunt stenosis	7 (4.6%)	6 (4.0%)	13 (4.3%)
Shunt occlusion	2 (1.3%)	3 (2.0%)	5 (1.7%)
Joint dislocation	0	1 (0.7%)	1 (0.3%)
Subcutaneous haematoma	1 (0.7%)	0	1 (0.3%)
Spinal column injury	0	1 (0.7%)	1 (0.3%)
Investigations	**1 (0.7%)**	**2 (1.3%)**	**3 (1.0%)**
Arteriogram coronary	0	1 (0.7%)	1 (0.3%)
Haemoglobin decreased	1 (0.7%)	0	1 (0.3%)
Investigation	0	1 (0.7%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Lumbar spinal stenosis	0	1 (0.7%)	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (2.6%)**	**1 (0.7%)**	**5 (1.7%)**
Basal cell carcinoma	1 (0.7%)	0	1 (0.3%)
Gastric cancer	0	1 (0.7%)	1 (0.3%)
Malignant neoplasm of renal pelvis	1 (0.7%)	0	1 (0.3%)
Transitional cell carcinoma	1 (0.7%)	0	1 (0.3%)
Lip and/or oral cavity cancer	1 (0.7%)	0	1 (0.3%)
Nervous system disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Cerebral infarction	0	1 (0.7%)	1 (0.3%)
Psychiatric disorders	**1 (0.7%)**	**0**	**1 (0.3%)**
Suicidal ideation	1 (0.7%)	0	1 (0.3%)

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MedDRA version 19.0 System Organ Class Preferred Term	Darbepoetin alfa (N=152)	ASP1517 (N=150)	Total (N=302)
Respiratory, thoracic and mediastinal disorders	**1 (0.7%)**	**1 (0.7%)**	**2 (0.7%)**
Asthma	0	1 (0.7%)	1 (0.3%)
Pulmonary oedema	1 (0.7%)	0	1 (0.3%)
Surgical and medical procedures	**2 (1.3%)**	**1 (0.7%)**	**3 (1.0%)**
Angioplasty	1 (0.7%)	0	1 (0.3%)
Coronary angioplasty	0	1 (0.7%)	1 (0.3%)
Large intestinal polypectomy	1 (0.7%)	0	1 (0.3%)
Vascular disorders	**1 (0.7%)**	**5 (3.3%)**	**6 (2.0%)**
Deep vein thrombosis	0	2 (1.3%)	2 (0.7%)
Orthostatic hypotension	0	1 (0.7%)	1 (0.3%)
Venous occlusion	0	1 (0.7%)	1 (0.3%)
Peripheral arterial occlusive disease	1 (0.7%)	0	1 (0.3%)
Subclavian vein stenosis	0	1 (0.7%)	1 (0.3%)

Source: Table 12.6.1.7

Table 14 Treatment-emergent Adverse Events Leading to Withdrawal of Treatment (SAF)

MedDRA version 19.0 System Organ Class Preferred Term	Darbepoetin alfa (N=152)	ASP1517 (N=150)	Total (N=302)
Overall	**8 (5.3%)**	**13 (8.7%)**	**21 (7.0%)**
Blood and lymphatic system disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Haemorrhagic anaemia	0	1 (0.7%)	1 (0.3%)
Cardiac disorders	**2 (1.3%)**	**2 (1.3%)**	**4 (1.3%)**
Acute myocardial infarction	0	1 (0.7%)	1 (0.3%)
Angina pectoris	1 (0.7%)	0	1 (0.3%)
Atrioventricular block complete	1 (0.7%)	0	1 (0.3%)
Cardiac failure congestive	0	1 (0.7%)	1 (0.3%)
Ear and labyrinth disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Sudden hearing loss	0	1 (0.7%)	1 (0.3%)
Eye disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Macular oedema	0	1 (0.7%)	1 (0.3%)
General disorders and administration site conditions	**0**	**1 (0.7%)**	**1 (0.3%)**
Vascular stent occlusion	0	1 (0.7%)	1 (0.3%)
Infections and infestations	**0**	**1 (0.7%)**	**1 (0.3%)**
Cellulitis	0	1 (0.7%)	1 (0.3%)
Investigations	**1 (0.7%)**	**0**	**1 (0.3%)**
Haemoglobin decreased	1 (0.7%)	0	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (2.6%)**	**0**	**4 (1.3%)**
Basal cell carcinoma	1 (0.7%)	0	1 (0.3%)
Malignant neoplasm of renal pelvis	1 (0.7%)	0	1 (0.3%)
Transitional cell carcinoma	1 (0.7%)	0	1 (0.3%)
Lip and/or oral cavity cancer	1 (0.7%)	0	1 (0.3%)
Nervous system disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Cerebral infarction	0	1 (0.7%)	1 (0.3%)
Psychiatric disorders	**0**	**1 (0.7%)**	**1 (0.3%)**
Anxiety	0	1 (0.7%)	1 (0.3%)
Surgical and medical procedures	**0**	**1 (0.7%)**	**1 (0.3%)**
Coronary angioplasty	0	1 (0.7%)	1 (0.3%)
Vascular disorders	**1 (0.7%)**	**3 (2.0%)**	**4 (1.3%)**
Hypertension	0	1 (0.7%)	1 (0.3%)
Jugular vein thrombosis	0	1 (0.7%)	1 (0.3%)
Deep vein thrombosis	0	1 (0.7%)	1 (0.3%)
Peripheral arterial occlusive disease	1 (0.7%)	0	1 (0.3%)

Source: Table 12.6.1.9

Table 15 New or Worsening Retinal Hemorrhage (SAF)

Analysis Visit	Darbepoetin alfa (N=152)	ASP1517 (N=150)	Total (N=302)
Treatment Period	53/145 (36.6%)	46/142 (32.4%)	99/287 (34.5%)
Week 12 compared to baseline	35/136 (25.7%)	31/132 (23.5%)	66/268 (24.6%)
Week 24 compared to baseline	34/126 (27.0%)	30/113 (26.5%)	64/239 (26.8%)
End of Treatment	42/145 (29.0%)	34/142 (23.9%)	76/287 (26.5%)

Source: Table 12.6.5.1.1.3.1