Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP3325		

SYNOPSIS

Title of Study: A Phase 1, Single and Multiple Dosing Study of ASP3325 to Evaluate Safety, Pharmacokinetics and Pharmacodynamics of ASP3325 in Patients With Chronic Kidney Disease and Hyperphosphatemia Undergoing Hemodialysis

Investigators/Coordinating Investigator: [redacted]

Study Center(s): 1 site (Part 1) and 4 sites (Part 2) in Japan

Publication Based on the Study: None

Study Period: Approximately 6 months

Study Initiation Date (Date of First Informed Consent): 12 May 2014

Study Completion Date (Date of Last Evaluation): 04 Nov 2014

Phase of Development: Phase 1

Objectives: The objectives of the study were to assess the following in patients with chronic kidney disease (CKD) and hyperphosphatemia undergoing hemodialysis.

Part 1

- To assess the pharmacokinetics, safety and tolerability of a single oral dose of ASP3325

Part 2

- To assess the pharmacodynamics, pharmacokinetics and safety of multiple oral doses of ASP3325 administered tid before or just after each meal

Methodology: This study consisted of two separate parts [Figure 1].

Part 1

This part was an open-label, uncontrolled study to evaluate the pharmacokinetics and safety of a single dose of ASP3325 in patients undergoing hemodialysis. After washout of therapeutic medication for hyperphosphatemia, 6 subjects were to receive a single oral dose of ASP3325 (300 mg) on a non-dialysis day (Day 1).

Part 2

This part was a multicenter, randomized, 2-arm, open-label, uncontrolled study to evaluate the pharmacodynamics, pharmacokinetics and safety of multiple oral doses of ASP3325 100 mg tid before or just after each meal in patients undergoing hemodialysis.

Eligible subjects at screening were entered in the washout period and their phosphate-binding treatment was stopped. Twenty subjects with a serum inorganic phosphorus (Pi) level of ≥ 6.0 and < 10.0 mg/dL during the washout period (Week 1 or Week 2 of the washout period) and an increase in serum Pi of ≥ 1.5 mg/dL from the start day of the washout period were to be randomized to the before meal or after meal group in equal numbers and ASP3325 was administered as multiple oral doses of 100 mg tid for 2 weeks until Day 14.

Figure 1 Study Flow Chart

Part 1

	Screening	Washout period		Assessment period				
Informed consent	Day −30 to Day −12	Day −5	Day −1	Day 1 Baseline	Day 2	Day 3	Day 5	Day 7
	Hemodialysis (HD)	HD	HD			HD	HD	HD
	x	x	x (hospitalization)			x	x	x
	Confirmation of inclusion/exclusion criteria	P binder washout		Day 1: study drug administration, pharmacokinetics (PK), safety		PK, safety	PK, safety	Follow-up

x: visit

Part 2

	Washout period			Study drug administration period							Follow-up period
Informed consent	Start day of washout	Washout 1w	Washout 2w	Day 1 Baseline	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Follow-up
	Day −21	Day −14	Day −7								Day 22
	HD	HD	HD	HD	HD	HD	HD	HD	HD	HD	HD
	x	x	x	x	x	x	x	x	x	x	x
	P binder washout			Day 1 to Day 14: study drug administration (tid)							Follow-up
	Confirmation of inclusion/exclusion criteria			Pharmacodynamics, PK, safety							

x: visit

Number of Patients (Planned, Enrolled and Analyzed):

Part 1

Planned: 6 subjects

Analyzed: 5 subjects in the safety analysis set (SAF) and pharmacokinetics analysis set (PKAS)

Part 2

Planned: 20 subjects (10 subjects per arm)

Analyzed: 19 subjects in the SAF, 18 subjects in the PKAS and 17 subjects in the pharmacodynamics analysis set (PDAS)

Diagnosis and Main Criteria for Inclusion: Patients with CKD and hyperphosphatemia (a pre-dialysis serum Pi level of ≥ 6.0 and < 10.0 mg/dL and an increase in serum Pi of ≥ 1.5 mg/dL after the maximum dialysis interval) undergoing hemodialysis with age of ≥ 20 years and < 75 years.

Test Product, Dose and Mode of Administration, Batch Numbers: ASP3325 tablet 50 mg (Packaging lot number: [redacted])

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

Part 1: single dose

Part 2: 2 weeks

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable

Criteria for Evaluation:

Pharmacokinetics

- Plasma concentration of the unchanged drug (ASP3325)

Pharmacodynamics

- Serum phosphorus level and corrected serum Ca level
- Serum intact parathyroid hormone (PTH), serum fibroblast growth factor-23 (FGF23)

Safety

- Adverse events (AEs)
- Laboratory tests (hematology and biochemistry)
- Vital signs (body temperature, blood pressure and pulse rate)
- Physical examination
- 12-lead electrocardiogram (ECG)

Other

- Normalized dialysis dose (Kt/V) urea, normalized protein catabolic rate (nPCR)

Statistical Methods:

Pharmacokinetics

The non-compartmental methods were employed to calculate pharmacokinetic parameters. The following pharmacokinetic parameters were estimated using plasma concentrations of ASP3325 and actual elapsed times from dosing.

- Part 1
  C_{max}, t_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$, Vz/F, CL/F
- Part 2
  C_{trough}

Concentrations and pharmacokinetic parameters were summarized descriptively. In Part 2, these summaries were provided for the before meal and after meal groups. Subjects who vomited during study were excluded from PKAS.

Pharmacodynamics

The following analyses were performed for the PDAS by treatment group.

- For each pharmacodynamic variable, descriptive statistics of measured values at each time point and changes from baseline were calculated.
- For each variable, mean ± SD plot of measured values were prepared.

Changes from baseline to end of treatment in serum phosphorus were analyzed with analysis of covariance model which included the baseline measurements as a covariate. The adjusted mean for each treatment group and the adjusted mean difference between treatment groups with 95% confidence interval were presented.

Safety

Treatment-emergent adverse event (TEAE) was defined as an AE observed after starting administration of the study drug. The coding dictionary for this study was MedDRA (Version 16.0). The number and percentage of subjects with TEAEs, drug-related TEAEs, deaths, serious TEAEs, TEAEs leading to permanent discontinuation were summarized.

Other safety variables were analyzed descriptively.

Summary of Results/Conclusions:

Study Population: In Part 1, 6 subjects signed informed consent form [Figure 2]. Of these, 1 subject discontinued before taking study drug due to screen failure and 5 subjects took study drug. All 5 subjects completed the study.

All 5 subjects who took study drug were included in the SAF and PKAS.

Of the 5 subjects in the SAF in Part 1, all subjects were male [Table 1]. The mean age was 64.8 years and the mean body weight on Day 1 was 66.02 kg. The primary disease of CKD was diabetic nephropathy in all subjects. The mean duration of hemodialysis was 45.6 months (range: 7 to 83 months). The hemodialysis timing of the week was Monday, Wednesday and Friday, the hemodialysis time of the week was 720 min/week and the blood flow rate was 200 mL/min in all subjects.

In Part 2, 30 subjects signed informed consent form [Figure 3]. Of these, 11 subjects discontinued before randomization due to screen failure and 19 subjects were randomized and took study drug.

A total of 17 of 19 (89.5%) subjects completed the study and 2 (10.5%) subjects discontinued. The primary reasons for discontinuation were “AE” in 1 subject and “withdrawal by subject” in 1 subject.

All 19 randomized subjects were included in the SAF, 18 (94.7%) subjects were included in the PKAS and 17 (89.5%) subjects were included in the PDAS.

Of the 19 subjects in the SAF in Part 2, 10 (52.6%) subjects were female and 9 (47.4%) subjects were male [Table 2]. The mean age was 61.5 years and the mean body weight on Day 1 was 56.94 kg. The majority of subjects had the primary disease of CKD of chronic glomerulonephritis (42.1%) or diabetic nephropathy (31.6%). The mean duration of hemodialysis was 83.3 months (range: 9 to 232 months). The hemodialysis timing of the week was Monday, Wednesday and Friday in 12 (63.2%) subjects and Tuesday, Thursday and Saturday in 7 (36.8%) subjects. The mean hemodialysis time of the week was 723.2 min/week and the mean blood flow rate was 214.7 mL/min.

Pharmacokinetic Results: Following a single oral dose of ASP3325 300 mg on Day 1 in Part 1, ASP3325 was rapidly absorbed to reach peak plasma concentration with median t_{max} of 1.483 h (excluding the subject who

vomited) [Figure 4, Table 3]. The mean C_{max} was 416.2 ng/mL, the mean AUC_{inf} was 3151 ng·h/mL and the mean $t_{1/2}$ was 24.38 h.

Following multiple oral doses of ASP3325 100 mg tid before meal in Part 2, the individual C_{trough} seemed to reach steady state on Day 3 in most subjects [End-of-Text Figure 12.4.2B.1 and Figure 12.4.2B.2]. The mean and median C_{trough} was generally higher in the after meal group compared with the before meal group [Table 4].

Pharmacodynamic Results: ASP3325 did not have an effect on serum phosphorus levels in patients undergoing hemodialysis after 2 weeks of treatment [Figure 5]. No apparent differences were observed in time courses of serum phosphorus in individual subjects between the before meal and after meal groups [Figure 6].

The mean corrected serum Ca slightly decreased in the before meal group and slightly increased in the after meal group during study treatment.

No consistent trend was observed in the median change from baseline in serum intact PTH.

The mean serum FGF23 increased during study treatment.

Safety Results: ASP3325 was safe and well tolerated in patients with CKD and hyperphosphatemia undergoing hemodialysis.

In Part 1, a TEAE (vomiting) was reported in 1 subject and the event was considered related to the study drug [Table 5, Table 6]. No deaths or serious TEAEs were reported.

In Part 2, TEAEs were reported in 6 of 19 (31.6%) subjects and drug-related TEAEs were reported in 3 (15.8%) subjects [Table 7]. TEAEs reported in ≥ 2 subjects included diarrhoea and vomiting (2 subjects each) and all these events were considered related to the study drug [Table 8]. No deaths or serious TEAEs were reported. TEAEs leading to permanent discontinuation were reported in 2 (10.5%) subjects and all these events were considered related to the study drug. All these events were mild or moderate in severity.

No notable safety concerns were identified in clinical laboratory evaluations, vital signs, ECGs or body weight.

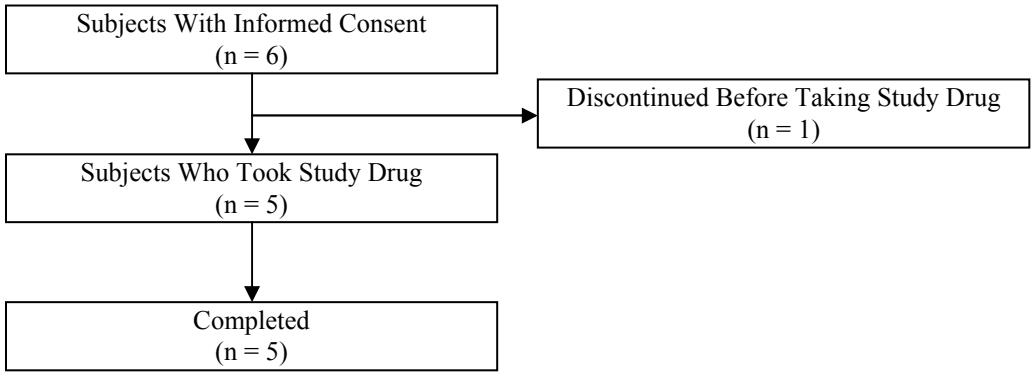
CONCLUSIONS:

In this study, the pharmacodynamics, pharmacokinetics and safety of ASP3325 were assessed in patients with CKD and hyperphosphatemia undergoing hemodialysis. A single oral dose of ASP3325 (300 mg) was administered in Part 1 and multiple oral doses of ASP3325 (100 mg tid) were administered for 2 weeks in Part 2.

ASP3325 was rapidly absorbed following a single oral dose and almost reached steady state on Day 3 following multiple oral doses in patients with CKD and hyperphosphatemia undergoing hemodialysis. ASP3325 did not have an effect on serum phosphorus levels in patients undergoing hemodialysis after 2 weeks of treatment. ASP3325 was safe and well tolerated.

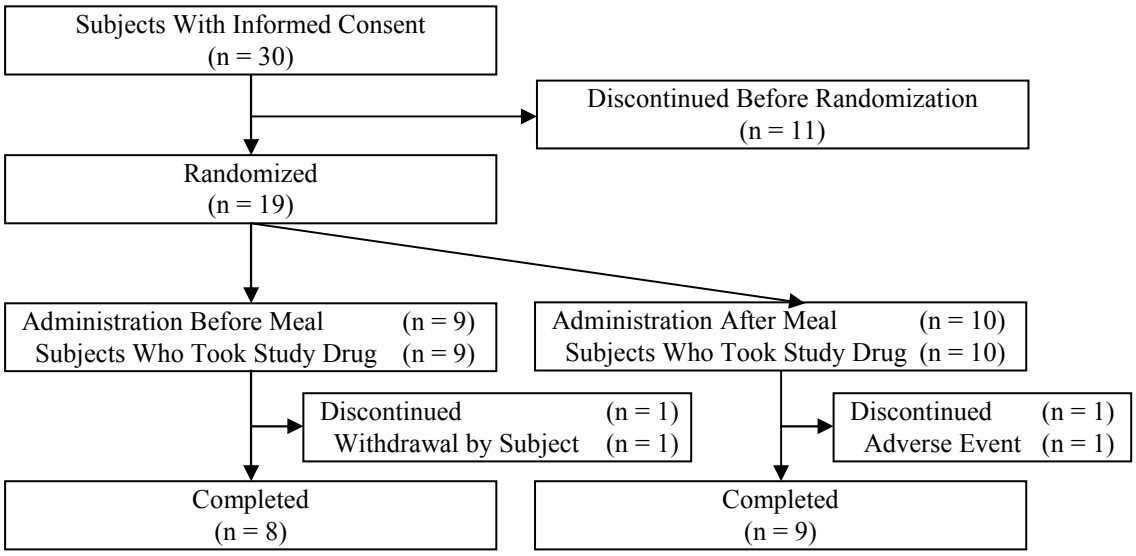
Date of Report: 12 May 2015

Figure 2 Disposition of Subjects: Part 1



Source: Table 12.1.1A.1, Table 12.1.1A.3

Figure 3 Disposition of Subjects: Part 2



Source: Table 12.1.1B.1, Table 12.1.1B.3

Table 1 Demographics and Baseline Characteristics (SAF): Part 1

Parameter	Category/Statistic	Total (N=5)
Age (years)	n	5
	Mean	64.8
	SD	5.5
	Min	57
	Median	65.0
	Max	72
Age (years)	< 65	2 (40.0%)
	65 ≤	3 (60.0%)
Sex	Male	5 (100.0%)
	Female	0
Race	Asian	5 (100.0%)
	Other	0
Height (cm)	n	5
	Mean	167.64
	SD	6.42
	Min	161.9
	Median	165.90
	Max	178.5
Weight on Day 1 (kg)	n	5
	Mean	66.02
	SD	4.37
	Min	61.8
	Median	65.50
	Max	73.2
Primary Disease of CKD	Chronic Glomerulonephritis	0
	Diabetic Nephropathy	5 (100.0%)
	Chronic Pyelonephritis	0
	Polycystic Kidney	0
	Nephrosclerosis	0
	Other	0
Duration of Hemodialysis (month)†	n	5
	Mean	45.6
	SD	30.8
	Min	7
	Median	50.0
	Max	83
Categorized Duration of Hemodialysis (month)†	< 6	0
	≥6 to < 12	1 (20.0%)
	≥12 to < 36	1 (20.0%)
	≥36 to < 60	1 (20.0%)
	≥60 to < 120	2 (40.0%)
	120 ≤	0
Hemodialysis Modality†	HD	5 (100.0%)
	HF	0
	Online-HDF	0
	Off-line HDF	0
	Other	0

Table continued on next page

Parameter	Category/Statistic	Total (N=5)
Categorized Dialysis Ca Concentration (mEq/L)†	2.5	5 (100.0%)
	2.75	0
	3.0	0
	Other	0
Dry Weight (kg)†	n	5
	Mean	65.70
	SD	4.34
	Min	61.8
	Median	65.50
	Max	72.8
Medical History	No	0
	Yes	5 (100.0%)

HD: hemodialysis, HF: hemofiltration, HDF: hemodiafiltration
† Condition at start of washout period (Day −5)
Source: Table 12.1.2A.1

Table 2 Demographics and Baseline Characteristics (SAF): Part 2

Parameter	Category/Statistic	Before Meal (N=9)	After Meal (N=10)	Total (N=19)
Age (years)	n	9	10	19
	Mean	60.7	62.2	61.5
	SD	10.0	8.9	9.2
	Min	47	44	44
	Median	64.0	63.0	64.0
	Max	73	73	73
Age (years)	< 65	5 (55.6%)	7 (70.0%)	12 (63.2%)
	65 ≤	4 (44.4%)	3 (30.0%)	7 (36.8%)
Sex	Male	4 (44.4%)	5 (50.0%)	9 (47.4%)
	Female	5 (55.6%)	5 (50.0%)	10 (52.6%)
Race	Asian	9 (100.0%)	10 (100.0%)	19 (100.0%)
	Other	0	0	0
Height (cm)	n	9	10	19
	Mean	157.02	156.35	156.67
	SD	8.63	7.38	7.78
	Min	142.0	147.0	142.0
	Median	159.90	158.00	159.50
	Max	167.0	167.0	167.0
Weight on Day 1 (kg)	n	9	10	19
	Mean	61.21	53.10	56.94
	SD	12.74	13.78	13.58
	Min	35.1	37.0	35.1
	Median	62.70	49.35	51.90
	Max	77.3	86.7	86.7
Primary Disease of CKD	Chronic Glomerulonephritis	4 (44.4%)	4 (40.0%)	8 (42.1%)
	Diabetic Nephropathy	2 (22.2%)	4 (40.0%)	6 (31.6%)
	Chronic Pyelonephritis	0	0	0
	Polycystic Kidney	2 (22.2%)	0	2 (10.5%)
	Nephrosclerosis	0	1 (10.0%)	1 (5.3%)
	Other	1 (11.1%)	1 (10.0%)	2 (10.5%)

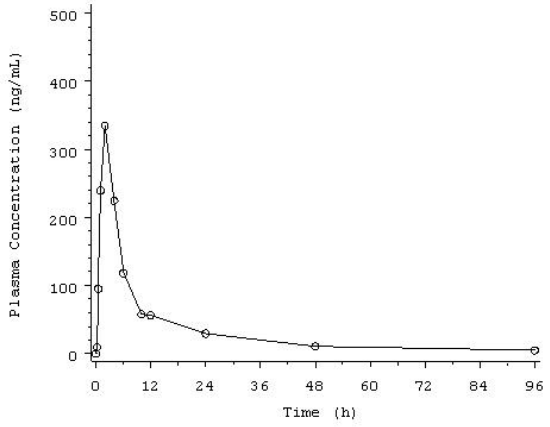
Table continued on next page

Parameter	Category/Statistic	Before Meal (N=9)	After Meal (N=10)	Total (N=19)
Duration of Hemodialysis (month)†	n	9	10	19
	Mean	76.9	89.1	83.3
	SD	47.7	70.5	59.5
	Min	29	9	9
	Median	77.0	92.0	88.0
	Max	163	232	232
Categorized Duration of Hemodialysis (month)†	< 6	0	0	0
	≥6 to < 12	0	1 (10.0%)	1 (5.3%)
	≥12 to < 36	4 (44.4%)	2 (20.0%)	6 (31.6%)
	≥36 to < 60	0	1 (10.0%)	1 (5.3%)
	≥60 to < 120	4 (44.4%)	4 (40.0%)	8 (42.1%)
	120 ≤	1 (11.1%)	2 (20.0%)	3 (15.8%)
Hemodialysis Modality†	HD	7 (77.8%)	6 (60.0%)	13 (68.4%)
	HF	0	0	0
	Online-HDF	2 (22.2%)	4 (40.0%)	6 (31.6%)
	Off-line HDF	0	0	0
	Other	0	0	0
Categorized Dialysis Ca Concentration (mEq/L)†	2.5	0	0	0
	2.75	0	0	0
	3.0	9 (100.0%)	10 (100.0%)	19 (100.0%)
	Other	0	0	0
Dry Weight (kg)†	n	9	10	19
	Mean	59.03	50.74	54.67
	SD	12.55	13.09	13.18
	Min	33.0	36.5	33.0
	Median	62.00	47.20	50.80
	Max	75.0	83.0	83.0
Medical History	No	0	0	0
	Yes	9 (100.0%)	10 (100.0%)	19 (100.0%)
Visit of Collection of Samples in Which the Serum Phosphorus Level Met the Inclusion Criteria	1 Week After Washout	7 (77.8%)	7 (70.0%)	14 (73.7%)
	2 Weeks After Washout	2 (22.2%)	3 (30.0%)	5 (26.3%)

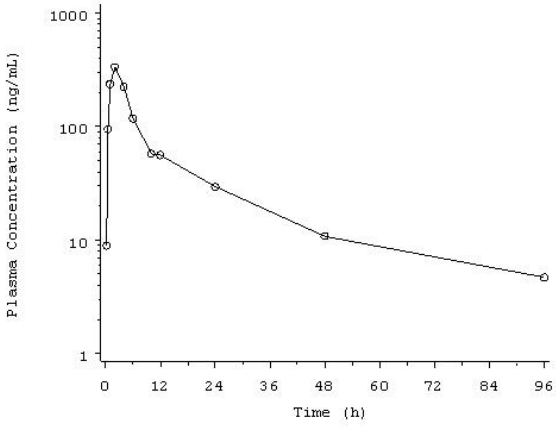
HD: hemodialysis, HF: hemofiltration, HDF: hemodiafiltration
† Condition at start of washout period
Source: Table 12.1.2B.1

Figure 4 **Mean Plasma Concentration of ASP3325 (Excluding the Subject Who Vomited) (PKAS): Part 1**

Linear Scale



Semi-log Scale



○ : 300 mg

Dose: 300 mg single dose, Visit: Day 1 (n=4)
Source: Figure 12.4.2A.1

Table 3 **Plasma Pharmacokinetic Parameters of ASP3325 (Excluding the Subject Who Vomited) (PKAS): Part 1**

Statistic	AUC_{last} (ng·h/mL)	AUC_{inf} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
n	4	4	4	4	4	4	4
Mean	2962	3151	416.2	1.938	24.38	154.0	4668
SD	2300	2482	311.6	1.336	6.390	115.6	2410
%CV	77.7	78.8	74.9	-	26.2	75.1	51.6
Min	959	970	161	0.950	16.3	45.6	2099
Median	2366	2525	318.8	1.483	24.64	130.5	4648
Max	6159	6585	866	3.83	31.9	309	7279
GM	2346	2467	343.0	-	23.72	121.6	4160

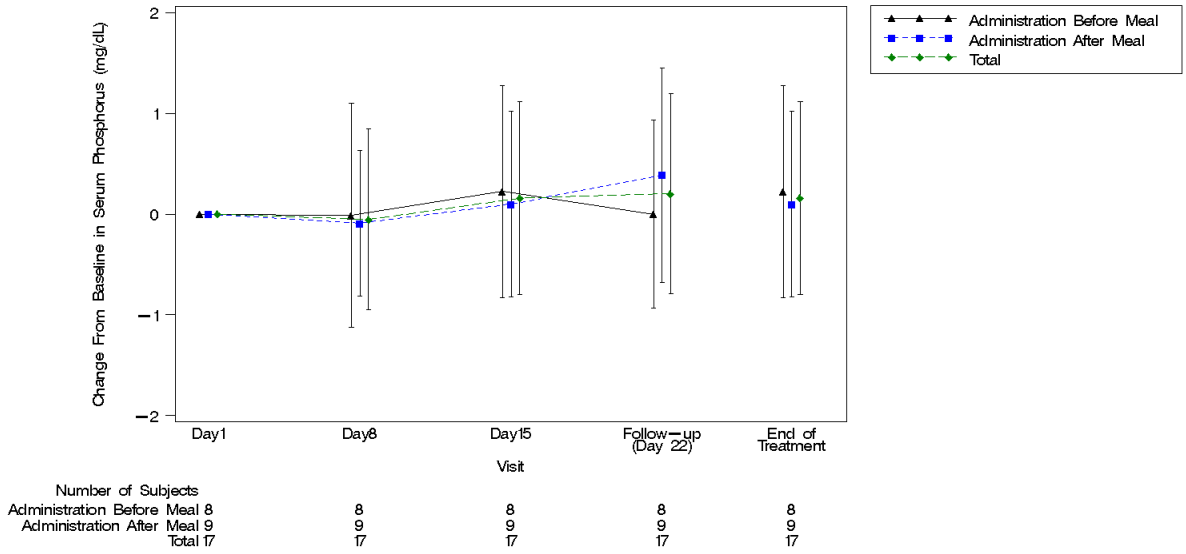
Source: Table 12.4.2A.1

Table 4 **Plasma C_{trough} (ng/mL) of ASP3325 (Excluding the Subject Who Vomited) (PKAS): Part 2**

Treatment Group	Statistic	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15
Before Meal	n	8	8	8	8	8	8
	Mean	99.09	109.9	137.1	206.4	184.7	343.2
	SD	68.69	77.29	98.15	313.7	221.6	685.0
	%CV	69.3	70.3	71.6	152.0	119.9	199.6
	Min	24.7	37.4	29.2	39.2	30.7	25.2
	Median	91.59	88.43	117.1	96.77	109.1	96.02
	Max	243	291	347	974	708	2030
	GM	79.69	93.66	110.4	115.0	115.1	123.1
After Meal	n	9	9	9	9	8	9
	Mean	143.7	179.3	174.6	209.4	352.9	299.8
	SD	81.60	166.7	185.9	190.7	389.5	279.2
	%CV	56.8	93.0	106.5	91.1	110.3	93.1
	Min	45.6	48.1	24.5	32.6	33.3	31.6
	Median	146.2	137.6	93.29	149.5	263.1	178.6
	Max	282	562	591	685	1251	921
	GM	121.8	127.6	107.3	156.2	216.9	199.1

Source: Table 12.4.2B.1, Table 12.4.2B.2

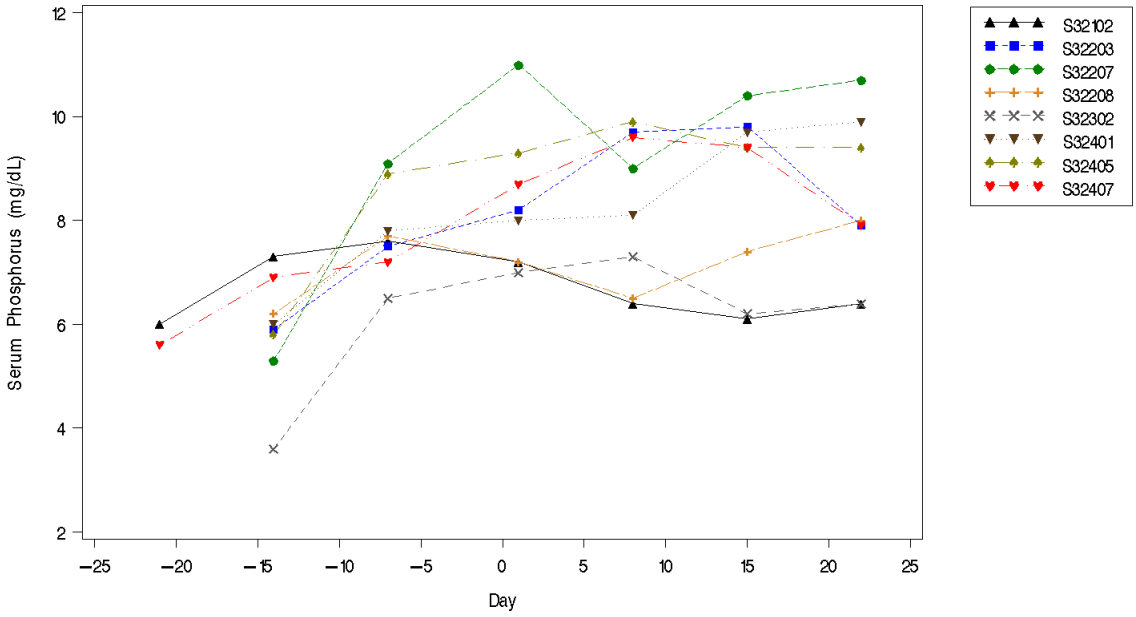
Figure 5 **Mean (± SD) Plot of Change From Baseline in Serum Phosphorus (PDAS): Part 2**



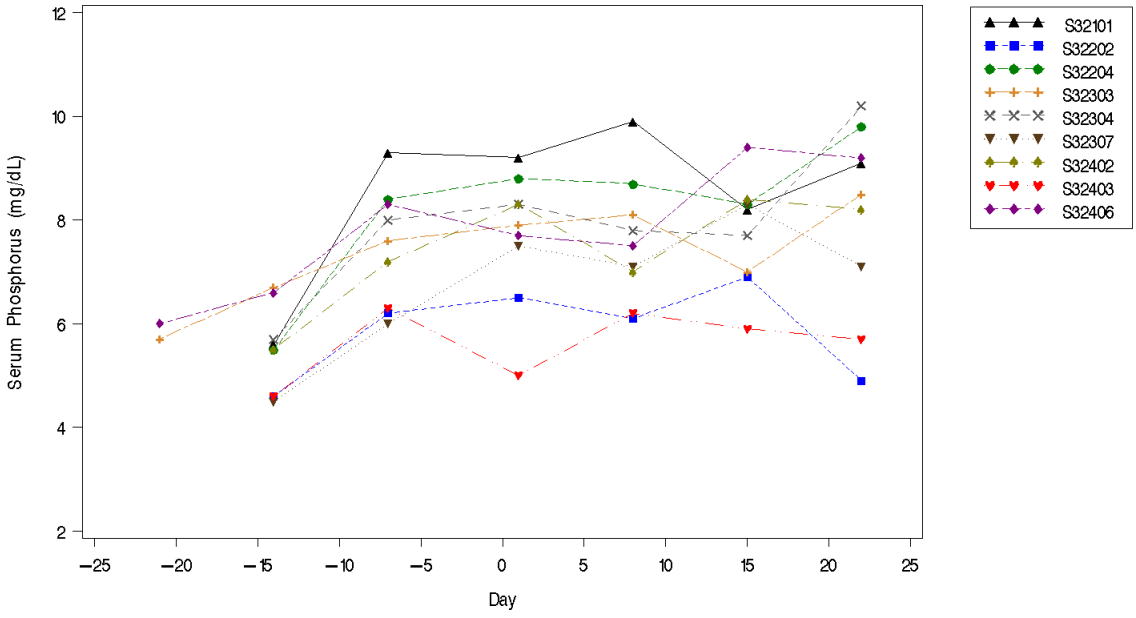
Source: Figure 12.5.1B.3.1

Figure 6 Spaghetti Plot of Serum Phosphorus (PDAS): Part 2

Before Meal



After Meal



Source: Figure 12.5.1B.1.1

Table 5 Overview of Treatment-Emergent Adverse Events (SAF): Part 1

	Total (N=5)
TEAEs	1 (20.0%)
Drug-Related† TEAEs	1 (20.0%)
Serious TEAEs	0
Drug-Related† Serious TEAEs	0
Deaths	0

Number of subjects (%)
† Possible or probable, as assessed by the investigator, or records where relationship was missing
Source: Table 12.6.1A.1

Table 6 Summary of Treatment-Emergent Adverse Events (MedDRA v16.0) (SAF): Part 1

	TEAEs	Drug-Related TEAEs†
System Organ Class Preferred Term	Total (N=5)	Total (N=5)
Overall	1 (20.0%)	1 (20.0%)
Gastrointestinal disorders	1 (20.0%)	1 (20.0%)
Vomiting	1 (20.0%)	1 (20.0%)

Number of subjects (%)
† Possible or probable, as assessed by the investigator, or records where relationship was missing
Source: Table 12.6.1A.2

Table 7 Overview of Treatment-Emergent Adverse Events (SAF): Part 2

	Before Meal (N=9)	After Meal (N=10)	Total (N=19)
TEAEs	2 (22.2%)	4 (40.0%)	6 (31.6%)
Drug-Related† TEAEs	1 (11.1%)	2 (20.0%)	3 (15.8%)
Serious TEAEs	0	0	0
Drug-Related† Serious TEAEs	0	0	0
Deaths	0	0	0
TEAEs Leading to Permanent Discontinuation	1 (11.1%)	1 (10.0%)	2 (10.5%)
Drug-Related† TEAEs Leading to Permanent Discontinuation	1 (11.1%)	1 (10.0%)	2 (10.5%)

Number of subjects (%)
† Possible or probable, as assessed by the investigator, or records where relationship was missing
Source: Table 12.6.1B.1

Table 8 Summary of Treatment-Emergent Adverse Events (MedDRA v16.0) (SAF): Part 2

System Organ Class Preferred Term	TEAEs			Drug-Related TEAEs†		
	Before Meal (N=9)	After Meal (N=10)	Total (N=19)	Before Meal (N=9)	After Meal (N=10)	Total (N=19)
Overall	2 (22.2%)	4 (40.0%)	6 (31.6%)	1 (11.1%)	2 (20.0%)	3 (15.8%)
Gastrointestinal disorders	1 (11.1%)	3 (30.0%)	4 (21.1%)	1 (11.1%)	2 (20.0%)	3 (15.8%)
Diarrhoea	1 (11.1%)	1 (10.0%)	2 (10.5%)	1 (11.1%)	1 (10.0%)	2 (10.5%)
Nausea	0	1 (10.0%)	1 (5.3%)	0	0	0
Vomiting	1 (11.1%)	1 (10.0%)	2 (10.5%)	1 (11.1%)	1 (10.0%)	2 (10.5%)
General disorders and administration site conditions	0	1 (10.0%)	1 (5.3%)	0	1 (10.0%)	1 (5.3%)
Malaise	0	1 (10.0%)	1 (5.3%)	0	1 (10.0%)	1 (5.3%)
Injury, poisoning and procedural complications	0	1 (10.0%)	1 (5.3%)	0	0	0
Contusion	0	1 (10.0%)	1 (5.3%)	0	0	0
Nervous system disorders	1 (11.1%)	0	1 (5.3%)	1 (11.1%)	0	1 (5.3%)
Headache	1 (11.1%)	0	1 (5.3%)	1 (11.1%)	0	1 (5.3%)
Skin and subcutaneous tissue disorders	1 (11.1%)	0	1 (5.3%)	0	0	0
Pruritus	1 (11.1%)	0	1 (5.3%)	0	0	0

Number of subjects (%)
Sorting order: alphabetical by system organ class and preferred term
† Possible or probable, as assessed by the investigator, or records where relationship was missing
Source: Table 12.6.1B.2